Medicinrådet

Bilag til Medicinrådets anbefaling vedr. tofersen til behandling af amyotrofisk lateral sklerose (ALS) med SOD1-mutation

Nationalt dansk appendix til fælles nordisk rapport

Vers. 1.0

Bilagsoversigt

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JNHB
Joint Nordic HTA-Bodies

Joint Nordic HTA-Bodies
Health Technology assessment report

Qalsody (tofersen)

Solution for injection

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

Date for publication of report: 2025-01-17

Case number DMC: EMS-2024-00112
Case number Fimea: FIMEA/2024/002898
Case number Landspitali: IS240003
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Joint Nordic HTA-Bodies

Joint Nordic HTA-Bodies (JNHB) formerly known as FINOSE started as a bottom-up initiative by the HTA authorities in Finland, Norway and Sweden and was launched in Stockholm in 2018. The collaboration extended to comprise Denmark in 2023 and Iceland in 2024. In June 2024 FINOSE changed its name and became Joint Nordic HTA-Bodies (JNHB).

JNHB offers efficient and transparent joint health technology assessments of medicinal products in the five Nordic countries. The assessments include both relative effectiveness and health economics. Decisions on price and reimbursement as well as recommendations for use, are made at the national level in each country. By working together and sharing knowledge, JNHB aims to produce high-quality assessment reports that provide solid support for national decisions.

The basis for the collaboration is outlined in a Memorandum of Understanding, signed in April 2024 by the collaborating HTA bodies;

- Danish Medicines Council (DMC),
- Finnish Medicines Agency (Fimea),
- Landspitali- The National University Hospital of Iceland,
- Norwegian Medical Products Agency (NOMA) and
- Dental and Pharmaceutical Benefits Agency (TLV) in Sweden.

In this assessment of Qalsody, NOMA was assessor, Fimea co-assessor, TLV, DMC and Landspitali reviewers.

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Summary

- JNHB has conducted a joint health economic assessment of Qalsody (tofersen) for the treatment of amyotrophic lateral sclerosis (ALS) associated with SOD1 mutations.
- ALS is a rare progressive neurodegenerative motor neuron disease, which results in loss of motor neurons and ultimately death. The motor symptoms associated with ALS include difficulty swallowing and speaking, respiratory insufficiency as well as cramps, spasticity, weakness and atrophy of muscles. Approximately 2% of all ALS cases are caused by mutations in the SOD1 gene.
- The speed of disease progression is highly variable between patients and is influenced by the type and location of SOD1 mutation.
- There are no curative treatments for ALS. Riluzole is approved in the EU and is the standard of care (SoC) treatment for adult ALS patients.
- Tofersen is a medicine for treating SOD1-ALS in adult patients. It is an antisense oligonucleotide, which binds to the SOD1 mRNA, resulting in the reduction in the amount of SOD1 protein synthesis. It is administered once every 28 days as an intrathecal injection using a lumbar puncture needle. According to the medical experts, tofersen will be given in addition to riluzole.
- In the pivotal VALOR Part C study, tofersen (n=72) was compared to placebo (n=36) over a 28-week randomized period. Across both arms, 62% of the participants also received riluzole. The baseline age and gender distributions are representative of the Nordic population. However, the distribution of the SOD1 gene variants differs between VALOR Part C and many Nordic populations since variants dominating in the Swedish, Norwegian and Finish population are associated with slower progressing ALS.
- At 28 weeks, the differences in physical function assessed by ALSFRS-R, respiratory function and muscle strength were not statistically significant compared to placebo. However, trends favoring tofersen over placebo were observed, e.g., the change between baseline and week 28 in the ALSFRS-R total score was -6.98 points in the tofersen group and -8.14 points in the placebo group. Tofersen administration did result in sustained reduction in total cerebrospinal fluid (CSF) SOD1 protein and plasma neurofilament light chain (NfL) levels.
- The repeated lumbar punctures associated with tofersen treatment regimen, as well as serious adverse events myelitis, increased intracranial pressure/papilloedema, radiculitis, and aseptic meningitis are a notable concern for slow-progressing and late-stage SOD1-ALS patients.
- The cost-utility analysis (CUA), conducted using a Markov model, evaluates cost-effectiveness of tofersen + SoC vs SoC where SoC consists of riluzole. The modelling of the disease progression is based on the transitions between five ordinal MiToS stages (calculated directly from ALSFRS-R) and death. Due to the short duration of VALOR Part C, the company chose to source transition probabilities for the comparator from an external publication based on the PRO-ACT ALS database. Each increasing MiToS stage is assigned a lower utility value (sourced from an external publication by Moore et al (1)) and higher costs. Caregiver utilities are included in the company's base case.
- Tofersen + SoC is modelled to have an effect on both progression (time to the first deterioration in the MiToS stage) and survival. The treatment effect of tofersen +SoC is based on a treatment switch-adjusted time-to-event analyses of VALOR data. Without adjustment for treatment switching, the hazard ratio (HR) for tofersen+SoC vs SoC is 0.69 (95%CI: 0.40, 1.20) for progression and 0.27 (95% CI:0.08; 0.89) for time to death in the ITT population. After treatment switch adjustment (via RPSFTM) the HR is 0.61 (95% CI: 0.29-1.27) for progression, and 0.10 (95% CI: 0.01-0.81) for time to death. The treatment effect of tofersen on progression is based on a very short follow-up in VALOR Part C, very few late stage MiToS events, and no patients remaining in the placebo group after week 28. The effect of tofersen on slowing progression is assumed to be the same across all MiToS stages which was not demonstrated empirically.

The treatment effect of tofersen on death is based on a few death events and model assumptions that may not be fulfilled.

- The JNHB's base case analysis excludes caregiver utilities, uses utility values from VALOR Part C and adjusts utility values so that they decrease with an increasing MiToS stage. Due to the large uncertainty around the representativeness of the modelled survival in the SoC arm to the Nordic population, JNHB opts for presenting results per different estimated survival in the SoC arm (by varying HR vs PRO-ACT based transition probabilities). Similarly, due to considerable uncertainties around the treatment effect of tofersen, the model results are presented across a range of HRs for progression (from 0.61 for crossover-adjusted SoC to 0.69 for ITT, based on datacut 2022) and death (from 0.12 for crossover-adjusted SoC to 0.66 for ITT, based on datacut 2023). Other key assumptions of the company's model are accepted (acceptance of MiToS as opposed to King's system, inclusion of backward transitions, and exclusion of genetic testing) but contribute to the high uncertainty in the model.
- The cost of treatment with tofersen+SoC is approximately 245,000 NOK per 28 days.
- When tofersen + SoC is compared to SoC, the cost per QALY in the JNHB base case is between 12 and 30 mln NOK. QALYs gained are between 0.20 and 1.6.
- JNHB's plausible sensitivity analyses show that parameters that have the largest impact on the ICER are the choice of a staging system MiToS vs King's (+4 mln NOK in ICER with King's vs JNHB's middle value base case), inclusion of backward transition probabilities (+5.5 mln NOK if excluded) and alternative utility sources (-3 mln NOK).

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1 Scope

This JNHB report is the result of a joint Nordic assessment of Qalsody (tofersen) for the treatment of amyotrophic lateral sclerosis (ALS).

The assessment is primarily based on the documentation presented by the company.

The aim of the JNHB report is to support national decisions on price and reimbursement as well as recommendations for use, in Denmark, Finland, Iceland, Norway and Sweden regarding tofersen. The primary focus of this report is the assessment of relative effectiveness, safety and cost effectiveness of tofersen. The JNHB report may be complemented with national appendices with additional local information and conclusions.

P (population)	Adult patients with amyotrophic lateral sclerosis (ALS), associated with a mutation in the superoxide dismutase 1 (*SOD1*) gene
I (intervention)	tofersen + SoC
C (comparison, comparators)	SoC
O (outcomes)	• Change in ALSFRS-R score • Change in percent predicted slow vital capacity (SVC) • Change in hand-held dynamometry (HHD) mega-score • Change in total SOD1 concentration in cerebrospinal fluid (CSF-SOD1) • Change in neurofilament light chain (NfL) concentration in plasma • Time to death • Time to death or permanent ventilation • Health-related quality of life • Adverse events
HE (health economy)	• Health-related quality of life • Costs • Incremental cost-effectiveness ratio (ICER) • Budget impact

SoC: Standard of care; ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised

2 Medical background

2.1 Amyotrophic lateral sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS) is a rare, progressive neurodegenerative motor neuron disease, which is characterized by loss of upper and lower motor neurons and their axons. The progressive loss of motor neurons results in motor symptoms, which can include difficulty swallowing and speaking, respiratory insufficiency as well as cramps, spasticity, weakness and atrophy of muscles (2). In addition, it is estimated that approximately half of ALS patients experience extra-motor symptoms, which include cognitive and behavioral impairment. ALS onset can be classified either as a spinal onset, in which patients' symptoms begin in the limbs, or as a bulbar onset, in which the first symptoms include difficulties in speech and swallowing. Eventually, regardless of the onset site, the symptoms progress to paralysis and death.

In addition to the onset site, progression pattern, speed of the disease and the onset age vary between patients. It is estimated that in approximately 3 years from symptom onset (with medians from different studies ranging from 1.6 to 5.2 years), ALS ultimately leads to death, usually due to respiratory failure. In a European population, the median age at diagnosis has been reported to be 67.0 (IQR: 59.0-74.0) years for women and 65.2 (IQR: 56.0-72.2) for men (3).

The causes of ALS are still largely unknown and they are considered to be multifactorial in nature, consisting of genetic, environmental and lifestyle factors. Estimates of the incidence and prevalence rates are presented in Table 1. Approximately 5-10% of ALS cases are classified as familial ALS cases based on family history, while the remaining majority (90-95%) of ALS cases are classified as sporadic ALS. It is estimated that 70% of familial ALS cases and 10% of sporadic ALS cases are attributed to genetic mutations, of which the most common are mutations in C9orf72, SOD1, TDP-43 and FUS genes (4).

Table 1: Incidence and prevalence rates of ALS in Europe and in Nordic countries.

	Europe	Denmark	Finland	Norway	Sweden
Incidence (per 100 000)	2.3	3.4	2.4	2.1	2.3
Prevalence (per 100 000)	6.2	3–7	6.4	5.3	6.2
Reference	(5)	(6)	(7)	(5)	(5)

Diagnosis of ALS is based on symptoms and signs as well as imaging and laboratory tests, but no single diagnostic test is currently in use. This, together with the heterogeneity of the disease symptoms can result in delays in diagnosis. Neurofilament light chains (NfLs), which are released into the cerebral spinal fluid (CSF) and serum during axonal injury and breakdown, has been proposed as a potential biomarker of neurodegeneration in ALS, however, this marker is non-specific as it can be a sign of many other neurodegenerative diseases as well (8).

2.1.1 SOD1-ALS

One of the sites of ALS-associated mutations is located in the superoxide dismutase 1 gene (*SOD1*), which encodes an abundant dimeric enzyme, copper/zinc superoxide dismutase (9). ALS-associated mutations in *SOD1* gene lead to accumulation of the toxic form of the SOD1 protein in the affected motor neurons, causing axonal injury and neurodegeneration and thus development of ALS. It is estimated that approximately 2% of ALS cases are caused by mutations in *SOD1* and according to EPAR, SOD1-ALS prevalence is estimated as 0.12 per 100 000 persons and incidence as 0.04 per 100 000 persons in Europe (10). However, geographic variation exists.

There are more than 200 identified ALS-associated mutations in *SOD1*, which are distributed throughout the gene. Although there is evidence suggesting that, *SOD1* mutation-driven ALS cases overall are more frequently of familial origin, with spinal onset as well as lower age of onset (11, 12) in comparison to the general ALS population, the type of pathogenic variant also appears to have an effect on the age of onset as well as on survival. For example, the A4V/A5V variant, which is the most prevalent *SOD1* mutation variant in North America, is associated with shorter survival (mean of 1.1 years) (11-13). Another common variant, homozygous D91A, is particularly common in Northern Europe and associated with notably longer survival (mean of 11.4 years) (11, 14). The heterogeneous effects of the *SOD1* mutation variants pose a challenge to treatment development and assessment.

Currently, genetic screening of known ALS mutations, including *SOD1* mutations, is inconsistent between countries, although recent publications call for broader genetic testing (15). In Denmark and Norway, most ALS patients are offered to be genetically tested. In the latter, this

is done through a national genetic mapping study (GAIN). Although similar procedures/studies are not currently present in Sweden and Finland, a national recommendation of genetic testing of ALS (NAG-ALS) is under development in Sweden and expected to be published in the coming year. With regards to *SOD1* variants, most patients with slowly progressing ALS with leg-onset are tested for SOD1*D91A variant in Finland due to its high prevalence.

2.2 Tofersen (Qalsody)

2.2.1 Therapeutic indication

Tofersen is indicated for the treatment of ALS in adult patients with a mutation in the *SOD1* gene. Tofersen has been granted marketing authorization under exceptional circumstances.

2.2.2 Mechanism of action

ALS-associated mutation(s) in the *SOD1* gene cause the accumulation of toxic form of SOD1 protein, which then results in axonal injury and neurodegeneration present in ALS. Tofersen, the active substance in Qalsody, is an antisense oligonucleotide (ASO), which binds to the SOD1 mRNA by hybridisation. This binding results in the degradation of the SOD1 mRNA and reduction in the amount of SOD1 protein synthesis.

2.2.3 Posology and method of administration

Tofersen is administered as an intrathecal injection using a lumbar puncture needle. Injections should be administered by, or under the direction of, healthcare professionals experienced in performing the procedure.

The recommended dose is 100 mg of tofersen per treatment. The treatment should be initiated with three loading doses administered at 14-day intervals, after which maintenance dose should be administered once every 28 days.

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

2.3 Current treatment options

Currently, there are no curative treatments for ALS and only a few medicinal products are in use worldwide. Of these, riluzole is approved in the EU and its use is also strongly recommended by the European Academy of Neurology (EAN) in its most recent guideline for management of ALS (16). In all Nordic countries, riluzole (50 mg twice daily) is therefore also the standard of care (SoC) treatment.

Based on clinical studies, use of riluzole can prolong ALS patient's life by approximately 2-3 months (17). The adverse effects from riluzole are considered rare and mostly minor and reversible upon discontinuation. Since riluzole is considered suitable for all types of ALS, riluzole is generally offered to all patients.

The individual symptoms of ALS can be treated with medicinal products as well as physical, occupational and speech therapy. However, none of these treatment options are able to preserve patients' physical functionality or prolong their life with the disease. In the later stages of the disease, mobility aids, tracheostomy, mechanical ventilation as well as palliative care are also usually required. Overall, the treatment of ALS requires a multidisciplinary team of healthcare experts to ease the physical symptoms caused by the disease progression.

2.3.1 Comparator

In this assessment, tofersen + standard of care (SoC) is compared to SoC. For the majority of ALS patients in Denmark, Finland, Norway and Sweden, SoC means riluzole treatment, which

is considered suitable for all ALS subtypes, including SOD1-ALS. The company assumes that if tofersen is implemented into the treatment regime, possible concomitant treatment with riluzole is anticipated in clinical practice for eligible SOD1-ALS patients.

JNHB conclusion:
JNHB agrees that SoC is the relevant comparator of tofersen + SoC. JNHB also agrees that, if approved for reimbursement, tofersen could be administered together with riluzole.

3 Clinical efficacy and safety

The assessment of clinical efficacy and safety is mainly based on the evidence included in the submission dossier prepared by the company. The authoring team has checked the information retrieval included in the company's submission dossier for completeness against
- a search in ClinicalTrials.gov and PubMed
- the studies included in the European public assessment report (10)

3.1 Clinical trials

3.1.1 Design and methods of the clinical trial(s)

Table 2: Summary of relevant trials.

Study	Study design	Treated study population	Intervention	Primary endpoints
233AS101, VALOR part A NCT02623699 Completed	- phase 1/2 - randomized - double-blind - placebo-controlled - single ascending dose (SAD)	20 adult ALS patients	Single dose of tofersen (10, 20 40 or 60 mg) (n=15) Single dose of placebo (n=5)	Safety, tolerability and PK
233AS101, VALOR part B NCT02623699 Completed	- phase 1/2 - randomized - double-blind - placebo-controlled - multiple ascending dose (MAD)	50 adult SOD1-ALS patients	Tofersen (20, 40, 60 or 100 mg) over a period of 12 weeks * (n=38) Placebo over a period of 12 weeks (n=12)	Safety, tolerability and PK
233AS101, VALOR part C NCT02623699 (18) Completed	- phase 3 - double-blind - randomized - placebo-controlled - multicentre	108 adult ALS patients with confirmed *SOD1* mutation	Tofersen 100 mg over a period of 24 weeks * (n=72) Placebo over a period of 24 weeks (n=36)	Change from baseline to week 28 in ALS-FRS-R total score
233AS102, OLE NCT03070119 Extension study to 233AS101 (19) Completed	- phase 3 - open-label - multicentre - long-term	139 adult SOD1-ALS patients who had completed tofersen or placebo treatment in VALOR part A, B or C	Tofersen 100 mg for up to 360 weeks *	Number of participants with adverse events (AEs) and serious adverse events (SAEs)
233AS303, ATLAS NCT04856982 (20) Ongoing	- phase 3 - randomized - double-blind - placebo-controlled	150 (planned) clinically presymptomatic adults with *SOD1* mutation	Tofersen 100 mg for up to 2 years * Placebo	Percentage of participants with emergence of clinically manifest ALS within 24 months from baseline

ALS: amyotrophic lateral sclerosis ; ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; PK: pharmacokinetics; SOD1: superoxide dismutase-1
* The treatment was initiated with three loading doses administered at 14-day intervals, after which maintenance doses was administered once every 28 days.

Study 233AS101 (VALOR)

The pivotal VALOR study is a completed phase 1/2/3 multicentre, randomised, double-blind, placebo-controlled trial consisting of three parts (A, B and C). Parts A and B are phase 1/2 single ascending dose (SAD) and multiple ascending dose (MAD) studies, respectively. Participants enrolled in parts A and B were not enrolled in part C. This assessment will focus on part C of the study, which evaluated the efficacy and safety of tofersen (100 mg) over 24 weeks compared to placebo in adult patients with weakness attributed to ALS and a confirmed *SOD1* mutation. Part C of the study included a 4-week screening period, a 24-week treatment period and a follow-up period of 4 to 8 weeks (10, 18).

A total of 108 adult participants (ITT population) with 42 unique *SOD1* mutations were enrolled into the study and randomized 2:1 to receive either tofersen (n=72) or placebo (n=36) for 24 weeks. Randomisation was stratified by two factors: patient's use of edaravone or riluzole at baseline and whether a patient met the prognostic criteria for the rapid disease progression subgroup. First three loading doses were administered once every two weeks and were

followed by five maintenance doses every four weeks. The treatment was administered intrathecally by lumbar puncture and alongside (optional) concomitant use of riluzole or edaravone.

The ITT population comprised of all the participants who were randomised and received at least one dose of treatment while the primary analysis population was a subgroup of participants who met a trial-defined prognostic criteria for faster-progressing disease (mITT)(18). The faster-progressing mITT subgroup was defined based on *SOD1* mutation type and prerandomisation ALSFRS-R (Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised) slope; participants had to have either both a protocol-defined *SOD1* mutation associated with shorter survival (p.Ala5Val, p.Ala5Thr, p.Leu39Val, p.Gly42Ser, p.His44Arg, p.Leu85Val, p.Gly94Ala, p.Leu107Val, and p.Val149Gly) as well as ≥0.2 points/month prerandomisation slope or ≥0.9 points/month prerandomisation slope (10) All other participants not meeting these criteria, were classified as slower-progressing (non-mITT). The participants in the mITT and non-mITT populations were also required to have SVC ≥65% and ≥50% of predicted value, respectively, as adjusted for age, sex, and height from the sitting position.

Baseline characteristics for the mITT, non-mITT and ITT populations are presented in Table 3. Baseline plasma concentrations of NfL were higher in the tofersen group than in the placebo group. In addition, the rate of decline in the ALSFRS-R score from screening to day 15 was greater in the tofersen group.

Table 3: Baseline characteristics of participants in the VALOR part C study (10, 18).

	mITT (n=60)		**non-mITT (n=48)**		**ITT (n=108)**	
	Placebo (n=21)	**Tofersen (n=39)**	**Placebo (n=15)**	**Tofersen (n=33)**	**Placebo (n=36)**	**Tofersen (n=72)**
Age, years						
mean (SD)	54.0 (12.2)	47.3 (14.3)	47.3 (9.8)	49.0 (10.5)	51.2 (11.6)	48.1 (12.6)
Sex, n (%)						
male	11 (52)	22 (56)	8 (53)	21 (64)	19 (53)	43 (60)
BMI						
mean (SD)	28.0 (6.2)	26.7 (6.4)	26.6 (7.0)	26.2 (4.6)	27.4 (6.5)	26.4 (5.6)
Riluzole use, n (%)						
Yes	13 (62)	25 (64)	9 (60)	20 (61)	22 (61)	45 (62)
Edaravone use, n (%)						
Yes	1 (5)	2 (5)	2 (13)	4 (12)	3 (8)	6 (8)
Mutation type, n (%) *						
p.Ile114Thr	6 (29)	5 (13)	4 (27)	5 (15)	10 (28)	10 (14)
p.Ala5Val	6 (29)	11 (28)	0	0	6 (17)	11 (15)
p.Gly94Cys	1 (5)	1 (3)	1 (7)	3 (9)	2 (6)	4 (6)
p.His47Arg	0	0	4 (27)	1 (3)	4 (11)	1 (4)
Site of onset, n (%)						
Bulbar	2 (10)	3 (8)	N	N	3 (8)	3 (4)
Lower limbs	14 (67)	19 (49)	12 (80)	27 (82)	26 (72)	46 (64)
Upper limbs	5 (24)	14 (36)	2 (13)	6 (18)	7 (19)	20 (28)
Respiratory	N	N	0	0	N	N
Multiple sites	N	N	0	0	N	N
Time from symptom onset, months						
median (min, max)	8.3 (2.4, 21.3)	8.3 (1.7, 18.5)	39.6 (11.8, 103.2)	35.5 (3.9, 145.7)	14.6 (2.4, 103.2)	11.4 (1.7, 145.7)
ALSFRS-R pre-randomisation slope						
median (min, max)	-1.51 (-4.9, -0.42)	-1.34 (-8.30, -0.39)	-0.17 (-0.84, -0.02)	-0.30 (-0.77, -0.00)	-0.89 (-4.91, -0.02)	-0.75 (-8.30, -0.00)

	mITT (n=60)		non-mITT (n=48)		ITT (n=108)	
	Placebo (n=21)	**Tofersen (n=39)**	**Placebo (n=15)**	**Tofersen (n=33)**	**Placebo (n=36)**	**Tofersen (n=72)**
ALSFRS-R baseline total score						
mean (SD)	35.4 (5.7)	36.0 (6.4)	39.9 (5.1)	38.1 (5.1)	37.3 (5.8)	36.9 (5.9)
min, max	24, 45	15, 44	32, 47	26, 48	24, 47	15, 48
ALSFRS-R run-in slope (Screening to day 15)						
raw mean (SD)	-1.3 (3.9)	-1.8 (2.5)	0.1 (1.9)	-0.1 (1.3)	-0.7 (3.3)	-1.0 (2.2)
% predicted SVC at baseline						
mean (SD)	83.7 (17.9)	80.3 (14.2)	87.1 (14.8)	84.2 (19.0)	85.1 (16.5)	82.1 (16.6)
min, max	57.4, 120.4	46.7, 114.8	54.8, 114.4	55.4, 134.7	54.8, 120.4	46.7, 134.7
Plasma NfL at baseline (pg/mL)						
mean (SD)	127.3 (94.4)	146.2 (82.6)	37.0 (29.5)	47.6 (41.8)	89.7 (86.5)	100.4 (82.8)
geometric mean	92.7	121.8	28.4	33.2	56.6	66.6
min, max	9, 370	12, 329	8, 99	5, 211	8, 370	5, 329
CSF-SOD1 protein levels, ng/mL						
mean	117.2	118.1	135.8	120.4	125.5	118.7

ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; BMI: body mass index; CSF: cerebral spinal fluid; NfL: neurofilament light chains; SD: standard deviation; SOD1: copper/zinc superoxide dismutase; SVC: slow vital capacity
* Most common mutations, n > 4
N: Numbers removed to avoid unblinding of treatment from study 101 in context of the ongoing open-label extension study 102

The primary endpoint of VALOR part C was the change from baseline to week 28 in Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised (**ALSFRS-R**) in mITT population. ALSFRS-R is a widely-used scoring system for the assessment of the disability status, function and progression of ALS in patients over time. It consists of four domains (bulbar, fine motor, gross motor and breathing), which all include three questions on topics as described in Figure 1 (18). Answers to questions range from 0 (loss of function) to 4 (normal function). Hence, the overall score range is 0–48 and higher scores indicate better function. Of the two most widely used ALS staging systems, Milano-Torino staging system (MiToS) is directly derived from ALSFRS-R score, while King's staging system can be estimated from ALSFRS-R scores.

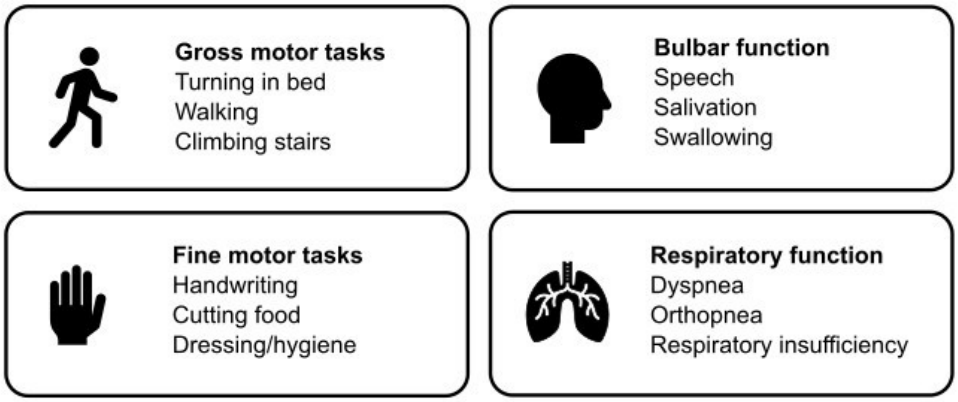

Figure 1: Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised (ALSFRS-R) questionnaire domains and their question topics.

Secondary endpoints in VALOR part C were the percentage of the predicted slow vital capacity (**SVC**), hand-held dynamometry (**HHD**) megascore, the change from baseline in total SOD1

concentration in cerebrospinal fluid (**CSF-SOD1**), the concentration of neurofilament light chains (**NfL**) in plasma, and survival (**time to death** and **time to death or permanent ventilation**) and safety.

- SVC is part of vital capacity and considered a clinically meaningful predictor of survival and ALS progression (21) since the respiratory muscle function of ALS patients deteriorates as the disease progresses. In VALOR part C, the volumes in SVC were standardized to the percentage of the predicted normal value on the basis of age, sex and height (18).
- HHD enables the evaluation of muscle strength (21) and in VALOR part C, HHD megascore was counted using the average of z-scores across 16 muscle groups (18).
- CSF-SOD1 has been proposed as a pharmacodynamic biomarker for SOD1-lowering therapies, such as tofersen (22) because mutations in the *SOD1* gene leads to accumulation of toxic forms of SOD1 protein, which cause axonal injury and neuro-degeneration. Neurofilaments are shed into the blood and CSF during neuronal injury and axonal damage in various neurological diseases, including ALS (23).
- Increased NfL level in serum and CSF is considered a nonspecific biomarker of neurodegeneration. Several studies have indicated that NfL levels can be used as a marker of presymptomatic ALS (~ 12 months before symptom onset) as well as ALS progression and survival. (8, 20, 24). Sun et al. found that high NfL levels in CSF indicated lower ALSFRS-R score and a more rapid disease progression in sALS patients (25).
- Time to death (i.e., overall survival) and time to death or permanent ventilation (PV) were analysed in VALOR part C as time-to-event endpoints using Kaplan-Meier estimates, log-rank test (stratified by treatment and riluzole or edaravone use) and Cox regression model (adjusted for baseline disease duration since symptom onset, and riluzole or edaravone use). The time to death or PV was defined as the time to the earlier occurrence of either event from the first dose of tofersen. In VALOR part C, PV was further defined as at least 22 hours of (invasive or non-invasive) mechanical ventilation per day for at least 21 consecutive days (10, 18).

The explorative endpoints included patient-reported outcomes, which were measured by questionnaires Amyotrophic Lateral Sclerosis Assessment Questionnaire 5-Item Form (ALSAQ-5), EuroQol 5-Dimension 5-Level Scale (EQ-5D-5L) and fatigue severity scale (FSS). The first two questionnaires measure health-related quality of life and the third measures fatigue. Lower scores in ALSAQ-5 and FSS and higher scores in EQ-5D-5L indicate better health.

In order to account for the relevant intercurrent events, i.e., deaths and withdrawals, Joint Rank Test (JRT) together with multiple imputation (MI) was used to combine and rank ALSFRS-R total scores and time to death in the primary efficacy analysis. In JRT, participants were ranked based on their outcomes in day 197. Death was treated as the worst outcome and those participants were further ranked based on the length of their survival. Participants who withdrew (for any other reason than death) from the study before ALSFRS-R was measured at week 28, had their scores imputed with MI under the missing at random assumption. Thus, participants who withdrew from the study early, followed the same trajectory as those who continued until the end of the study, conditional on observed data. It should be noted that JRT was implemented only to obtain p-values and the treatment group estimates as well as estimated treatment differences are based on absolute changes from baseline to week 28. Percentage of predicted SVC was also analysed in the same way (10, 18).

The mITT population, i.e., fast-progressors, was used in the primary analyses for both primary and secondary efficacy endpoints. Analysis of covariance (ANCOVA) was used to analyse differences in changes between baseline and week 28 between treatment arms with adjustment for, baseline disease duration since symptom onset, relevant endpoint baseline score, and use

of riluzole or edaravone in the primary analysis. A similar approach was implemented for both primary and secondary efficacy endpoints.

However, for percentage of predicted SVC, baseline ALSFRS-R total score was also included as a adjustment variable. Total CFS-SOD1 protein and plasma NfL values were log-transformed. Non-mITT, i.e., slower-progressors, and ITT populations were also tested but treated as secondary analyses (except for total CSF-SOD1 in the non-mITT population, which was a primary endpoint for this population). For the ITT population, post hoc analyses in clinical function and QoL endpoints were conducted with similar ANCOVA model with the exception that baseline disease duration since symptom onset was replaced with baseline plasma NfL as one of the adjustment variables (10, 18).

Extension study 233AS102 (VALOR+OLE)

Participants who completed part A, B or C of VALOR could enrol into the ongoing long-term, open-label extension study 233AS102 (OLE), where all participants, regardless of earlier treatment assignment, received 100 mg doses of tofersen according to the administration routine. Altogether 139 of the eligible 159 participants enrolled into the extension study; 44 participants from VALOR parts A and B and 95 participants from VALOR part C. Participants from the A and B parts had to have a washout of ≥ 16 weeks between the last dose of treatment received in VALOR and the first dose of tofersen in the extension study. The endpoints were the same as in the VALOR part C study.

Of the 95 participants of VALOR part C who continued into the extension study, 63 participants came from the tofersen arm and 32 participants from the placebo arm. One participant from each of the treatment arms did not enrol in the extension study. Participants remained unaware of their trial-group assignment in VALOR. Patients who started tofersen treatment at the beginning of OLE were labelled **delayed-start tofersen** group and participants who had received tofersen treatment in VALOR were labelled **early-start tofersen** group (10, 18).

Prespecified interim data cuts were conducted on 16 July 2021 (VALOR study completion), on 16 January 2022 (52 weeks of follow-up) and on 28 February 2023 (104 weeks of follow-up), when all participants from VALOR part C had received 100 mg tofersen for at least two years with maximum treatment duration of 245 weeks (10). Median follow up time was 3.4 years (range: 2.2, 3.9 years).

Analysis methods were similar to VALOR part C, i.e. ANCOVA and MI, were implemented in the VALOR+OLE analysis. However, contrary to VALOR part C, ITT population was used in the primary analysis. In addition, imbalances in the baseline NfL levels and ALSFRS-R run-in slope (higher in the tofersen group) led to an adjustment in the statistical analysis plan for the 52 follow-up and subsequent data cuts. As a result, the following covariates were included in the model: (1) corresponding baseline score for the endpoint, (2) baseline plasma NfL and (3) riluzole or edaravone use (10, 18).

JNHB assessment of design and methods of clinical trials

The evaluation of treatment effect is complicated by the disease heterogeneity, which is evident in the study population. Overall, over 200 *SOD1* mutation variants have been identified, of which 42 were identified in the study population. Therefore, generalization of results from VALOR part C and its open label extension study to all *SOD1* mutations is problematic. Furthermore, no subgroup analyses were presented between the variants, although it is well-established that different mutation variants affect the disease onset and progression and could therefore potentially produce varying clinical outcomes to tofersen treatment. However, the small sample size and heterogeneous variant selection makes comparisons between variants mostly unfeasible.

In relation to the *SOD1* mutation variants, another issue in the clinical trial is associated with the differing variant distribution in the Nordic countries. Within the VALOR part C participant population, there were 17 (16%) participants with A4V/A5V (p.Ala5Val) mutation variant, which is considered the fastest progressing mutation variant enrolled in VALOR. It is also the main mutation variant in North America with median survival of 1.2 years. However, in Finland, according to the clinical experts, p.D91A constitutes about 90% of *SOD1* mutations and p.A90V about 9%, thus representing 99% of the discovered *SOD1* mutations. Both p.D91A and p.A90V mutation variants are associated with early disease onset and slow progression with mean survival of 14 years and with some patients living up to 30 years (26). Similarly in Sweden and Norway, the most common *SOD1* mutation variants are considered to be variants associated with slow progression (p.D91A and p.His47Arg, respectively) according to the clinical experts. In Denmark, no particular variant is considered more common than others. There were five (4.6%) participants with p.His47Arg variant in the study and two (1.9%) with the p.D91A variant. The *SOD1* variant distribution in the study can thus not be considered representable of the Nordic countries.

A hypothetical estimand was implemented in the analysis of the primary endpoint, ALSFRS-R, where the missing data (withdrawal due to a reason other than death) was imputed under a missing at random (MAR) assumption. It can be argued, that instead of the MAR assumption, which implies that the treatment effect of tofersen does not diminish after discontinuation, assuming a loss of potential benefit from treatment after treatment discontinuation could be a more plausible, as well as conservative, approach. Raw Data Pilot Project, which is further described in EPAR, indicated that the choice of assumption had a notable impact on the outcome.

Prior to the 52- and 104-week follow-ups of VALOR+OLE, the statistical analysis plan was amended to include baseline levels of plasma NfL as a covariate. The company noted that there was an observable imbalance in NfL baseline levels between tofersen and placebo groups, which indicated a potentially faster disease progression at baseline in the tofersen group. According to the company, through adjusting for baseline NfL as a continuous covariate, the analysis can account for more baseline disease heterogeneity and thus enables analyses in the complete ITT population including both fast- and slower-progressing participants. This amendment was not prespecified and can be considered a major amendment to the study protocol.

JNHB conclusion:
The short duration of the randomized controlled trial together with placebo patients switching to tofersen treatment in the open label extension study are considered major limitations in the interpretation of the study results. In addition, the patient population is not fully representative of the Nordic population.

3.2 Results for clinical efficacy and safety for VALOR+OLE

3.2.1 Results from VALOR part C

In VALOR part C, the baseline mean ALSFRS-R total score was similar between the tofersen (35.4) and placebo groups (36.0) in the mITT population (Table 4). By week 28, the change from the baseline in the ALSFRS-R total score was -6.98 points in the tofersen group and -8.14 points in the placebo group. The non-mITT participants experienced a smaller ALSFRS-R score decline of -1.33 and -2.73, respectively. Although previous research indicates that the decrease rate of ALSFRS-R varies between patients and also within ALS patients (27), a study by McElhiney et al. estimated that on average the ALSFRS-R total score declined by one point per month in patients with ALS (28). This is somewhat consistent with the mITT population's

results from VALOR part C. The adjusted mean difference in ALSFRS-R score between the groups was 1.2 points (95% CI: -3.2, 5.5), however, this difference was not statistically significant (p-value: 0.97).

Further post-hoc and sensitivity analyses on mITT population also failed to produce statistically significant differences (10). Similarly, analysis on the non-mITT population was favouring tofersen (adjusted mean difference 1.4, 95%CI: -1.1, 3.9) yet remained statistically non-significant (p-value: 0.27).

Despite the non-significant ALSFRS-R score differences between the groups, one of the post-hoc analyses indicated numerically larger differences between tofersen and placebo over 28 weeks in patients with baseline NfL values above median (mean difference 3.9, 95% CI: -1.0, 8.9). For patients with baseline NfL values below median the corresponding differences were smaller (mean difference 0.6, 95% CI: -1.3, 4.2) (10).

Since the primary endpoint did not achieve statistical significance, all differences in the secondary endpoints in mITT population between tofersen and placebo group, i.e., changes between baseline and week 28 in CSF-SOD1 protein, plasma NfL, percent predicted SVC and HHD megascore as well as time to death or PV, were considered to be statistically non-significant (18). Nonetheless, the differences and associated significance are still described in Table 4, together with results from non-mITT and full ITT populations.

At 28 weeks, the percentage of predicted SVC and HHD megascore outcomes favoured tofersen despite the lack of statistical significance in both subgroups. The levels of total CSF-SOD1 protein and plasma NfL were nominally statistically significantly reduced in the tofersen group, indicating functional target engagement of tofersen treatment in both subgroups. The total CSF-SOD1 protein level was reduced by 29 % in the tofersen group and increased by 16 % in the placebo group while the mean concentration of plasma NfL was reduced by 60 % in the tofersen group and increased by 20 % in the placebo group in the mITT subgroup. In addition, the percentage of participants with an event of death or PV was similar in the tofersen and placebo groups although the number of events was limited.

Table 4: Change from baseline to week 28 in primary and secondary endpoints in VALOR part C in mITT, non-mITT and ITT subgroups (10, 18).

	mITT (n=60)		non-mITT (n=48)		ITT (n=108)	
	Placebo (n=21)	Tofersen (n=39)	Placebo (n=15)	Tofersen (n=33)	Placebo (n=36)	Tofersen (n=72)
ALS-FRS-R total score						
Adjusted mean	-8.14	-6.98	-2.73	-1.33	-6.2	-4.1
Adjusted mean difference (95% CI)	1.2 (-3.2, 5.5)		1.4 (-1.1, 3.9)		2.1 (-0.3, 4.5)	
p-value	0.97*		0.27**		0.50*	
%-predicted SVC						
Adjusted mean	-22.20	-14.31	-4.90	-0.26	-15.82	-7.34
Adjusted mean difference (95% CI)	7.9 (-3.5, 19.3)		4.6 (-1.2, 10.5)		8.5 (1.8, 15.2)	
p-value	0.32*		0.12**		0.069*	
HHD						
Adjusted mean	-0.37	-0.34	-0.18	-0.09	-0.32	-0.23
Adjusted mean difference (95% CI)	0.02 (-0.21, 0.26)		0.09 (-0.08, 0.26)		0.10 (-0.04, 0.23)	
p-value	0.84**		0.28**		0.15**	
Total CSF-SOD1 protein						
Adjusted GMR to baseline	1.16	0.71	0.81	0.60	0.98	0.65
Adjusted GMR difference (95% CI)	0.62 (0.49, 0.79)		0.74 (0.63, 0.88)		0.66 (0.57, 0.77)	
p-value	<0.0001**		0.0007**		<0.0001**	
Plasma NfL						
Adjusted GMR to baseline	1.20	0.40	0.95	0.50	1.12	0.45
Adjusted GMR difference (95% CI)	0.33 (0.25, 0.45)		0.52 (0.43, 0.63)		0.40 (0.33, 0.49)	
p-value	<0.0001**		<0.0001**		<0.0001**	
Death or PV						

	mITT (n=60)		non-mITT (n=48)		ITT (n=108)	
	Placebo (n=21)	Tofersen (n=39)	Placebo (n=15)	Tofersen (n=33)	Placebo (n=36)	Tofersen (n=72)
ALS-FRS-R total score						
n (%)	2/21 (9.5)	4/39 (10.3)	0/15	0/33	2/36 (5.6)	4/72 (5.6)
HR (95% CI)	1.39 (0.22, 8.80)		NE		0.97 (0.16, 5.71)	
Death						
n (%)	0/21	1/39 (2.6)	N	N	N	N
HR (95% CI)	NE		NE		NE	

CI: confidence interval; GMR: geometric mean ratio; CSF: cerebral spinal fluid; HHD: hand-held-dynamometry; HR: hazard ratio; N: Numbers removed to avoid unblinding of treatment allocation from VALOR in the context of the ongoing OLE study; NE: not estimable; NfL: neurofilament light chains; PV: permanent ventilation; SOD1: superoxide dismutase 1; SVC: slow vital capacity
NOTE: Analyses of the ITT population are post hoc and based on analyses where baseline plasma NfL is a covariate.
* P-value is based on joint rank test (JRT) and multiple imputation (MI).
** P-value is based on analysis of covariance (ANCOVA) and multiple imputation (MI).

At week 28, the results of the explorative endpoints showed a small trend in favour of tofersen in the mITT subgroup (10). Results for quality of life in the mITT, non-mITT and ITT populations are presented in more detail in Table 5 as changes from baseline to week 28.

Table 5: Change from baseline to week 28 in quality of life endpoints in VALOR part C in mITT, non-mITT and ITT subgroups (10, 18).

	mITT (n=60)		non-mITT (n=48)		ITT (n=108)*	
	Placebo (n=21)	Tofersen (n=39)	Placebo (n=15)	Tofersen (n=33)	Placebo (n=36)	Tofersen (n=72)
ALSAQ-5						
Adjusted mean	15.6	10.0	3.0	1.3	12.6	6.9
Adjusted mean difference (95% CI)	–5.6 (–15.6, 4.4)		–1.6 (–9.6, 6.3)		–5.7 (–11.8, 0.4)	
p-value	0.27		0.69		0.07	
**EQ-5D-5L utility ** **						
Adjusted mean	–0.35	–0.16	–0.03	–0.03	–0.21	–0.08
Adjusted mean difference (95% CI)	0.20 (0.06, 0.33)		–0.01 (–0.11, 0.10)		0.14 (0.05, 0.23)	
p-value	0.004		0.92		0.003	
FSS						
Adjusted mean	10.5	5.6	–0.5	2.3	6.3	3.9
Adjusted mean difference (95% CI)	–4.9 (–11.2, 1.4)		2.8 (–4.7, 10.4)		–2.4 (–7.5, 2.6)	
p-value	0.13		0.46		0.34	

ALSAQ-5: Amyotrophic Lateral Sclerosis Assessment Questionnaire 5-Item Form, EQ-5D-5L: EuroQol 5-Dimension 5-Level Scale; FSS: fatigue severity scale
*Results for ITT population were adjusted for baseline plasma NfL.
**The company mapped the EQ-5D-5L to EQ-5D-3L UK value set

Eight participants (11 %) in the tofersen group discontinued during VALOR part C; two due to adverse events, two withdrew consent, one died and three had experienced a disease progression. Three participants (8 %) discontinued the study in the placebo group; one due to consent withdrawal and two due to disease progression (18, 19).

3.2.2 Results from VALOR+OLE

The results from the week 52 and 104 data cuts are displayed in Table 6. The change in the ALSFRS-R score continued to differ between the early-start group and delayed-start group at week 52 (adjusted mean difference 3.5 points) in the ITT population. The difference was maintained until week 104 (adjusted mean difference 3.7 points) (10). Although there is no consensus on a clinically meaningful change in ALSFRS-R score, according to a study by Castrillo-Viguera et al. 90% of clinical experts rated that ≥20% change in decline of the ALSFRS-R score was at least somewhat clinically meaningful (29). According to another study by Fournier et al. (2022), mean change of less than 3.24 points in the ALSFRS-R score may not be clinically meaningful according to a patient-defined approach (30).

At week 52, the differences between treatment groups were small in the percentage of predicted SVC and HHD megascore (9.2 % and 0.28, respectively) but the results were nominally statistically significant. At week 104, the effects on SVC and HHD were sustained (mean differences 9.7 % and 0.19, respectively) in favour of early-start tofersen group (10).

Data from VALOR+OLE showed, that total CSF-SOD1 protein level had decreased noticeably at week 12 in the early-start group and reached the lowest point by week 28, after which it remained at decreased level until week 104. In the delayed-start group, the levels remained high and close to the baseline level until week 28, when these participants were on placebo treatment. After week 28, i.e., once participants received tofersen, the levels decreased until week 40 after which the CSF-SOD1 levels remained at a level comparable to the early-start group.

Plasma and CSF NfL reductions in the early-start tofersen group were sustained and similar reductions were observed in the delayed-start tofersen group by the weeks 52 and 104. Reductions were 60–70% from the baseline at week 104 (10, 18).

By week 52, 8 (11.1 %) patients had died in the early-start tofersen group and 6 (16.7 %) patients in the delayed-start tofersen group. By week 104, the proportion of patients who had died was more similar (15.3 % and 19.4 %, respectively) between the groups and 44 participants in the early-start group and 16 participants in the delayed-start group were continuing in the study (18).

Table 6: Change from baseline to weeks 52 and 104 in endpoints for tofersen-treated participants in VALOR+OLE study.

	Week 52		Week 104	
	Delayed-start tofersen (n=72)	Early-start tofersen (n=36)	Delayed-start tofersen (n=72)	Early-start tofersen (n=36)
ALSFRS-R total score				
Adjusted mean	-9.5	-6.0	-13.2	-9.5
Adjusted mean difference (95% CI)	3.5 (0.4, 6.7)		3.7 (-0.7, 8.2)	
p-value	0.027		0.10	
% of predicted SVC				
Adjusted mean	-18.6	-9.4	-24.2	-14.5
Adjusted mean difference (95% CI)	9.2 (1.7, 16.6)		9.7 (-0.8, 20.2)	
p-value	0.016		0.07	
HHD				
Adjusted mean	-0.45	-0.17	-0.58	-0.39
Adjusted mean difference (95% CI)	0.28 (0.047, 0.517)		0.19 (-0.098, 0.474)	
p-value	0.019		0.20	
Total CSF-SOD1				
Adjusted GMR to baseline	0.79	0.67	0.19	0.27
Plasma NfL				
Adjusted GMR to baseline	0.59	0.49	0.60	0.66
Death or PV				
n (%)	8/36 (22.2)	12/72 (16.7)	9/36 (25.0)	16/72 (22.2)
HR (95%CI)	0.36 (0.14, 0.94)		0.76 (0.33, 1.72)	
p-value	0.037		0.52	
Death				
n (%)	6/36 (16.7)	8/72 (11.1)	7/36 (19.4)	11/72 (15.3)
HR (95%CI)	0.27 (0.08, 0.89)		0.66 (0.25, 1.71)	
p-value	0.031		0.40	

GMR: geometric mean ratio; HHD: hand-held-dynamometry; HR: Hazard ratio; NE: not estimable; NfL: neurofilament light chains; SVC: slow vital capacity, PV: permanent ventilation; slow vital capacity
NOTE: P-values for survival outcomes (death or PV) are based on Cox regression analysis.

At week 52 nominally statistically significant differences in quality of life were observed between early-start and delayed-start tofersen in the favour of early-start tofersen. The

differences were in ALSAQ-5: -10.3 (p=0.0044), FSS: -3.8 (p=0.15) and EQ-5D-5L: 0.2 (p<0.0001) (10). At 104 weeks the difference in the mean change from the baseline in ALSAQ-5 was smaller than at 52 weeks (adjusted mean difference: -6.6; 95% CI: -16.34, 3.15). The mean difference remained the same (adjusted mean difference: 0.2; 95% CI: 0.03, 0.29) in the EQ-5D-5L between the early- and delayed-start tofersen groups. The FSS result favoured delayed-start tofersen group at week 104 (adjusted mean difference: 2.7; 95% CI: -2.64, 8.13) (19).

The company has an ongoing study 233AS303 (ATLAS) which is a phase 3, randomized, double-blind placebo-controlled 4-part study (20). In this study, tofersen is given to pre-symptomatic SOD1-carriers. The study evaluates whether tofersen can halt or delay the emergence of clinically manifested ALS and/or slow the decline of function after disease manifestation. No results from this study are currently available.

3.2.3 Results for safety

The information presented in this section includes integrated safety data from VALOR (parts B and C) and OLE studies. The data cuts for safety were the same ones presented in the clinical efficacy assessment, i.e., 16 July 2021 (VALOR part C completion), 16 January 2022 (52 week follow- up) and 28 February 2023 (104 week follow- up). Additional information is available from a global extended access program, which is still ongoing.

Patient exposure

The ABCL1 cohort consisted of participants who received at least one dose of 100mg tofersen during VALOR part B or C or the OLE study. This cohort included 147 participants, whose median duration of exposure was 148.4 weeks and median number of doses 33. More specified cohorts of only VALOR part C participants during the placebo-controlled period (RC) and VALOR part C+OLE participants during tofersen-treated period (CL) were also analysed with 108 and 104 participants, respectively.

Summary of adverse events

Adverse events (AEs) are summarized in Table 7. Nearly all participants experienced at least one adverse event. In the ABCL1 cohort, 99.3% of the participants had experienced at least one adverse event, 44.2% of participants had experienced a serious adverse event (SAE) and 15.0% of participants had died by the 28 February 2023 data cut. The safety findings in CL cohort are very similar. In RC cohort, numbers of adverse events are lower, however, the observation period is shorter (28 weeks).

In the RC cohort, the adverse events are not further specified to avoid unblinding of treatment allocation in the associated, ongoing OLE study. According to the 104 week follow-up data cut, the most common adverse events in the ABCL1 cohort 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%). Within 24 hours of administration the most common adverse events were pain and fatigue. Most of the adverse events that lead to drug withdrawal (30 participants) were associated with the underlying ALS disease (9, 10).

Table 7: Summary of adverse events in different safety cohorts in 28 February 2023 data cut ((10) table 35).

	RC		CL	ABCL1
	Tofersen (n=72)	Placebo (n=36)	Tofersen (n=104)	Tofersen (n=147)
Number of participants with adverse event, n (%)				
Any event	69 (95.8)	34 (94.4)	103 (99.0)	146 (99.3)
CTCAE grade*				
Grade 1	25 (34.7)	15 (41.7)	12 (11.5)	17 (11.6)
Grade 2	32 (44.4)	15 (41.7)	43 (41.3)	64 (43.5)
Grade 3	10 (13.9)	4 (11.1)	25 (24.0)	36 (24.5)
Grade 4	N	N	5 (4.8)	7 (4.8)
Grade 5	N	N	18 (17.3)	22 (15.0)

	RC		CL	ABCL1
	Tofersen (n=72)	Placebo (n=36)	Tofersen (n=104)	Tofersen (n=147)
Serious event	13 (18.1)	5 (13.9)	48 (46.2)	65 (44.2)
Events leading to drug withdrawal	N	N	23 (22.1)	30 (20.4)
Events leading to study withdrawal	3 (4.2)	0	22 (21.2)	28 (19.0)
Events leading to drug interruption	3 (4.2)	0	22 (21.2)	28 (19.0)
Events leading to hospitalisation	13 (18.1)	4 (11.1)	41 (39.4)	55 (37.4)
Number of subjects who died	1 (1.4)	0	18 (17.3)	22 (15.0)
Number of participants with treatment-related adverse event, n (%)				
Any treatment-related event**	28 (38.9)	2 (5.6)	66 (63.5)	98 (66.7)
Events related to lumbar puncture**	58 (80.6)	29 (80.6)	87 (83.7)	126 (85.7)
Treatment-related serious event	N	N	7 (6.7)	10 (6.8)

ABCL1: participants who received at least one dose of 100 mg tofersen during VALOR part B or C or the OLE study; CL: VALOR part C+OLE participants during tofersen-treated period; CTCAE: Common Terminology Criteria for Adverse Events; N: Numbers removed to avoid unblinding of treatment allocation from VALOR in the context of the ongoing OLE study; RC: VALOR part C participants during the placebo-controlled period
* Each subjects maximum CTCAE counted.
** Related adverse events assessed by the investigator.

Treatment-related adverse events occurred in two-third (66.7%) of the tofersen-treated participants in the ABCL1 cohort. In addition, more adverse events were reported in the tofersen arm during the placebo-controlled period (RC cohort). Serious adverse events related to tofersen were experienced by 6.8% of the participants. According to EPAR, the most frequent treatment-related adverse events in ABCL1 cohort (104 week follow-up) were increased CSF protein (22.4%), pain in extremity (17.7%), increased CSF white blood cell count (14.3%), headache (13.6%), myalgia (10.2%), pleocytosis (8.2%), procedural pain (6.8%), paraesthesia and back pain (6.1% each), and fatigue (5.4%).

Adverse events of special interest

European Medicines Agency has reported that the market authorization holder considers the following adverse events as topics of interest: adverse events related to lumbar puncture procedure, thrombocytopenia, coagulation abnormalities, and renal toxicity. Furthermore, a hypothetical risk of SOD1 deficiency due to tofersen exists.

As shown in Table 7, 85.7% of participants in ABCL1 cohort reported adverse events associated with lumbar puncture (as assessed by the investigator). These adverse events included procedural pain, headache, back pain and post lumbar puncture syndrome (10). During the placebo-controlled period (RC cohort), both tofersen and placebo treated participants reported similar frequencies of lumbar puncture -related adverse events (80.6%).

Thrombocytopenia, coagulation abnormalities and renal toxicity have previously been associated with treatments similar to tofersen (ASOs). According to the safety results, there were no evidence of increased risk of thrombocytopenia or renal toxicity. In addition, although abnormal coagulation values were observed, it was concluded that these findings did not infer any clinically meaningful changes in coagulation for participants.

Serious adverse events

During the placebo-controlled period in VALOR part C serious adverse events (SAEs) were more frequent in the tofersen arm than in the placebo arm (18.1% vs. 13.9%). The serious adverse events in tofersen-treated participants were myelitis (4/147 [2.7%]), increased intracranial pressure and/or papilloedema (4/147 [2.7%]), radiculitis (2/147 [1.4%]), and aseptic meningitis (2/147 [1.4%]) (9).

All reported SAEs were symptomatic except for two cases of myelitis . Two of the participants with myelitis, one with increased intracranial pressure and/or papilloedema and one with aseptic meningitis discontinued tofersen treatment. In addition, one participant with increased intracranial pressure and/or papilloedema had their tofersen treatment interrupted (temporary).

Deaths
Twenty-five deaths have been reported in the tofersen-treated participants during the clinical studies (any tofersen dose) and all of these were deemed unrelated to tofersen. During the placebo-controlled period, two (2/38 [5.6%]) tofersen treated participants died in VALOR part B (cardiovascular disorder and respiratory failure secondary to ALS) and one (1/72 [1.4%]) in VALOR part C (cardiovascular failure congestive). In comparison, one (1/12 [8.3%]) placebo-treated participant died in part B of the study. The remaining deaths, 22 in total, occurred in OLE and were due to the following causes; 13 participants died of respiratory failure, two of respiratory arrest, two of pneumonia aspiration, and one participant each of septic shock, euthanasia, cardiac arrest, cardio-respiratory arrest and sudden death (10).

JNHB assessment of results of clinical trials

Efficacy
The VALOR part C study failed to provide confirmatory evidence of efficacy after the 28-week placebo-controlled study period based on the primary and secondary efficacy endpoints measuring physical function (ALSFRS-R, SCV and HHD). Although tofersen did not demonstrate efficacy in a confirmatory way, the observed physical function outcomes consistently favoured tofersen over placebo in these endpoints. At the same timepoint, the percentage of participants dying or entering PV was similar between tofersen and placebo groups, although the number of events in the study was too low for reliable and meaningful conclusions to be drawn from these numbers.

Similar to EMA's opinion, JNHB considers the 28-week duration of VALOR part C to be too short to show any convincing clinical treatment effects between tofersen and placebo groups. As described in EPAR, the company assumed, based on previous data, a 24.7-point decline of ALSFRS-R score in the placebo arm over the 28 weeks, which turned out to be an overestimation as the observed decline in the placebo arm was 8.1. This misestimation resulted in an underpowered trial, which was not able to overcome the disease heterogeneity.

Consistent with tofersen's mechanism of action, tofersen-treated participants experienced a sustained 60–70% reduction of the CSF-SOD1 protein levels from baseline, which implies some level of target engagement. The difference to placebo group was nominally statistically significant at week 28. In addition, consistent reductions of 40–50% in plasma NfL levels for tofersen-treated participants further indicated beneficial changes in molecular functions, i.e., reductions in axonal injury and motor neuron loss. The majority of the scientific advisory groups' neurology experts (SAG-N) convened by the CHMP agreed that there is evidence, although not a strong one, supporting that the observed reduction in plasma NfL in tofersen-treated patients can translate into a clinical benefit in patients with SOD1-ALS (10). According the Danish experts, NfL could potentially be used as a diagnostic and prognostic biomarker for ALS and over the natural disease course of ALS, the NfL levels remain relatively stable making it easier to attribute possible changes in its levels to an effect of a treatment itself. However, there is still a need for more evidence to fully support the assumption that changes in NfL levels can reliably predict clinical benefits of experimental treatments. Furthermore, there is no external data to support what levels of reduction of CFS-SOD1 and plasma NfL might be required for clinical efficacy for patients with symptomatic ALS (31, 32).

Since the primary results of VALOR part C were obtained from the fast-progressing mITT population, the results cannot be generalized to the Nordic populations since the most frequent mutation variants in these countries are associated with slow disease progression. With regards to the slower-progressing participant population (non-mITT), which could be more relevant to the Nordic countries, the results were similar to the fast-progressing population; the differences in primary and secondary efficacy endpoints measuring physical function and survival participants were not statistically significantly different between treatment arms,

whilst they still favoured tofersen in comparison to placebo. Furthermore, nominally statistically significant reductions of total CSF-SOD1 protein and plasma NfL were also observed in the tofersen arm of the slower-progressing population, implying target engagement and reductions in axonal injury and motor neuron loss.

In the VALOR+OLE study, as all patients had effectively switched to tofersen treatment, the results for the ITT population at 52 weeks showed nominally statistically significant difference between early-start and delayed-start tofersen group in primary and secondary efficacy endpoints measuring physical function and survival when adjusting for baseline NfL. It would therefore appear, that the long-term results favour early-start of the treatment although at week 104, the results between early-start and delayed-start tofersen groups were no longer statistically significant. The total CSF-SOD1 protein levels and plasma NfL remained consistently reduced for the early-start tofersen group, while the delayed-start tofersen group experienced similar reductions after the initiation of tofersen. However, the ability to derive long-term efficacy estimates of tofersen is limited due to the eventual tofersen treatment of all participants in an open-label setup and the resulting lack of a control group.

The survival data from weeks 52 and 104 are more mature than in VALOR part C, but the numbers of deaths or PV events remain low, causing notable variation in the reported hazard ratios (HRs) from those data cuts. Further uncertainty to the analysis robustness is caused by the model's assumption of proportional hazards, which is questionable especially due to the small number of events. At week 104 data cut, 16 (44.4%) participants in the delayed-start group and 44 (61.1%) participants in the early-start group were alive and ongoing in the study. This long-term data also indicate that tofersen-treated participants are exceeding the expected survival time indicated by natural history data. Due to the lack of control arm in the long-term follow-up, it is difficult to evaluate whether this is due to beneficial effects of tofersen or due to, e.g., disease heterogeneity.

It is currently not known how early treatment with tofersen could be beneficial, i.e., whether it could be used for presymptomatic SOD1 variant carriers as a preventive treatment. The ATLAS study examining this is still ongoing. Furthermore, despite around 60% of the patients in the VALOR part C study being treated with riluzole in all analysis populations, no subgroup analyses were provided comparing these subgroups. It is therefore not known whether riluzole has any additional effects on tofersen treatment.

Safety

The safety profile of tofersen in treating ALS was evaluated through both the VALOR part C study and its open-label extension, focusing on adverse events and their management. In the placebo-controlled VALOR part C study, nearly all participants experienced adverse events, with higher incidences of treatment-related and serious adverse events in the tofersen group compared to placebo by week 28. Long-term exposure to tofersen showed high proportions of treatment-related (66.7%) and serious adverse events (44.2%). The most common side effects observed were pain, arthralgia, fatigue, increased white blood cells in CSF, increased CSF protein, myalgia, and pyrexia.

Adverse events associated with lumbar puncture were common (experienced by more than 80% of the participants), and serious neuroinflammatory events such as myelitis and increased intracranial pressure were reported more frequently than expected. Clinical experts were concerned that repeated monthly lumbar punctures may prove unnecessarily burdensome for patients with slow-progressing or end-stage ALS. Similarly, some clinical experts are concerned of the serious adverse events occurrences in slower-progressing SOD1-ALS, as less risk and side effects are acceptable in comparison to fast-progressing SOD1-ALS patients. Similar concerns apply to patients, who are at the end-stages of ALS disease course. At the same time, some clinical experts do point out that the treatment effect is clinically important

and the benefits outweigh the risks in the case of a rapidly progressing, fatal disease. Therefore, the risk-benefit should be carefully assessed for each individual patient.

In relation to this matter, no specific stopping rules have been implemented in the VALOR and OLE studies, although the repeated lumbar punctures and potential adverse effects can be expected to become more burdensome towards the end of the disease course. Patients should be carefully monitored and in final stages, when the number of functioning motor neurons becomes low, it is no longer advisable to treat patients according to the clinical experts.

The number of tofersen-treated participants in the presented clinical trials, and particularly the placebo-controlled VALOR part C, is small considering the broad spectrum of potential symptoms originating from SOD1-ALS. Similarly, the follow-up time, again especially for the placebo-controlled part of the study, is considered short for detecting a range of adverse events.

JNHB conclusion:
The placebo-controlled VALOR part C trial failed to demonstrate statistically significant differences between tofersen and placebo groups in the physical function endpoints, including the primary endpoint. Therefore, the evidence of efficacy relies on the observed differences in endpoints, which favoured tofersen over placebo. The nominally significantly reduced levels of CSF-SOD1 protein and plasma NfL in tofersen group indicate that tofersen's mechanism of action was functioning. However, there is no established estimates on how large improvements in these biomarkers are needed to produce a clinically meaningful difference in patient-relevant outcomes. The open-label extension (OLE) study indicated that earlier start of tofersen treatment could also be more favourable in long-term but the lack of control arm limits the interpretation of these findings and causes major uncertainties in the assessment.

JNHB considers that the short duration of the placebo-controlled study and its heterogeneous patient population result in notable uncertainty regarding the effects of tofersen. In addition, the different prevalence of SOD1 mutation variants in the Nordics compared to other regions also causes major uncertainty of the validity of the clinical studies in a Nordic context. The repeated lumbar punctures, its potential adverse effects as well as other serious adverse effects are a notable concern for slow-progressing and late-stage SOD1-ALS patients.

3.3 Systematic overviews, meta-analysis and indirect comparisons

The company provided a clinical systematic literature review (cSLR), which identified evidence of the efficacy and safety of tofersen, riluzole, edaravone and AMX0035 for adult patients with ALS. The cSLR identified 11 trials and 29 real-world studies (RWS) which were relevant to the indication. However, only studies associated with tofersen (one three-part trial, i.e. VALOR) and riluzole (four trials and 12 real-world studies) were relevant to this assessment.

According to the review, comparisons between treatments were considered inappropriate as there were several sources of clinical and methodological heterogeneity. The clinical heterogeneity was due to different inclusion criteria, baseline characteristics and measured confounders, while the methodological heterogeneity was associated with differences in study design and follow-up durations as well as endpoint assessment definition, methods, and timing.

JNHB conclusion:
None of the comparator (SoC) studies were directly used in the cost-effectiveness model, which is considered appropriate due to the evident clinical and methodological heterogeneity between the studies.

4 Cost-effectiveness methods

The following chapter is based on the dossier submitted by the company. All assumptions described are based on the application if not otherwise stated. The conclusion boxes after each section give a short assessment of the choices related to key parameter inputs, methods used, simplifications and scientific judgements made by the company. The results of the JNHB analyses are presented in section 5.2.

4.1 Company model description

The company has submitted a cost-effectiveness analysis using a Markov model, in which patients who have been treated with tofersen + standard of care (SoC) are compared with patients who have received SoC, where SoC consists of riluzole. The model structure depends on the use of either MiToS functional classification system (FCS) (the company's base case) or King's ALS clinical staging system (CSS) (sensitivity analysis). Both systems follow a structure that includes death as the final health state and allows transition between all the other health states.

The MiToS system (Figure 2) is based on functional domains of movement, swallowing, communication and breathing, and is directly calculated from the ALSFRS-R score. The King's system (Figure 3) is based on disease burden as measured by clinical involvement and significant feeding or respiratory failure, and is indirectly based on ALSFRS-R.

Patients can transfer to a better or worse health state over time. They can also transfer to the absorbing death state from any of the other five health states. The time horizon of the model is a lifetime horizon, represented as a maximum duration of 50 years given the baseline age of the population. The model has a cycle length of four weeks and half-cycle corrections are applied.

Baseline characteristics of the patient group entering the model (age of 49 years old and 43% women) are sourced from VALOR Part C.

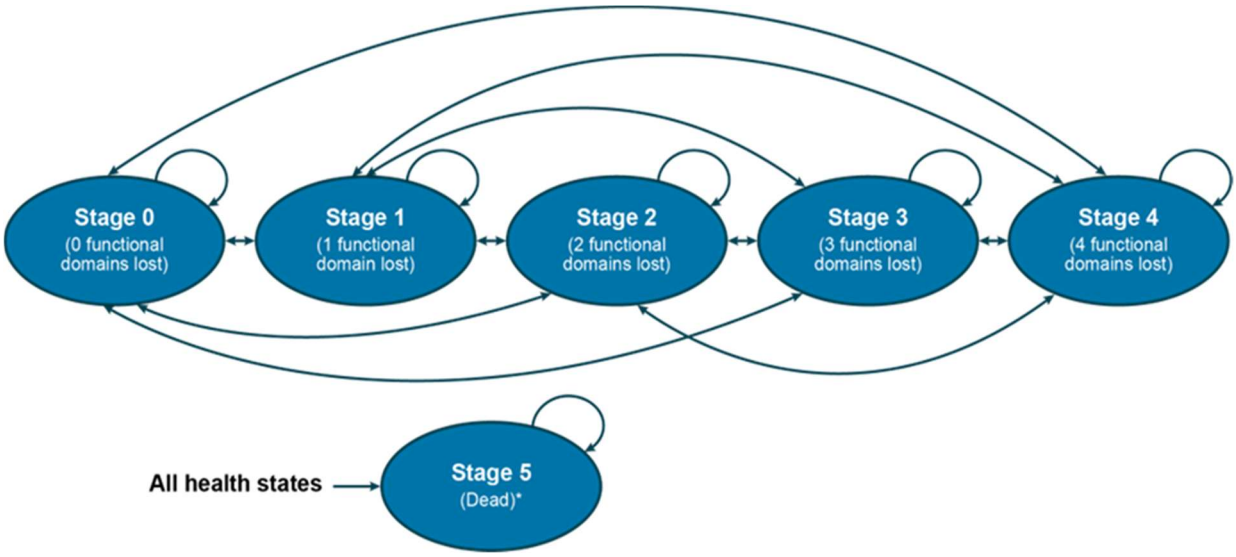

Figure 2: Markov model structure based on MiToS functional classification system (FCS).

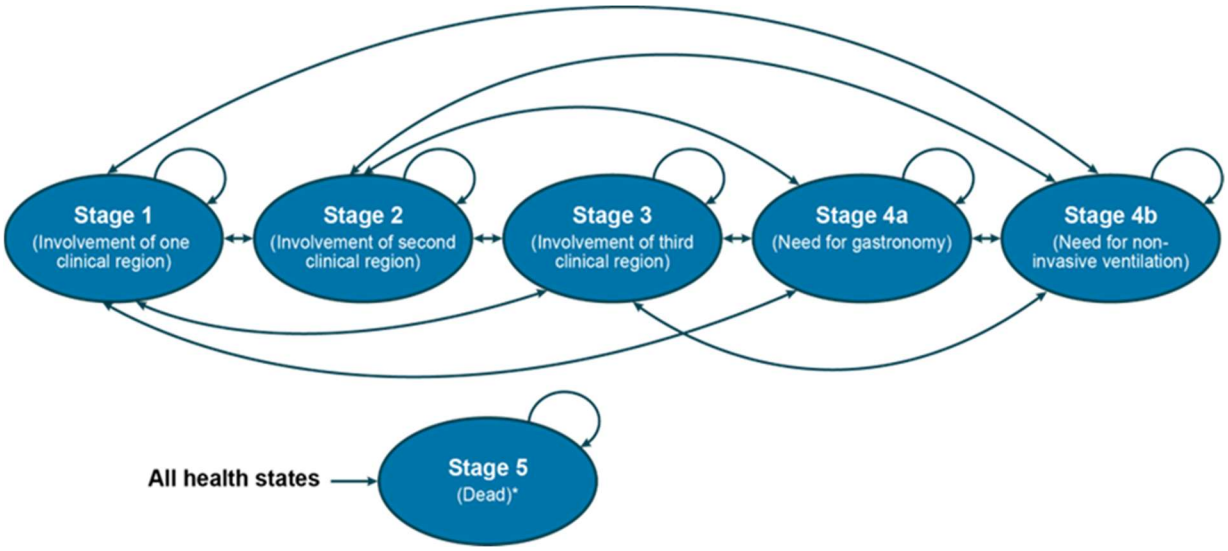

Figure 3: Markov model structure based on King's clinical staging system (CSS).

JNHB discussion

JNHB concludes that the model structure is suitable to evaluate the decision problem, however, some assumptions must be discussed. The model is based on transitions between either MiToS or King's stages and while they capture the functional aspects of ALS, the classification systems do not consider cognitive and behavioral impairment and hence, do not represent the full picture of the disease. According to the Nordic clinical expert, MiTos or Kings stages are not used in the clinical practice except of Sweden where King's staging is used. In addition, both staging systems are based on the ALSFRS-R endpoint (direct calculation or indirectly via an algorithm) which did not reach statistical significance in VALOR Part C. Modelling of a long-term effect of tofersen based on a pivotal study that did not show a statistically significant effect is a major limitation.

In the model, patients can transfer to a lower stage (i.e. about 5% in both arms per cycle) which may not be representative of the clinical practice since King's and MiToS classification systems only capture progression. In VALOR Part C, 2/72 (3%) patients in the tofersen group shifted from MiToS stage 1 to 0, compared to no patient improved over 28 weeks in the SoC group (Biogen's data on file). In VALOR+OLE a subset of patients treated with tofersen experienced sustained stabilization or improvement in function and strength. In the early-start tofersen group, 19.5% of participants experienced improvement on the ALSFRS-R, 29.3% improvement on percent-predicted SVC, and 25.8% improvement on HHD megascore over 104 weeks. An even larger proportion of patients treated with tofersen experienced stabilization (no loss of function/strength) or improvement over 104 weeks (29.3%, 21.4%, and 25.8% in the early-start tofersen group for ALSFRS-R, SVC, and HHD, respectively) (10). According to the SAG-N experts convened by the CHMP, it appears biologically plausible that dysfunctional nerves might recover, while degenerated nerves are lost. This could explain the improvement of function in some patients in VALOR (33). In addition, an analysis of ALSFRS changes in overall ALS population (based on PRO-ACT database), shows that small ALS reversals are not uncommon, especially over shorter follow-up intervals, however, large, sustained ALS reversals are rare (34). Overall, the company has not presented empirical evidence that supports improvement in MiToS/King's staging in the SoC arm, although backward transitions may be plausible for tofersen. Inclusion of backward transitions in the model results in a lower ICER, mainly driven by higher total QALYs in the tofersen arm. JNHB accepts the inclusion of backward transitions, but notes that the evidence to support it is sparse. The impact of backward transitions is tested in a scenario analysis.

Baseline characteristics of the patient group entering the model (age of 49 years old and 43% women) are representative of the Nordic SOD1-ALS population (11, 13, 35). The age of onset for ALS patients carrying different SOD1 variants is reported to be 46 and 52 years old for D91A homozygous and heterozygous variants, respectively, 48 years old for H47R variant (12).

JNHB conclusion:
JNHB concludes that the model structure is suitable to evaluate the decision problem, however, some limitations must be listed. The model is based on transitions between MiToS or King's stages and while they capture the functional aspects of ALS, the classification systems do not consider cognitive and behavioral impairment and hence do not represent the full picture of the disease. Further it is possible for patients in the model to transfer to a lower stage (i.e. 5% per cycle) but evidence to support this assumption is limited. Sensitivity to the choice of the classification system and the inclusion of backward transitions is tested in scenario analyses.

JNHB concludes that the baseline characteristics of the patient group entering the model (age of 49 years old and 43% women) are representative for the Nordic SOD1-ALS population.

4.2 Effectiveness outcomes

4.2.1 Clinical effectiveness

The primary endpoint from VALOR Part C, change in ALSFRS-R, is not used directly in the economic model. Instead, the disease model is based on the transitions between five ordinal stages (calculated from ALSFRS-R from VALOR+OLE) and death. The transition probabilities for the comparator were derived from a natural history disease study, and the treatment effect of tofersen was based on a treatment switch-adjusted time-to-event analyses. Those aspects are described below.

MiToS vs. King's staging system
The choice of two ALS staging systems is available in the economic model. The company has chosen the MiToS system for their base case. The MiToS system uses 6 stages (0 = normal function; 5 = death) and assesses complete loss of independence in 4 functional domains (swallowing, walking/self-care, communicating, and breathing) (Figure 2, Table 8) (36, 37). MiToS is directly based on the ALSFRS-R, and inherently consistent with sequential disease progression (38). A function (bulbar, fine motor, gross motor and breathing) is lost when the item(s) of the ALSFRS-R scale correspondent to this function (see Figure 1) is or are graded 1. Tracheostomy events are evenly spread across stages as the loss of breathing function can occur in MiTOS stage 1-4 (39). ALSFRS-R has been shown to have a flooring effect as many patients might score very low in the late stages of ALS which makes it difficult to detect a subtle change (i.e. lack of sensitivity) (40). These limitations are avoided when using MiToS, because it combines different parts of the ALSFRS-R to assess functional burden (41).

The King's system uses 6 stages (1 = symptom onset; 5 = death) and assesses the clinical or anatomical spread of the disease (42). The first 3 stages of King's are defined by functional involvement of central nervous system regions (43). Stages 4a (need for gastrostomy/feeding tube) and 4b (need for noninvasive ventilation) are not regarded as sequential stages.

Table 8: MiToS and King's Staging Systems for ALS, and the baseline distribution in the economic model based on VALOR(Part C).

Health state = Stage	MiToS	MiToS Distribution, %(n/N)	King's	King's Distribution, %(n/N)
0 (MiToS)/1 (King's)	0 functional domains[a] lost	75.0% (81/108)	Involvement of 1 region[b]	26.9% (29/108)
1 (MiToS)/2 (King's)	1 functional domain[a] lost	21.3% (23/108)	Involvement of 2 regions[b]	39.8% (43/108)
2 (MiToS)/3 (King's)	2 functional domains[a] lost	2.8% (3/108)	Involvement of 3 regions[b]	23.1% (25/108)
3 (MiToS)/4a (King's)	3 functional domains[a] lost	0.9% (1/108)	Need for gastrostomy	0.9%(1/108)
4 (MiToS)/4b (King's)	4 functional domains[a] lost	0.0% (0/108)	Need for NIV	9.3%(10/108)
5 Death	Death		Death	

ALS = amyotrophic lateral sclerosis; MiToS = Milano-Torino functional staging system; NIV = noninvasive ventilation.
[a] Functional domains defined as swallowing, walking/self-care, communicating, and/or breathing.
[b] Functional involvement of the central nervous system regions bulbar, lower limb (leg), and/or upper limb (arm).

King's has a higher resolution in early-mid disease stages, whereas MiToS differentiates better in more advanced disease stages (Figure 4) (39, 41, 44). MiToS is directly based on ALSFRS-R, whereas King's can be estimated from ALSFRS-R scores using a published mapping algorithm (45). Although it has been shown that the King's stage can be reliably estimated using the ALSFRS-R algorithm in historical data, misclassification (i.e., over-staging and under-staging) vs King's staging from the medical notes (based on the number of central nervous system regions involved) occurred in 20 out of 103 cases (19.4%) in a British study (45).

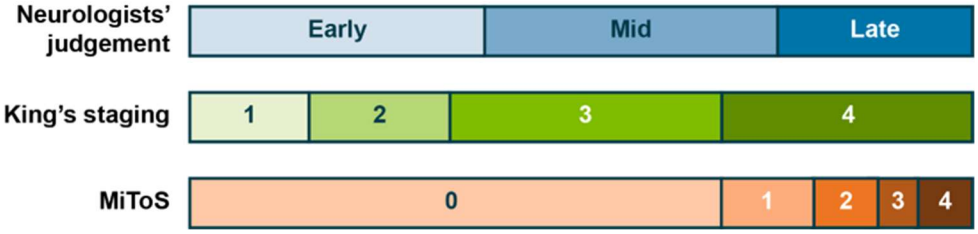

Figure 4: Illustration of How Staging Systems Correspond to Each Another

MiToS = Milano-Torino functional staging system.
Source: (46)

The use of natural history study and calibration

The economic model was structured as an ALS disease model informed by natural history data from the PRO-ACT database. The impact of tofersen treatment was implemented by applying a relative treatment effect estimated from the direct treatment comparison of tofersen (early-start) and placebo/tofersen (delayed-start by six months) in VALOR Part C and its OLE study. A natural history disease model was preferred over the disease model by VALOR data since it was not possible to derive transition probability matrices for MiToS and King's staging using VALOR trial data, due to the small sample size

The PRO-ACT database is a multinational registry of prospective clinical trials. It includes merged, deidentified data from over 10,700 patients with ALS who participated in 23 phase

2/3 clinical trials (47). The database consists of 40% female participants with an overall mean age of 56.2 years (48) and more than 3,500 patients have longitudinal records of ALSFRS-R. PRO-ACT generalizability is limited by selection bias, heterogeneity, and limited duration of follow-up. Time-invariant stage transition probabilities have been estimated under Markov assumptions from PRO-ACT data (49).

Thakore et al (49) analyzed the PRO-ACT database to derive ALS patients' 3-monthly transition probabilities for health states defined by King's and MiToS staging systems. The transition probabilities reported (49) provide a good fit for the patient numbers observed at each disease stage and death at 12 months. However, progression and mortality are underestimated in extrapolations covering the period beyond 12 months when comparing with the PRO-ACT database (Figure 5). As a result, the company adjusted the transition probabilities (see Appendix 1 for details) to provide a better fit with the reported patient numbers at each stage and mortality for the period beyond 12 months. After adjustment, the model-predicted median survival in the SoC arm (15.69 months) matches the reported median survival time in the PRO-ACT database of 479 days (15.75 months) from trial entry (Figure 6) (48).

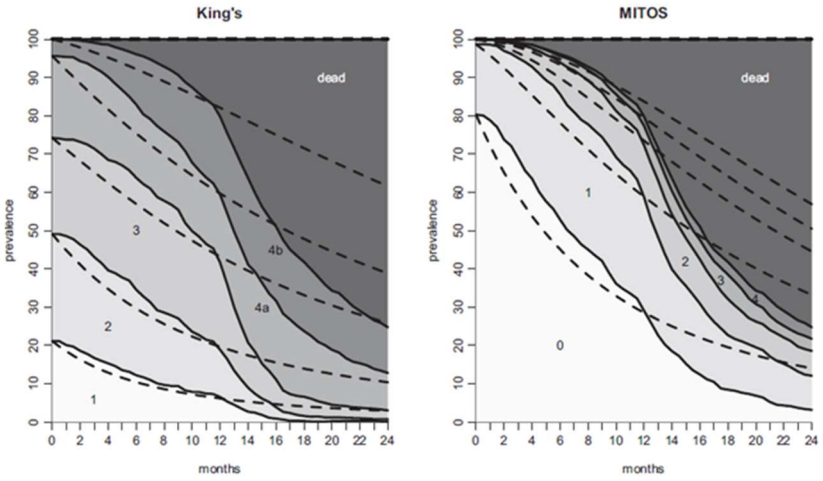

Figure 5: Stacked prevalence plots of stages and death for each system over the first 24 months of observation (49) before calibration. The shaded areas depict observed prevalences, whereas areas separated by dashed lines depict modeled prevalences employing time-homogeneous Markov models.

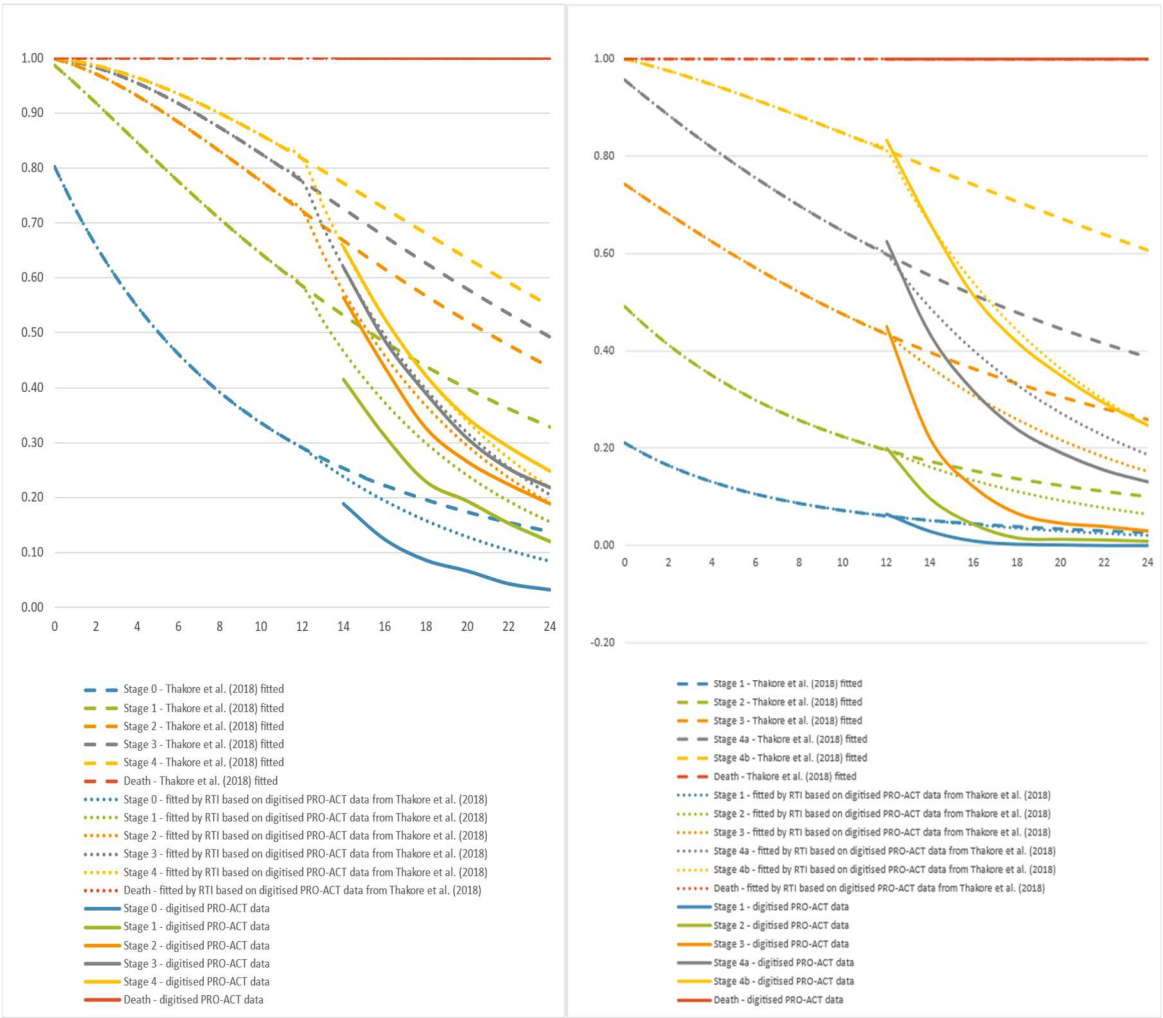

Figure 6: Stacked prevalence plots of stages and death estimated after calibration; MiToS on the left, King's on the right. The dashed lines depict modeled prevalences pre-calibration, the dotted lines depict modeled prevalences post-calibration, and the solid lines depict digitalized PRO-ACT data.

Lastly, the company assumes that on average patients with SOD1-ALS have faster disease progression than the overall ALS population. This assumption is based on an international, retrospective observational study, which compared phenotypic and demographic characteristics between patients with SOD1-ALS and patients with ALS and no recorded SOD1 variant (11). In the economic model, a hazard ratio for death of 1.3 for the SOD1-ALS population compared to the ALS population is applied to the adjusted transition probabilities based on the publication by Thakore et al.

Transition probabilities before and after calibration are presented in Appendix 1.

Modelling of treatment effect and adjustment for treatment-switch

The reduction in transition rates is estimated using hazard ratios for tofersen +SoC versus SoC that were estimated from time-to-event data, defined as the time from baseline to the first time that a patient progresses by at least 1 MiToS stage (or respective King's stage), and the time from baseline to death, respectively (
Table **9**). Time to progression was compared using Kaplan-Meier time-to-event analyses and a Cox proportional hazards model.

To adjust for the treatment switch for patient completing VALOR Part C and entering the OLE study the company applied a rank-preserving structural failure time model (RPSFTM).

The RPSFTM was used to estimate (for each trial participant) the counterfactual time to progression in the absence of tofersen treatment. The methodology is described further in Appendix 2. The results are presented in Table 9, Figure 7 and Figure 8.

Analyses based on datacut from 2022 were used in the economic model. However, time to death analyses results were also reported in the EPAR for datacut from 2023.

Table 9: Estimated hazard ratios applied in the economic model in the ITT population and after treatment-switch adjustment (RPSFTM). Estimates are based on VALOR+OLE, DCO 2022. Estimates from DCO 2023 (10) are presented in addition, but not used by the company.

HR (95% CI)	ITT	RPSFTM	Number of events (n/N)
SOD1-ALS vs. ALS	1.3 (1.2-1.4a)		
	Time to transition from original baseline to later MITOS stages (DCO 2022)		
Tofersen+SoC vs. SoC	0.69 (0.40, 1.20)	0.61 (0.29-1.27)	21/36 (delayed-start tofersen) 34/72 (early-start tofersen)
	Time to transition from original baseline to later King's stages (DCO 2022)		
Tofersen+SoC vs. SoC	0.98 (0.56, 1.71)	0.98 (0.51-1.87)	19/36 (delayed-start tofersen) 40/72 (early-start tofersen)
	Time to death (DCO 2022)		
Tofersen+SoC vs. SoC	0.27 (0.08, 0.89)	0.10 (0.01-0.81)	6/36 (delayed-start tofersen) 8/72 (early-start tofersen)
	Time to death (DCO 2023) – not used the company's base case		
Tofersen+SoC vs. SoC	0.66 (0.252, 1.705)	0.12 (0.033, 0.433)	7/36 (delayed-start tofersen) 11/72 (early-start tofersen)

ALS = amyotrophic lateral sclerosis; CI = confidence interval; CL = VALOR (Part C) and OLE data; HR = hazard ratio; ITT = intention to treat; RPSFTM = rank-preserving structural failure time model; SoC = standard of care; SOD1 = superoxide dismutase 1.

Note: HRs for tofersen vs. SoC are for time to transition from Week 0 stage to later stages (excluding death), or from Week 0 to death. For pooled group CL using RPSFTM, ITT population.

[a] 95% CI were derived based on an assumed standard error of 10% of the mean value.

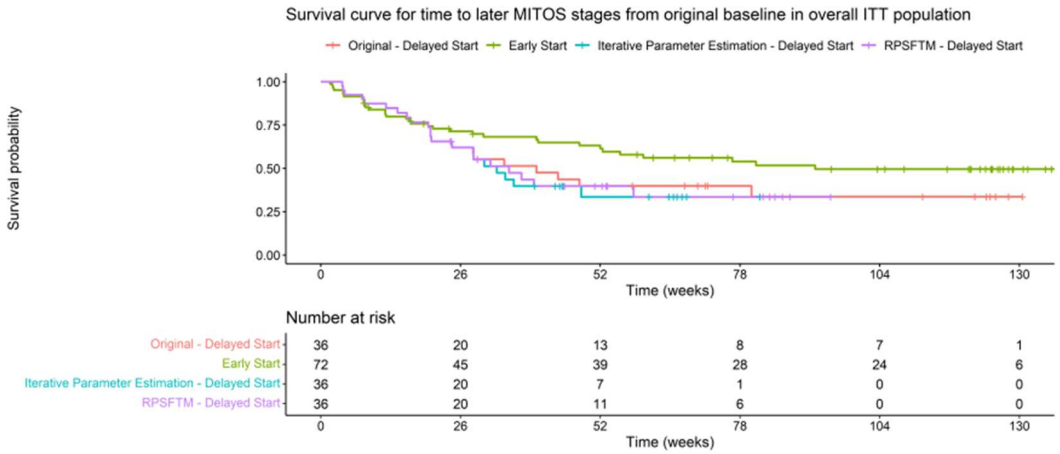

Figure 7: Survival curve for time to transition from VALOR baseline stage to later MiToS stages (excluding death), DCO 2022.

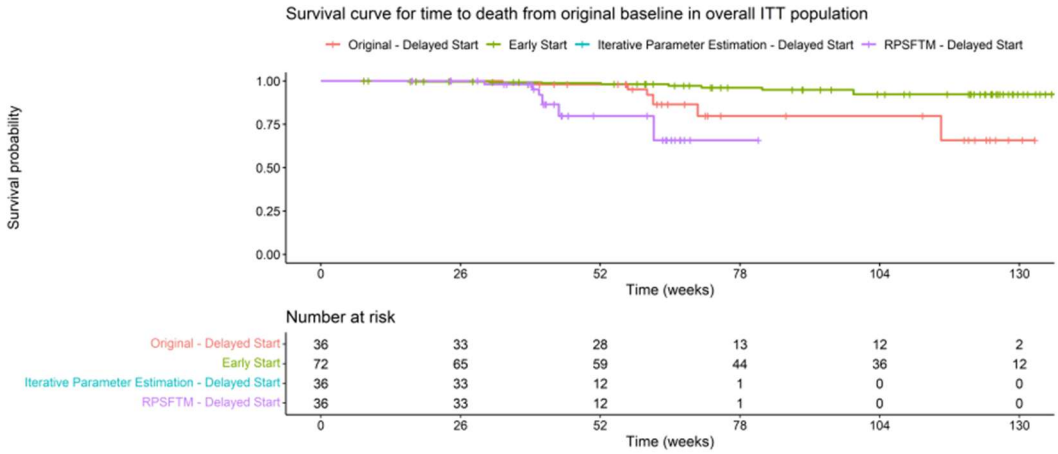

Figure 8: Survival curve for time to death from VALOR baseline, DCO 2022.

Model result validation

The estimated disease progression per arm is presented in Figure 9. The Figure shows that tofersen + SoC is associated with more than doubled gain in life years per MiToS stage compared to SoC. The estimated median time to death in the model is 2.77 vs 1.15 years from baseline with tofersen and comparator, respectively, when modelled with the MiToS staging system. The reported median time to death from entry in the PRO-ACT database was 479 days = 1.31 years (48).

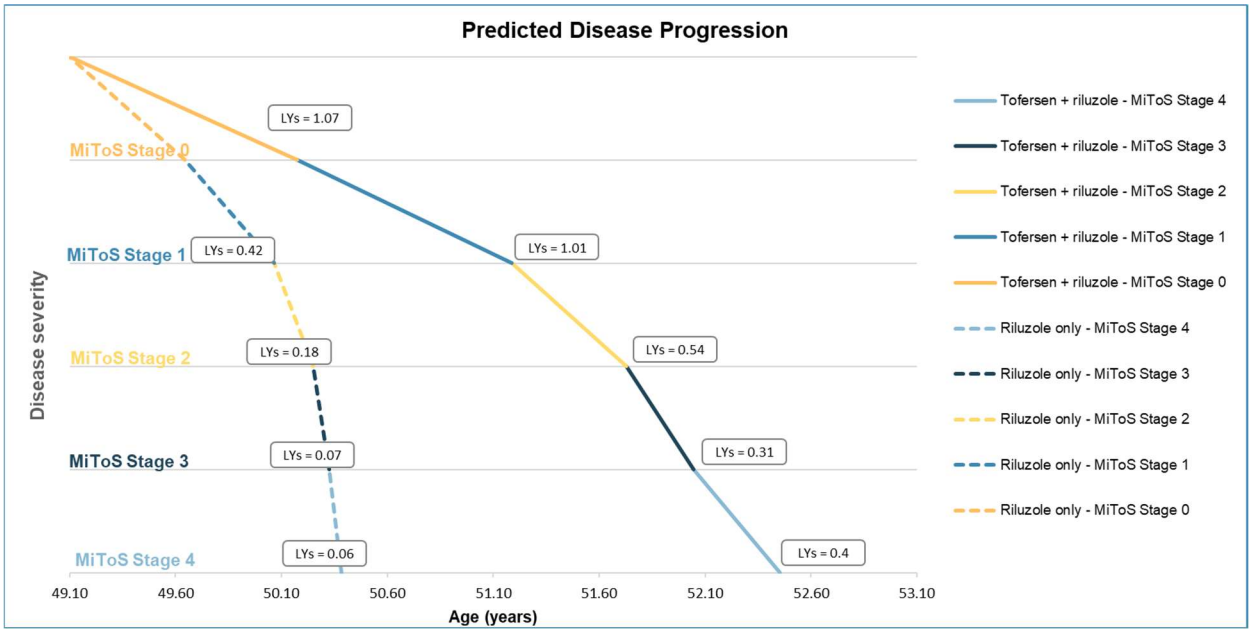

Figure 9: The predicted disease progression in the company's base case. It is calculated by adding the cumulative life years (LYs) accrued per stage to the mean baseline age. In the figure, the LYs accrued per stage are represented by each colored line section and are shown in grey outlined boxes.

Upon request, the company validated the model results with the empirical VALOR Part C study results. Figure 10 shows that disease progression in the model was faster than in VALOR.

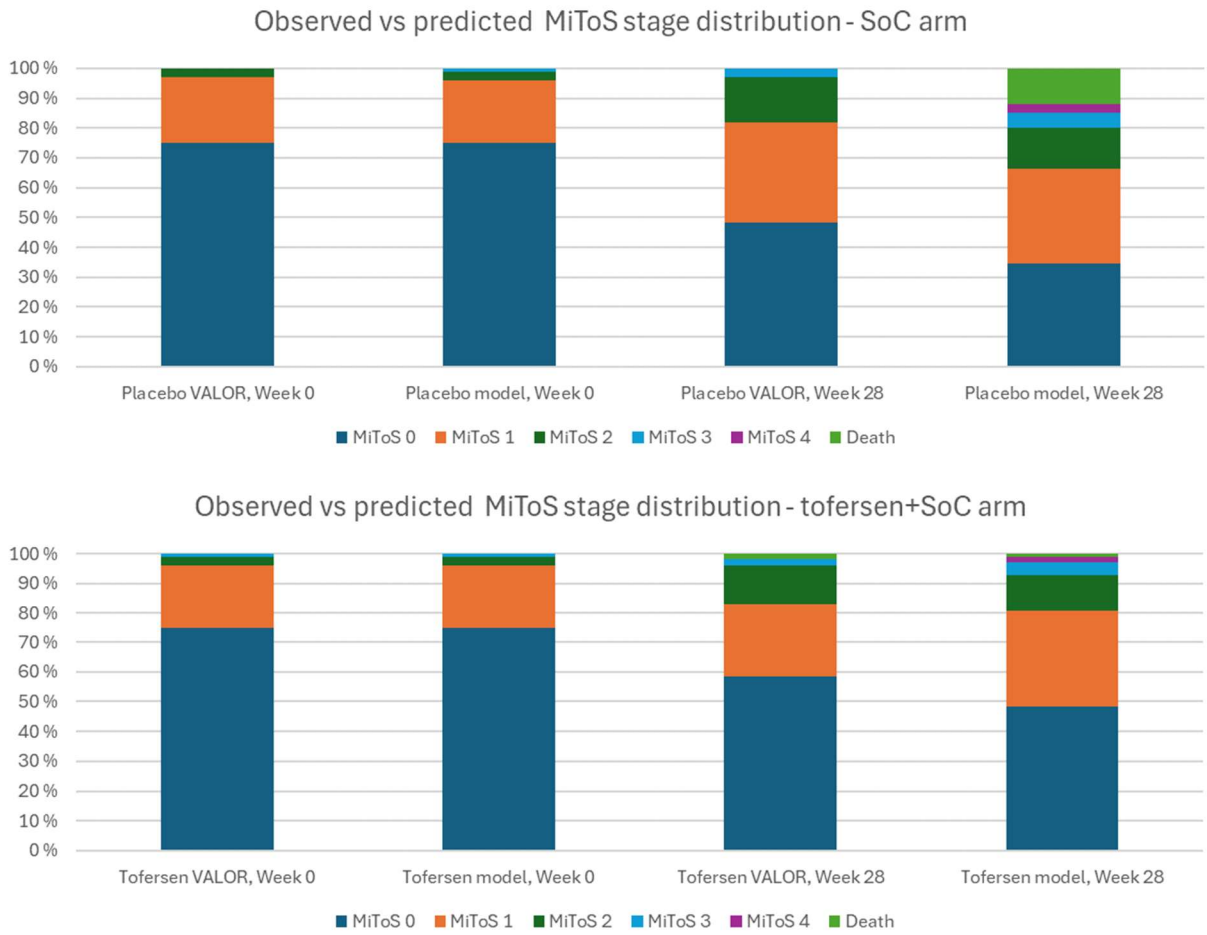

Figure 10: Validation of the model results with MiToS stage distribution observed in the VALOR Part C trial at week 0 and 28. Based on the company's base case.

JNHB discussion

The economic model is based on indirect measures of disease progression and external data due to short follow-up time in VALOR. The categorization of disease stages instead of using the primary endpoint from VALOR Part C, change in ALSFRS-R, offers some benefits like simplicity, and the availability of stage specific costs and utilities but also results in loss of information. Similarly, the application of a treatment effect, which was not directly derived from the VALOR study, but instead was based on a "transformed" measure from a time-to-event analysis, introduces additional assumptions and uncertainties. Those are discussed below.

MiToS vs. King's staging system

MiToS and King's staging systems are two scales developed during the last 12 years to measure functional burden or anatomical involvement in ALS patients (36, 37, 42). According to the Norwegian and Danish clinical expert, these are not used in the clinical practice. In contrast, King's staging is used in clinical practice in Sweden, and staging can also be obtained from the ALSFRS-R scale.

There does not seem to be a clear superiority of one staging system over another (41). Instead, the two staging systems are considered complementary, with King's being able to differentiate early to mid-disease well due to focusing on anatomical disease spread and significant involvement of respiratory muscles, and with MiToS staging being able to differentiate late stages by focusing on loss of functional capabilities. As loss of functional capacity follows

anatomical involvement, MiToS staging logically tends to lag behind the King's staging. As the MiToS staging moves a patient to a higher class only as one loses independence in one function, which is rarely seen early in the disease course, it is not surprising that the MiToS staging has low resolution at early stages of ALS compared to King's. In that sense, King's appears better suited for the early stages in the economic model, whereas MiToS can be considered better suited over long-time horizon.

It is considered a strength that MiToS is directly based on ALSFRS-R. The King's system, on the other hand, requires a mapping algorithm in order to be converted from ALSFRS-R scores. Although results from a British study show excellent correlation between ALSFRS-R score and King's staging, misclassification of a King's stage occurred in 19.4% of cases (45).

The baseline distribution of MiToS and King's stages is consistent with other clinical trials in ALS (50, 51). However, the King's or MiToS distributions have not been described in the literature for the Nordic countries, and the clinical experts could not validate them.

Overall, JNHB uses the company's modelling via MiToS staging and tests the impact of the King's staging in a scenario analysis.

The use of natural history study and calibration

The company used published transition probabilities based on a natural history study, PRO-ACT, to model the comparator arm in the economic model (49). The PRO-ACT database is a repository of repeated ALSFRS-R measures and other data elements drawn from 10,723 patients who participated in 23 clinical trials over more than 20 years. The database does not specifically represent the SOD1-ALS subpopulation. The overall ALS population included in the database was older than the SOD1-ALS population in VALOR (57 vs 50 years old) but had a similar initial ALSFRS-R score to VALOR (39 vs 37) as well as baseline distribution of MiToS/King's stages.

JNHB agrees that PRO-ACT is a more mature source of transition probabilities for the comparator arm than VALOR part C. A total of 29,947 ALSFRS-R scores were used from the database to derive transition probabilities for the Markov model. Median number of scores recorded per patient was 8, and median duration between first and last ALSFRS-R was about 12 months. Dates of death were known in 719 patients. In contrast, 0/21 deaths were recorded at 6 months in the placebo arm in VALOR Part C.

It is evident from Figure 5, that modelled prevalence plots of stages and death (based on transition probabilities from the Thakore publication) are aligned with empirical PRO-ACT data up to 12 months, after which the fit is poor. Consequently, the company adjusted the transition probabilities from 12 months in order to better align with empirical data. Figure 6 shows that adjustment considerably improved the fit post 12 months. The fit was better for MiToS staging than King's staging, providing additional arguments for choosing MiToS over King's classification systems.

In order to reflect a difference between SOD1-ALS and ALS populations, the company applied a HR of 1.3 to adjust for more rapid progression and shorter survival in the subpopulation. The company cites an international retrospective observational study (11) that examined a database reporting 1,122 patients with SOD1-ALS with a comparative ALS population of 10,214 patients for age of disease onset. The HR of 1.3 forthe SOD1 subpopulation in the study was mainly driven by A5V, D91A, G94A, L145F and V149G variants. Meanwhile, H47R is the most frequent variant in Norway and D91A (in early literature called D90A) and A90V are the most common variants in Finland and Sweden. All of these variants usually lead to a slow-progressing ALS phenotype (clinical expert opinion and (11, 12, 52, 53)). Given that the estimate sourced from Opie-Martin is not representative to the Nordic population, JNHB does not accept the additional adjustment of HR=1.3. One alternative HR could not be selected as the precise

distribution of SOD1 variants in the Nordics is unknown and the survival data per variant are sparce. According to the Nordic clinical experts the prognosis can differ substantially also within patient with the same genetic variant/mutation. In addition, there is uncertainty in how tofersen will be used in clinical practice. According to some clinical experts, tofersen will rather be reserved to fast progressing patients who have the highest unmet need and for whom the severity of side effects may be acceptable. Others do not anticipate such a restriction, as both slow and fast progressors would be treated given that the side effects are reversible, and that the treatment can be discontinued if the side effects are too severe. For patients with the D91A mutation, the symptoms most often start in the legs and rarely involve cognitive decline. For that reason, clinicians would start the treatment early, to prevent motor nerve and muscle degeneration and secondary complications and disabilities. Many clinicians stated that criteria should be established via the national specialist group for ALS for both the initiation and discontinuation of treatment if tofersen is approved for reimbursement. The use of NfL was suggested instead of waiting for a progression slope since this will lead to delayed treatment for very fast progressors. Consequently, JNHB chose to test a range of HRs in the base case analyses due to uncertainties around the target population and its survival. HRs varying from 1 to 0.1 result in a median survival in the SoC arm of between 1.3 to 11.15 years.

Modelling of treatment effect and adjustment for treatment-switch

Treatment effect of tofersen + SoC on progression and mortality is expressed as a difference in time to transition from original baseline to later MiToS (King's) stages. That means that only the first transition is effectively taken into consideration and subsequent transitions between MiToS (King's) stages are ignored in the Cox regression model. Given that the majority of patients were at MiToS stage 0 or 1 at baseline in VALOR Part C, and very few were in later stages over the follow-up time (Figure 10 and Table 10), the captured progression events are mainly based on the early stages. In addition, estimated duration of MiToS stage 0 and 1 in the PRO-ACT database is 12.8 and 11.00 months, respectively (49). Given that patients in VALOR Part C were mostly in those stages, later transitions could not be observed.

The Cox model-derived hazard ratios are next applied to the calibrated transition probabilities for the comparator arm (the same HR of 0.61 for MiToS stage 0-4 transition probabilities, and a HR of 0.1 for transitions to death) to obtain reduced transitions for tofersen + SoC. By applying the same HR to all stage transitions, it is implied that the effect of tofersen + SoC on slowing progression is the same irrespectively of the stage. This is a strong assumption, which is not supported by the empirical data.

Table 10: Observed MiToS stage distribution in VALOR Part C from week 0 to 28

233AS101 Part C: ALS MITOS of ALSFRS-R shift from baseline by visit (observed data) - ITT population
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	placebo (N=36)	tofersen 100 mg (N=72)
End of Study	36	72
Number of stages moved		
None	23 (63.9)	49 (68.1)
Shifted to later stages	13 (36.1)	21 (29.2)
1 Stage	9 (25.0)	16 (22.2)
2 Stages	4 (11.1)	3 (4.2)
3 Stages	0	1 (1.4)
4 Stages	0	1 (1.4)
5 Stages	0	0
Shifted to earlier stages	0	2 (2.8)
1 Stage	0	2 (2.8)
2 Stages	0	0
3 Stages	0	0
4 Stages	0	0
5 Stages	0	0

NOTE 1: Baseline is defined as day 1 value prior to the 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: For non-Japanese subjects, the Global ALSFRS-R is used. For Japanese subjects, the Japanese (Ohashi) ALSFRS-R is used except for Q5a and Q11 where the Japanese translated Global ALSFRS-R is used. ALS MITOS staging representing the number of lost functional domains; stage 5 represents death. For the subjects who died, the visits after death are imputed as stage 5.
NOTE 3: Percentages calculated based on the number of subjects with data at both baseline and the specific post-baseline visit.
NOTE 4: End of study summarizes the last available assessment for all subjects including withdrawals.
Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised; MITOS = Milano-Torinos Staging.
Source: biib067/233as101-parte/csr/t-cf-exp-mitos-shft-itt.sas **Run Date:** 22SEP2021

Standard diagnostics for proportional hazard to justify the constant treatment effect assumption over time between tofersen and RPSFTM-adjusted placebo has been requested but not submitted by the company. The company claims that even if the proportional hazard assumption is not met, the hazard ratio still represents an interpretable measure of the treatment effect. JNHB recognizes that a HR has been routinely presented in regulatory settings even though proportionality of hazards has not been tested. However, for the HTA purposes where the treatment effect is extrapolated over the time horizon, not meeting the constant effect assumptions may have severe consequences on long-term projections and bias the model results.

The effect of tofersen on survival has not been tested inferentially in VALOR Part C or VALOR+OLE. At the 52-week data cut-off, 8/72 (11.1%) deaths were observed in the early-start tofersen group vs 6/36 (16.7%) in the late-start tofersen group (data cut-off 28 february 2022). At the 104-week data cut-off, the number of deaths increased to 11/72 (15.3%) in the early-start tofersen vs 7/36 (19.4%) late-start tofersen groups (the latest data cut off, 28 february 2023) (10). The HR of 0.27 (95% CI 0.08, 0.89) (analysis unadjusted for crossover) at week 52 seems low, and somehow unexpected given the similar crude event probability and similar KM curves. Surprisingly the HR increased to 0.66 (0.25, 1.71) at week 104 with not many more additional deaths. Even the CHMP expressed their concern about the size of the HR for time to death or permanent ventilation at week 52. Under the Raw Data Pilot Project under the MAA procedure, where the robustness of the HR was tested under various analysis settings, the resulting HR varied from HR=0.36 to 0.87 (10). The CHMP concluded that although numerical trends in favour of the early-start tofersen group were observed, no conclusions regarding the effect of tofersen on survival could be made due to the small event numbers, immature data and strong assumptions (i.e proportionality of hazards) made for analysis.

As placebo patients in VALOR part C switched to tofersen (i.e delayed-start tofersen) in OLE, the company adjusted treatment effect estimates of tofersen using RPSFTM (base case) and IPE (supplementary analysis) in order to account for treatment switching. An alternative would be to use the treatment effect from the randomized part of the VALOR study, however, given the short duration of 6 months, very few death events were observed. In response to the request for HR for progression based on VALOR Part C only, the company stated that KM graphs and HR estimates have not been produced on VALOR Part C data alone. According to the company, the timeline for biological action is expected to be as follows: 8 weeks to see CSF SOD1 total protein knockdown, 12-16 weeks to see NfL reduction and 28 weeks and beyond to see benefit on clinical function and survival. JNHB acknowledges that the use of the

randomized VALOR Part C study alone would give limited information of the treatment effect given the short study duration. At the same time the use of RPSFTM has a number of limitations as described below.

JNHB agrees that RPSFTM is the most appropriate approach to handle high switching proportions. However, with 32/36 initially randomized placebo-patients switching to tofersen, estimating counterfactual (untreated) survival times for the control group becomes difficult, as no patient continued on placebo beyond 28 weeks. This is because estimating the treatment effect parameter (by choosing a value that minimizes the difference in survival times between the treatment and control groups, see Appendix 2) becomes challenging as the model relies heavily on data from the control group's very short untreated time (i.e., 6 months in VALOR Part C). In addition, the results of the crossover adjustment cannot be validated against a proper control group in which patients never switched. It is unclear how the lack of a proper control group biased the treatment effect. Importantly, Figure 16 and Figure 17 in Appendix 2 show that the counterfactual survival curves under no treatment for both arms for time to death and time to later MiToS stages give a poor overlap of survival times, which raises concerns about the validity of the treatment effect estimation.

The main assumption behind the validity of the RPSFM is the common treatment effect assumption, i.e., that the size of the treatment effect of tofersen is the same at randomization, and at the point of treatment switch from placebo to tofersen. The company did not test this assumption due to lack of knowledge about the "predictive patient characteristics" that can potentially separate those with higher treatment effect from those with lower treatment effect. Instead, the company provided sensitivity analyses with decreasing ratio of the treatment effect in the delayed-start group vs the early-start group. These showed that even with 50% retained treatment effect parameter, the hazard ratio for death does not change much (from 0.1 to 0.13) and remains stable (at 0.61) for time to later MiToS stages.

Overall, the modelling of the treatment effect of tofersen + SoC on progression and survival is highly uncertain. To demonstrate the impact the size of the effect has on the model results, JNHB chooses to present a range of plausible effect estimates as base case analyses. The newest available data are used in the economic model. For progression, HRs range from 0.61 (treatment-switch adjusted analysis, DCO 2022, regarded by JNHB as least conservative) to 0.69 (ITT analysis, DCO 2022). For survival, HRs range from 0.12 (treatment-switch adjusted analysis, DCO 2023, regarded by JNHB as least conservative) to 0.66 (ITT analysis, DCO 2023).

Model result validation

The company compared the modeled MiToS distribution with the observed MiToS class proportions in VALOR Part C (Figure 10). The validation was based on the company's base case. i.e., HR for SOD1-ALS vs ALS of 1.3, HR for tofersen + SoC vs. SoC for progression of 0.61 and 0.10 for death. The modelled progression was faster in both arms, but particularly in the SoC arm with predicted proportion of deaths at 28 weeks was 12% vs 0% in VALOR. This is clearly a concern, as the model biases the results in favour of tofersen + SoC already at 28 weeks. JNHB has tested the internal validity of HRs for SOD1-ALS vs ALS ranging from 1 to 0.1 as used in the JNHB's base case scenarios. The HR=0.8 had the best internal validity with the model predictions almost aligned with the VALOR study results at week 28. However, the model still predicted 6% deaths in the SoC arm at week 28.

The predicted disease progression depicted in Figure 9 indicates that tofersen increases life year gain at least 2 times at every MiToS stage in the company's base case. These results cannot be easily validated as there was only one death observed in VALOR Part C. In addition, only one placebo patient and 5 tofersen patients transitioned to MiToS class 3 or 4 in the randomized period.

There appears to be a survival benefit between early-start tofersen and delayed-start tofersen as observed in VALOR+OLE at the newest datacut (Figure 11). However, due to the modelling approach (i.e a HR applied to transition probabilities from PRO-ACT) the modelled survival at 4 years (68% survival for tofersen+SoC) cannot be directly validated with the empirical data from VALOR OLE (80% survival for early-start tofersen).

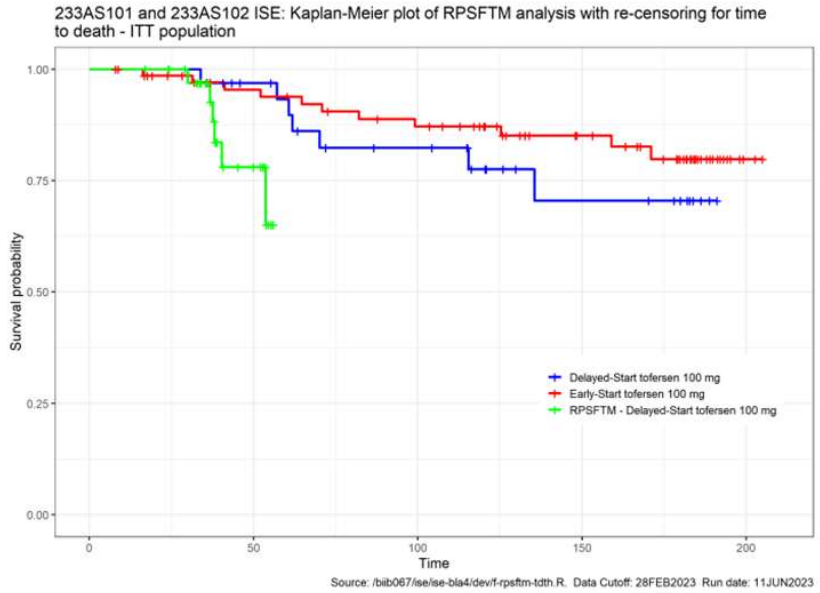

Figure 11: Overall survival observed in VALOR+OLE. Time in months. Datacut 18.02.2023.

JNHB conclusion:
JNHB does not expect faster progression of SOD1-ALS patients compared to PRO-ACT and such an assumption also overestimates the disease progression in the placebo arm of VALOR Part C. Therefore, JNHB excludes the HR of 1.3 for SOD1-ALS vs overall ALS population. As the disease progression may be slower for patients in some Nordic countries the results are presented at different values for slower disease progression, ranging from HR=1 to HR=0.1.

There is also considerable uncertainty around the effect of tofersen, due to the limited duration of VALOR and crossover to tofersen for all patients. Therefore, JNHB explores different scenarios instead of applying one base case. HRs sourced from ITT analyses and crossover-adjusted analyses for progression and death are used together with interval values. Proportional hazards may not hold true but cannot be explored in sensitivity analyses.

4.2.2 Health related quality of life- patients

The company identified three studies from the systematic literature search that reported utilities per MiToS stage, and 6 studies that reported utilities per King's stage (Appendix 3). Briefly, standard electronic database searches were performed to identify studies published from 1 January 1999 to 1 August 2023. The inclusion and exclusion processes were documented thoroughly, including completion of a PRISMA flowchart. Altogether 26 utility studies were included in the systematic review, with 7 studies reporting utilities per MiToS and/or King's health state.

In the economic model, three utility sources were available; studies by Moore et al 2019 (base case) and Stenson et al 2024 (sensitivity analysis) (1, 54, 55), which were selected for inclusion in the model as they reported utility values that logically decreased with increasing disease severity, as well as utility data from VALOR+OLE. VALOR+OLE was not used as the pivotal source since according to the company it is illogical that MiToS stage 3 is assigned a higher utility value than stage 2.

The comparison of sources (as compiled by JNHB) is presented in Table 11.

Table 11: Comparison of the sources of utilities in the economic model, as compiled by JNHB based on publications and information provided by the company for VALOR+OLE.

Source	Moore et al 2019	Stenson et al 2022 Stenson et al 2024	VALOR + OLE, DCO 2022
MiToS Stage 0 Stage 1 Stage 2 Stage 3 Stage 4	**EQ-5D-5L (n)** 0.71 (n = 301) 0.48 (n = 198) 0.36 (n = 73) 0.33 (n = 18) 0.25 (n = 5)	**EQ-5D-3L (n)** 0.53 (n = 116) 0.34 (n = 17) 0.00 (n = 10)* 0.01 (n = 8)* -0.10 (n = 14)* **small/negative values due to mapping from 5L (collected from patients) to 3L*	**EQ-5D-3L (n*)** 0.60 (n = 810) 0.40 (n = 303) 0.18 (n = 109) 0.28 (n = 22) 0.15 (n = 15) **nr of questionnaires filled*
King's Stage 1 Stage 2 Stage 3 Stage 4(a) Stage 4b	**EQ-5D-5L (n)** 0.76 (n = 89) 0.60 (n = 135) 0.53 (n = 206) 0.50 (n = 162)* **collected per stage 4 (not 4a/4b)*	**EQ-5D-3L (n)** 0.65 (n=29) 0.61 (n=27) 0.45 (n=56) 0.11 (n=50)* **collected per stage 4 (not 4a/4b)*	**EQ-5D-3L (n*)** 0.68 (n=253) 0.52 (n=490) 0.43 (n=248) 0.60 (n=19) 0.31 (n=231) **nr of questionnaires filled*
Sample size, n Age in years, mean (SD) Female, n (%)	595 65.07 (10.89) 232 (39%)	172 60.8 (11.5) 68 (39.5%)	108 51.2 (11,6) (placebo), 48.1 (12,6) (tofersen) 46(43%)
Included ALS population	UK patients across 22 MND clinics	EU5, US	Europe, Canada, US, Japan
Statistical model	Details not provided. Simple calculation of mean values is implied	Correlations of outcomes with King's and MiToS stages were assessed through linear regression and were adjusted for age, sex, body mass index (BMI), and number of comorbidities. Adjusted marginal means were reported.	The values represent the mean value of all observations (N=1259) by disease stage, across all visits including baseline, and both study arms (N=108 patients).
Missing data handling	Patients were omitted from the analysis of health utility if they had not completed the EQ-5D-5L in full	ALS patients with missing data (N=3) for a particular variable was removed from all analyses involving that variable	Assumed not to be imputed.
Patient-level mapping onto EQ-5D-3L?	No	Assumed, but not explicitly stated	Yes. The "crosswalk" method (EuroQol Group) was used to map the EQ-5D-5L to the EQ-5D-3L UK value set (56)

The impact of aging on QoL was modeled by applying an age-adjustment index to utility values. The age-adjustment index was calculated based on the Swedish general population utilities reported by Bjurström et al. [212] and a mean baseline age of 49.1 years [188]. Adjustment indices were calculated by dividing the general population utility value for each age group by utility value for the mean age of 49 years old used in the model for the baseline population, based on the VALOR trial population (18).

Utility decrements of -0.0072 associated with limb pain and back pain, radiculitis and myelitis were included in the model. The disutility for limb pain and back pain was sourced from (57) and was assumed to be the same for other adverse events (AEs). Each AE considered in the model was assumed to last for 7 days. AE incidences were derived from the tofersen and placebo arms of the VALOR Part C trial and converted to 4-weekly AE probabilities for use in the model. AE data from the placebo arm of the VALOR trial were assumed to be reflective of AEs of SoC (riluzole, edaravone).

4.2.3 Health related quality of life- caregivers

Caregiver HRQoL impacts were incorporated in the model, under the assumption that each patient has an average of 1 caregiver in base case analyses, with mean age equal to the patient. Carer utility values were reported by Stenson et al. (Stenson, Agnese [208]) using the EQ-5D-5L instrument by MiToS or King's stage.

JNHB discussion

Patient HRQoL
The company has chosen the publication by Moore et al. as a source of utility values for patients, and the Biogen-funded publication by Stenson et al. as a sensitivity analysis. The company claims that the Moore and Stenson publications were most appropriate from other SLR-identified studies as they showed declining utilities per disease severity. JNHB partially supports such selection process, however, upon a closer inspection of some of the excluded publications, the utility value stabilisation at the latest stages could be a result of a random variation or show an actual lack of a difference at later stages. For instance, Peseschkian et al. (58) reports utility scores per King's stage 4a and 4b (whereas Moore et al. and Stenson et al. reported utilities per pooled stage 4) and shows that stage 4a has a slightly lower mean utility than stage 4b. In addition, some of the excluded studies reported declining utilities per stage (59, 60) so their exclusion is not well justified.

The primary source of efficacy data is usually preferred as the source of utility data in the economic model as it ensures consistency between input data. The use of the pivotal trial avoids subjectivity of selecting an external source. EQ-5D-5L responses were collected in VALOR +OLE. The 5L profile values were then mapped onto 3L values at patient -level data using the "crosswalk" method by Hernadez-Alava and then directly mapped to the UK value set in agreement with reference cases for the majority of JNHB country members. In contrast, no 5L to 3L mapping was performed in the Moore et al. publication, whereas the mapping in the publication by Stenson et al. resulted in very small or negative values. The response rate in VALOR Part C was high (86% of placebo patients and 85% of tofersen patients responded to the EQ-5D questionnaire at week 28) but dropped, as is expected with time, in VALOR+OLE (65% for early-start tofersen, 72% for delayed-start tofersen at week 52). Although the response rate is considered reasonably high, no description of the reason for non-response was provided so the response bias cannot be assessed. The number of observations for MiToS stages 0, 1 and 2 (810, 303 and 109, respectively) is considered high but decreases considerably for stages 3 and 4 (22 and 15, respectively). The small sample size could explain the unexpected stabilisation of utility values 0.18, 0.28 and 0.15 between stages 2, 3 and 4. The company argues that those values are illogical and hence preferred to use external sources. JNHB agrees that higher utility at stage 3 (3 functional domains lost) than at stage 2 (2 functional domains lost) seems implausible, but this should not exclude VALOR as the primary source of utility values. Instead, JNHB chooses to use a weighted average value of 0.20 for stages 2 and 3 in the model. Alternative values (e.g., 0.18 for stage 2, and values 0.15 for stages 3 and 4, as well as values from external sources) are tested in scenario analyses.

Age-adjustment of utilities based on an adjustment factor from Burström et al. (61) was used in the economic model and is accepted.

Caregiver HRQoL
A large proportion of ALS patients stay at home with the support of a personal assistant, home nurse, safety alarm in addition to support from family/friends (informal caregivers). According to the Norwegian medical expert, a minority of ALS patients stay in nursing homes. In Sweden, every patient uses communal services in combination with help from informal caregivers. A recent Finnish paper showed that during the 20-year follow up period, 20% among ALS patients died at home, 28% at primary ward, 15% in hospital, 13% in specialized hospice care and 21% at sheltered home (62). JNHB acknowledges that informal caregivers play an important role in patients' care, and given the debilitating nature of ALS, the burden to caregivers is considerable. This is supported by the findings from a systematic review based on 25 articles, which show that higher caregiver burden is associated with greater behavioural and physical impairment of the patient and with more depressive feelings of the caregiver (63).

Caregivers' HRQoL data have not been collected in VALOR, and the literature providing utility values per MiToS or King's staging is limited. Biogen chose a paper by Stenson et al. that reported EQ-5D-5L caregiver utility score by MiToS or King's stage among 79 caregivers. No significant correlation between caregiver EQ-5D-5L and MiTOS staging was observed, although there was a significant negative correlation between EQ-5D-5L utility score and King's staging. The analyses are based on a very small caregiver numbers per stage (N= 43, 12, 8,5 and 11 for respective MiToS stages 0, 1,2,3 and 4) and hence considered very uncertain. Interestingly, in the economic model the value of caregiver utilities per stage does not greatly impact the results. Even if all utilities per stage are set to one value (for example a perfect health for caregivers at every MiToS stage), the ICER does not change considerably. Instead, the proportion of patient deaths drives the incremental caregiver utilities and have a considerable impact on the ICER. Since this proportion is higher in the comparator arm, and since caregiver utilities are not accounted for after the patient's death, the total accumulated caregiver utilities are naturally greater in the tofersen arm. This insensitivity to the value of caregiver utilities implies that decreasing caregiver quality of life through gradual changes in patient functioning (rather than solely extending survival) does not have as much impact, which might not reflect the real-world complexities of caregiving. In addition, it does not seem intuitive that as long as a patient stays alive, even in the worst health state close to death, the caregivers' QALYs continue to be generated and drive the model results.

The impact of caregivers' utilities in the economic model is considerable. However, the quality of caregiver's utility source data is judged to be low and the insensitivity to the value of a caregiver utility concerning. In alignment with the different guidelines within Norway, Denmark, Finland and Sweden, caregivers' QoL are not included in the JNHB base case.

JNHB conclusion:
JNHB concludes that using utility values from VALOR+OLE is preferable to external utility value sources to maintain consistency in model inputs. The response proportion in VALOR+OLE was high, but the number of completed EQ-5D questionnaire per MiToS stage 3 and 4 was low, which could have resulted in implausibly higher utility value per stage 3 (0.25) as compared to stage 2 (0.18). To eliminate the inconsistency in utility values, JNHB chooses to use a weighted average value of 0.20 for both stages. An alternative value of 0.18 for stages 2-4 was tested in a scenario analysis but did not impact the results much. Age-adjustment of utilities based on Burström et al. 2001 is accepted.

Caregiver utilities are excluded from the model in line with the majority of reference cases from JNHB member countries. JNHB acknowledges, however, that informal caregivers play an important role in patients' care, and the burden to caregivers is considerable. The inclusion of caregiver utilities is tested in scenario analyses.

4.3 Costs and resource utilization

The following direct medical costs have been considered in the model: drug acquisition and administration, monitoring, health care resource use and adverse events.

In the base case analysis, the company has used Sweden as the reference country. Swedish unit costs are used throughout the model with some exceptions where British pound is used. The model can change all unit costs to the other countries' currencies using a currency conversion. Currency exchange rates are presented in Table 12. For the JNHB base case Norwegian currency is used.

Table 12: Currency exchange rates applied in the model

Country	Value of 1 SEK	Value of 1 GBP	Source
Sweden	-	13.57634	Riksbanken, mean exchange rate SEK/GBP in May 2024
Norway	0.99815	13.54940	Riksbanken, mean exchange rate NOK/SEK May 2024 Norges Bank, mean exchange rate NOK/GBP May 2024
Finland	0.08610	1.16870	ECB, mean exchange rate EUR/SEK May 2024 Bank Norge, mean exchange rate EUR/GBP May 2024
Denmark	0.64240	8.72432	Riksbanken, mean exchange rate DKK/SEK May 2024 Danmarks Nationalbank, mean exchange rate DKK/GBP May 2024
Iceland	12.91470	175.31	Riksbanken, mean exchange rate ISK/SEK May 2024 Sedlabanki Islands, mean exchange rate ISK/GBP May 2024

4.3.1 Dosage/administration

Tofersen is administered as an intrathecal bolus injection with a dose of 100 mg (15ml x 6,7 mg/ml) once daily on day 1, 15, 29, and then every subsequent 28 days. The dose corresponds to one pack of tofersen, hence there is no wastage according to the company.

Riluzole is administered orally at a dose of 50 mg twice daily. In the model, all patients in the comparator arm receive riluzole. In VALOR, 60% of patients in the intervention arm received riluzole background treatment. In the model, it is assumed that all patients are co-administered riluzole in the intervention arm. One pack of riluzole contains 56 tablets.

JNHB discussion

Dosage/administration

Riluzole is the standard for treatment of ALS, and clinical experts in the Nordic countries have confirmed that patients in both the intervention arm and the comparator arm will receive riluzole as background treatment. Each pack of riluzole and injection of tofersen corresponds to one cycle of treatment, which indicates that wastage will not have a major impact. Patients may not finish a pack of riluzole, but the cost is low and affects both arms.

JNHB conclusion:
JNHB accepts Biogen's modelling of dosage and administration.

4.3.2 Medicine and administration costs

Medicine cost
The cost of treatment with tofersen is approximately 244 000 NOK per 28 days. Medicine acquisition cost for riluzole is 1 688 NOK per 28 days (based on maximum AUP ex VAT). Costs for tofersen and riluzole are presented in Table 13 below. There are no treatment stopping rules in the model, and the mean time on treatment in the model is 3.3 years for tofersen.

Biogen argues that it is not appropriate to calculate stage-specific discontinuation rates from the VALOR trial, as patients may transition forward and backward between disease stages. Therefore, the probability of discontinuation was assumed to be the same across all health states (1.02% per treatment cycle in the model). This is based on the rate of discontinuation in the VALOR trial, which was 6.94% over 28 weeks, converted to a 4-weekly probability. If patients discontinue tofersen treatment, they are still assumed to remain on riluzole over the lifetime horizon. Biogen assumes no stopping rules for treatment with tofersen. This means that other than the 1.02% of patients discontinuing treatment each cycle, everyone will receive treatment until death.

Table 13: Medicine acquisition cost

Drug	Formulation	Drug unit	Pack size	Cost per pack (NOK, AUP excl VAT)
Tofersen	Bolus injection	100 mg	1	243,895.04
Riluzole	Oral	50 mg	56	1,688.16

Drug administration costs
Tofersen is administered as an intrathecal bolus injection. The unit cost for intrathecal bolus injection is based on different DRG tariffs in the Nordic countries. In Norway, Biogen has chosen DRG 801H. Riluzole is administered orally and does not incur any administration costs. The administration costs are included as a per cycle cost in the model and presented in Table 14 below.

Table 14: Administration unit cost

Items	Unit cost (NOK)	Source
Intrathecal bolus injection	12,383	DRG 801H: Outpatient treatment of neurological disorders with the infusion of special drugs (DRG system Norwegian Directorate of Health)
Oral administration	0	Assumption

JNHB discussion

Medicine cost
There are no criteria for tofersen treatment discontinuation according to the SPC (9). In the model Biogen have used a fixed probability of 1.02% for treatment discontinuation per 4 weeks regardless of health state and staging system. This is based on data from the VALOR (64).

Respiratory support is mentioned as one possible reason for discontinuation of tofersen treatment. At this point the patient has lost the function of breathing independently. JNHB explored the consequences of using this as a criterion for treatment discontinuation. In Norway

approximately 6% of all ALS patients undergo tracheostomy treatment (65). In the MiToS staging system this event seems to be evenly spread out for stages 0-3 (0: 21.5%, 1: 21.5%, 2: 23%, 3: 25%, 4: 9%) (39), therefore it is reasonable to not differentiate between the stages.

In the model, the expected life years in the tofersen arm is 3.29, which is approximately 171 weeks. The weekly rate of tracheostomy is then calculated as - [ln (1-0,06)]/171 = 0.000362, and the 4-weekly probability as 1-exp (-0.000362*4) = 0.14%.

This probability is lower than the 1.02% 4-weekly probabilities that are included in the model but could give an indication of a higher discontinuation percentage if criterions for discontinuation are included. Other factors, like adverse events, could also influence discontinuation of treatment with tofersen.

There are currently no guidelines on when to discontinue treatment, but the clinical experts in Finland, Sweden, Denmark and Norway agree that treatment might discontinue at advanced stages of the disease. One patient representative explain that the most important purpose of treatment must be to prolong the active part of life. The possible reasons for discontinuation may be moving to a nursing home or being on respiratory support or having no living motoneurons left since the treatment is designed to maintain motoneuron function. The decision of discontinuation might also come from the individual tolerance of the patient.

Drug administration costs
Biogen has provided a Norwegian DRG that covers intrathecal bolus injection. The DRG used is *outpatient treatment of neurological disorders with the infusion of special drugs,* with a cost of 12,383 NOK. There is no tariff explicitly covering intrathecal bolus injection in Norway, but it is in Sweden. The Swedish cost for administration is lower, and using the Swedish cost would lower the incremental cost with approximately 230,000 NOK.

JNHB conclusion:
JNHB concludes that treatment discontinuation could be underestimated, but accepts Biogens choice due to lack of better data. Higher probability of treatment discontinuation is explored in a sensitivity analysis. There are reasons to introduce stopping rules for the treatment, however, since there are no guidelines for this in the Nordics yet, JNHB accepts the company's base case assumption in the model. JNHB will adjust the treatment stop parameter in sensitivity analyses exploring 100% treatment discontinuation in MiToS stage 4 and stage 3/4.

JNHB accepts the Norwegian cost of intrathecal bolus injection.

4.3.3 Costs for health care and use of resources and other directs costs

Monitoring and disease management costs
The company assumes that all patients treated with tofersen is requiring urine analysis, platelet count and coagulation tests every 3 months. Treatment with riluzole is assumed not to require any form of monitoring. Unit costs of monitoring were sourced from the pricelist from the Swedish southern hospital region (Södra Sjukvårdsregionen) and converted from SEK to NOK (Table 15). The costs of monitoring are included as a per cycle cost in the model.

Table 15: Monitoring unit costs

Items	Unit cost (NOK)	Source
Urinalysis	908	Prislista södra sjukvårdsregionen - Klinisk Kemi och farmakologi - Njurmedicin Laboratoriediagnostik 310 Urinsediment

Items	Unit cost (NOK)	Source
Platelet count	19	Prislista södra sjukvårdsregionen - Klinisk Kemi och farmakologi - NPU03568 B-Trombocyter
Coagulation tests	118	Prislista södra sjukvårdsregionen - Klinisk Kemi och farmakologi - SKA02366 Provtagning vid Klinisk kemis provtagningsenhet

Subsequent treatment costs
Biogen assumes lifelong treatment with tofersen, hence there are no relevant subsequent treatments. Patients who discontinue the tofersen treatment in the model are assumed to continue riluzole treatment over the lifetime horizon.

Costs for adverse events
Unit costs for adverse events were sourced from Södra Sjukvårdsregionen. The company assumes that all non-serious adverse events are transient and easily treated with paracetamol and NSAIDs, except for limb pain and back pain. Since treatment with paracetamol and NSAIDs have negligible costs, they were not included in the model. The company chose to only include adverse events, which were likely to have an important impact on costs. Therefore, limb pain and back pain, in addition to the serious adverse events, radiculitis and myelitis, were included. The adverse events included are listed below in Table 16 along with their incidence and probability. The 4-weekly probability was calculated assuming a duration of 7 days per event.

Table 16: Adverse events included with cycle probabilities applied in the model.

Adverse event	tofersen		SoC	
	Incidence	4-weekly probability[2]	Incidence	4-weekly probability[2]
Limb pain and back pain	41.7%[1]	0.0741	22.2%[1]	0.0353
Radiculitis	1.39%[1]	0.0020	0%[1]	0
Myelitis	2.78%[1]	0.0040	0%[1]	0

[1] *VALOR (Part C) trial, reported incidence per 28 weeks. Note that this incidence is different than the observed higher incidence of adverse events over longer treatment periods (147 patients; 368.83 patient years; median exposure 148.4 weeks) as described in chapter 3.1.6.*

[2] *Calculated as 1 - (1 - Incidence) ^ (4 weeks / Duration in weeks)*

The cost per event is based on different Swedish DRG tariffs converted from SEK to NOK and presented in Table 17 below.

Table 17: Adverse event unit costs applied in the model.

Adverse event	Unit cost (NOK)	Source
Limb pain and back pain	8,191	Södra sjukvårdsregionen 2024 - W98O Läkarbesök smärtproblem O
Radiculitis	7,406	Södra sjukvårdsregionen 2024 - A99Q Läkarbes sjd i nervsystemet U O
Myelitis	7,406	Södra sjukvårdsregionen 2024 - A99Q Läkarbes sjd i nervsystemet U O

Health state costs
The company has presented a list of different resource units from primary care, secondary care, tests and community care that patients are assumed to incur every 3-months based on their MiToS stage (Table 18). If using King's staging in the model, the resource use will change and reflect the distribution of patients in King's staging. The estimated resource use is derived from a UK study (1).

The company identified Nordic studies on health care costs associated with ALS. However, the studies did not cover all the different stages. In Kierkegaard et al only King's stage 4a/b was

included (66) and in Jennum the resource use was across all stages (67). In the two studies, the average annual costs were estimated to 340,000 (King's stage 4a/b) and 230,000 (across all stages). Both values are in 2021 SEK, which is similar to NOK used in the model. The company argues that resource use from the UK study provides more appropriate inputs for the model, and the data are expected to be roughly comparable to treatment practice in the Nordic countries. The resource use and costs were adjusted to reflect 4-weekly cycles in the model.

Unit costs for the healthcare services were sourced from Swedish price lists. The unit costs are then converted from SEK to NOK and presented below in Table 19. Annual costs in the different health stages are also calculated and presented in Table 20.

Table 18: Health care resource use per 3 months by MiToS stage from Moore et al. 2019

Resource category	MiToS stage				
	0	1	2	3	4
Primary care					
Nurse GP surgery visits	0.48	0.54	0.30	0.50	2.20
Doctor GP surgery visits	1.05	0.83	0.58	0.50	1.60
Nurse at home visits	0.61	1.78	6.25	5.38	15.20
Doctor at home visits	0.04	0.43	0.63	1.17	2.20
Secondary care					
Emergency department visits	0.18	0.31	0.40	0.17	0.00
Nurse outpatient visits	0.71	1.29	1.10	1.61	0.40
Doctor outpatient visits	2.17	2.19	1.31	3.00	1.80
Ambulance use	0.10	0.27	0.60	0.11	0.00
Inpatient stays, number of admissions	0.10	0.40	0.34	0.11	0.20
Tests					
Blood tests	1.10	1.04	1.54	1.00	0.40
Urine tests	0.06	0.14	0.21	0.33	1.20
Ultrasound scans	0.04	0.09	0.10	0.11	0.00
X-ray scans	0.14	0.21	0.30	0.11	0.00
CT scan	0.12	0.16	0.05	0.00	0.00
MRI scans	0.23	0.20	0.15	0.00	0.00
EMG scans	0.25	0.25	0.16	0.06	0.00
Community care					
Health visitor visits	0.44	1.25	1.36	1.00	1.00
Social worker visits	0.22	0.52	0.67	1.28	1.20
Physiotherapist visits	1.72	2.31	2.60	4.95	2.40
Psychologist visits	0.07	0.18	0.15	0.33	0.00
Counsellor visits	0.04	0.10	0.27	0.22	0.00

Table 19: Health care resource unit costs.

Health care resource	Unit cost (NOK)	Source
Nurse GP surgery	928	Utomregional prislista 2023 Region Stockholm / Gotland. Prislista övrig öppen vård. Besök hos övrigt hälso+och sjukvårdpersonal, vårdgivare med avtal
Doctor GP surgery	2,089	Utomregional prislista 2023 Region Stockholm / Gotland. Prislista övrig öppen vårdÖ Privatpraktiserande specialist med avtal
Nurse home	2,319	Södra sjukvårdsregionen prislista 2024 HEMBSVB Hembesök, kompl till besökstjänst BSVB01
Doctor home	4,550	Södra sjukvårdsregionen prislista 2024, ZV025 Hembesök, kmpl till besökstjänst
Casualty dpt.	5,986	Södra sjukvårdsregionen prislista 2024, BLÄK10 Läkarbesök, akutmottagning
Nurse outpatient	4,982	Södra sjukvårdsregionen prislista 2024, BSVB01 Besök annan HS personal (neurologi)
Doc outpatient	5,285	Södra sjukvårdsregionen prislista 2024, BLÄK01Å Läkarbesök, återbesök (outpatient)
Ambulance use	1,996	Lägsta ersättning för ambulanstransporter uppgår till kilometerersättning 100 kr x 20 km = 2000 kr
Inpatient stay	2,867	Södra sjukvårdsregionen prislista 2024, Omvårdnadsdag + Intagning (Neurologi)
Blood	45	Södra sjukvårdsregionen prislista 2024, Klinisk Kemi och farmakologi - Laboratoriemedicin Bas (Baskemi)
Urine	45	Södra sjukvårdsregionen prislista 2024, Klinisk Kemi och farmakologi - Laboratoriemedicin Bas (Baskemi)
Ultrasound	1,381	Södra sjukvårdsregionen prislista 2024, Användande av ultrljud (Neurologi) SKA00000 Urintestremsa (7 parametrar) 45
X Ray	1,065	Södra sjukvårdsregionen prislista 2024, 62230, Rtg med tomosyntes bröstrygg
CT scan	1,523	Södra sjukvårdsregionen prislista 2024, DT huvud och hals (Onkologi och stråliningsfysik)
MRI	2,464	Södra sjukvårdsregionen prislista 2024, MRT Hjärna (Onkologi och stråliningsfysik)
EMG	5,026	Södra sjukvårdsregionen prislista 2024, Elektromyo- och neurografier (Högspecialiserad vård och länssjukvård)
Health visitor	1,216	Södra sjukvårdsregionen prislista 2024, Besök annan HS personal (Rehabiliteringsmedicin)
Social worker	1,216	Södra sjukvårdsregionen prislista 2024, Besök annan HS personal (Rehabiliteringsmedicin)
Physiotherapist	2,507	Fysioterapeutbesök O (DRG code Y82O), from: https://www.regionstockholm.se/491c61/contentassets/6f0275ce70be462193c2480734710703/bilaga-2-utomregional-prislista-karolinska-universitetssjukhuset-2024.pdf
Psychologist	12,145	Södra sjukvårdsregionen prislista 2024, Psykologbesök (neurologi)
Counselor	1,891	Södra sjukvårdsregionen prislista 2024, Besök annan HS personal, psycholog (Rehabiliteringsmedicin)

Table 20: Annual disease management costs by MiToS and King's stage

Country	MiToS stage/King's stage (NOK)				
	HS 0/1	HS 1/2	HS 2/3	HS 3/4a	HS 4/4b
MiToS stage	120,435	186,298	209,299	264,292	293,927
King's stage	115,361	133,556	141,091	229,478	229,478

Genetic testing
Only ALS patients with a mutation in the SOD1 gene are eligible for treatment with tofersen. Hence, genetic testing to identify patients with a mutation in the SOD1 gene is necessary, if tofersen is introduced. The company argues that genetic testing for mutations in the SOD1 gene are already performed in Sweden and have therefore not included costs for genetic testing in the model.

JNHB discussion

Monitoring and disease management costs
The monitoring costs only affect the tofersen arm and are small compared to the other costs in the model. The costs are sourced from the British NHS and may vary in the Nordic countries, but do not impact the ICER by a lot. If the unit costs were doubled for example, the incremental cost and the ICER would increase with around 15,000 NOK.

Subsequent treatment cost
For ALS riluzole is the only current treatment and it will be given to the patients regardless of treatment with tofersen. Hence, there are no relevant subsequent treatments. This is confirmed by clinicians from all countries, who say that tofersen will be an add-on to existing treatment.

Cost for adverse events
In the model only the cost for three adverse events is included. The Finnish expert argues that all AEs should be addressed, and the long-term AEs are not currently known. Increasing the cost or probabilities for AEs or adding more AEs is expected to have low impact on the results.

Health state costs
The company has used health state costs from a UK perspective. The justification was that only the UK study differentiated between the different health stages. Costs from Moore (1) are similar to Kierkegaard (66), but lower than Jennum (68). Increasing the annual cost of health care resource use also increases the incremental cost of tofersen. This is because patients stay longer in each health state in the tofersen arm in the model. Consequently, underestimating the health care resource use and cost would underestimate the ICER. Overestimating the use and cost would have the opposite effect. The company shows in a one-way sensitivity (OWSA) that health state costs only have a minor impact on the cost-effectiveness results.

The health state resource categories the company use show relatively short time spent in inpatient and outpatient stays, this implies that most patients are treated at home. This is confirmed by the Norwegian clinical expert, who said that most ALS patients do not stay in nursing homes but stay at home. It was however not possible to give an estimate of the share of patients living at home versus at an institution. The clinical experts in Finland, Sweden and Norway say that almost all patients need some form of communal services. The Swedish expert estimates that in at least 90 % of the patients receives communal services in combination with help from family members. Resource use could vary in the Nordic countries compared with the values from the UK study, but it is difficult to estimate just by how much. For example, in Sweden there are no social workers involved, and emergency department visits as well as ambulance use may occur at all health stages according to the Swedish expert. Urine tests and EMG may also be less frequent in the later MiToS stages.

A key difference between the scales is how tracheostomies are distributed across the categories. In King's system, 90% of tracheostomies occur during stages 4 with 62% of cases during stage 4B which matches with what would be expected. In MiToS, tracheostomy is evenly distributed across stages which is clinically implausible. The company has not explicitly accounted for tracheostomy in the model since this is indirectly captured though staging and the accompanying costs and utilities. JNHB agrees with the company that including tracheostomies (as well as

tube feeding, mechanical respiratory support or invasive mechanical ventilation) as additional parameters in the model might be considered as double counting.

The costs of the different resource categories are based on Swedish DRG tariffs and converted to NOK. Uncertainty is introduced since the data on frequency is from UK, and the fact that the patient population is very heterogenous. However, it is unlikely that the resource use will affect the cost per QALY significantly. This is because it is the increased time spent in each health state that will increase the costs, at the same time this will also increase QALYs and LYs. The uncertainty regarding the resource use and costs of resource use in the health stages may lead to an overestimation or underestimation of the health state costs for the patient group.

Genetic testing
The Swedish clinical expert says that at Karolinska University Hospital patients with familial ALS (fALS) are tested routinely, but patients with sporadic ALS (sALS) are not tested genetically. This is also the case with most clinics in Sweden. There is an ongoing effort to create Swedish guidelines of the management and treatment of genetic testing of ALS. According to these recommendations, all patients will be tested for SOD1 ALS. In Finland, according to the clinical expert, most patients with slowly progressive leg onset disease are tested for SOD1*D91A, and SOD1 sequencing are sometimes performed. In Norway most ALS patients are currently tested as part of the GAIN study, and the clinical expert also believes all fALS cases will be tested in the future. Danish clinical experts explain that genetic testing should be offered to everyone already, but there may be differences across the country on how often patients are actually tested. They believe that reimbursement of tofersen could lead to more and faster genetic testing.

Inclusion of genetic testing in the tofersen arm of the model would increase the ICER considerably, and is relevant to include if reimbursement of tofersen is expected to change testing routines. In Norway 28 % of fALS cases were caused by a SOD1 mutation, while only 0.4 % of sALS cases were caused by a SOD1 mutation (53). Since most patients have sALS, 88.5 % in Norway (53), a large number of patients still need to be tested to identify SOD1 mutations.

The cost of next-generation sequencing (NGS) test is 4,378 NOK. This is the average weighted cost according to the population size of the six healthcare regions included in TLV's assessment of FoundationOne CDx converted from SEK to NOK.

In order to identify one patient with sALS and SOD1 mutation when 0.4% sALS cases are caused by SOD1 mutation, 250 sALS patients would have to be tested. The cost of testing 250 patients is 1,094,500 NOK. In the study by Olsen et al (53) 10 of 279 Norwegian ALS patients were found to have genetic mutations in the SOD1 gene, with 9 being fALS cases and 1 being a sALS case. Assuming the patients with fALS are already being tested, only 10 % of the total SOD1 ALS population will be included in the test costs. Using the unit cost of 4,378 NOK for 250 patients (0,4%) testing costs totals 1,094,500 NOK. Assuming 10% of the SOD1 ALS cases are sALS and the remaining 90% does not require additional testing, the weighted cost will be 109,450 NOK.

JNHB conclusion:
JNHB concludes that the use of Swedish costs for monitoring, adverse event and health state is acceptable.

JNHB concludes that it is appropriate to exclude the costs of genetic testing in line with the company's base case. However, since sALS patients are not excluded from the indication, JNHB has run a sensitivity analysis accounting for the additional tests needed in order to identify SOD1 patients in the sALS population. Those costs are only applied in the tofersen arm of the model.

4.3.4 Indirect costs

The company has chosen to not include transportation cost and patient time cost in their model. This resource use and unit cost have not been described in the submitted dossier.

Societal costs are included in the model as indirect costs but are not used in the base case analysis. The company has explored scenario analysis where societal costs for the different stages of the disease are included. The costs are defined as non-treatment-related out-of-pocket costs and are obtained from Ploug et al (69). The costs were initially reported in 2021 Euros but were converted to current value annual GBP cost in the core CE model. The costs were then converted to NOK using the mean GBP exchange rate in May 2024. This pragmatic approach was justified by the company since the costs are only used in sensitivity analyses. Annual societal costs by MiToS stage used in the model are presented below in Table 21.

Table 21: Annual societal costs by MiToS stage

MiToS stage	Annual societal cost (NOK)	
HS0	13,811	Ploug et al. (69)
HS1	122,992	
HS2	1,076	
HS3	49,177	
HS4	3,342	

JNHB discussion

The inclusion of transportation cost and patient time cost varies in the Nordic countries. According to Danish and Norwegian guidelines, it should be included when it is expected to differ between the intervention and the comparator. In Sweden and Finland, these costs are not included.

Tofersen is administered through intrathecal bolus injection which requires the patient to visit a hospital. Riluzole on the other hand is administered orally and does not require the patient to travel. JNHB therefore includes transportation cost and patient time cost in the base case. The costs are from NOMAs unit cost database; 838 NOK for transportation each way and 326 NOK for 1 hour of patient time. This totals 2002 NOK, which is included in the model at each administration of tofersen. Intrathecal injections may be very burdensome for patients, as well as requiring more time and health personnel than estimated. The total costs associated with administration of tofersen could therefore be underestimated.

JNHB also presents a sensitivity analysis where transportation and patient time costs are excluded.

JNHB conclusion:

JNHB concludes that the exclusion of societal costs is acceptable and does not include them as part of the assessment.
JNHB does not accept the exclusion of transportation costs and patient time costs. These costs are included in the base case.

5 Results of the cost-effectiveness analysis

5.1 Biogen's base case

5.1.1 Key assumptions in Biogen's base case scenario

- Progression is modelled via MiToS staging system, with transition probabilities (TPs) for the control group (i.e. SoC) sourced from the PRO-ACT database. A HR of 1.3 is applied to TPs to account for a different survival of SOD1 ALS population vs overall ALS population analyzed in the PRO-ACT database.
- Treatment effect of tofersen + SoC is based on the time to event analysis for progression (i.e. time to increase in a MiToS stage, HR=0.61) and death (HR=0.1). The HRs were calculated using crossover-adjusted control group from VALOR+OLE.
- Backward transitions (i.e. improvement in MiToS staging) were allowed for in the economic model.
- No stopping rules for tofersen were applied per stage. Instead, a 1.02% 4-weeks probability of discontinuation of tofersen was applied.
- Health state utility source was an external study by Moore et al. Caregiver utilities were included and sourced from an external study by Stenson et al.
- Three adverse events were considered in the model: limb pain and back pain, radiculitis and myelitis. Those were assigned a disutility (-0.0072, 7 days duration) and costs.
- Costs of subsequent treatments and genetic testing were not included.
- Resource use sourced from Moore et al in a UK perspective. Supported by studies from Kierkegaard and Jennum.
- Discount rates according to Norwegian guidelines, 4% up to year 40, and 3% onwards.

5.1.2 Results in Biogen's base case scenario

Table 22: Company base case results for tofersen + SoC vs SoC, NOK

	Tofersen + SoC	SoC	Diff.
Drug Acquisition	9,933,963	28,090	9,905,873
Administration Costs	519,100	0	519,100
Monitoring Costs	12,681	0	12,681
Adverse Event Costs	38,039	4,806	33,233
Total treatment Costs (NOK)	10,503,782	32,896	10,470,886
Healthstate Costs (NOK)			
MiToS Stage 0	127,854	65,501	62,352
MiToS Stage 1	185,146	78,254	106,892
MiToS Stage 2	111,052	38,221	72,831
MiToS Stage 3	81,022	19,438	61,584
MiToS Stage 4	116,125	17,597	98,528
Total Healthstate Costs (NOK)	621,198	219,011	402,187
Total Costs (NOK)	**11,124,980**	**251,907**	**10,873,073**
Life years (LY)	**3.29**	**1.28**	**2.01**
Total Patient QALYs	1.58	0.69	0.90
Total Caregiver QALYs	2.51	1.01	1.50
Total QALYs	**4.09**	**1.69**	**2.40**
Cost per QALY gained			**4,538,531**

5.2 JNHB base case

5.2.1 Changes in assumptions in the JNHB base case scenarios

- The HR of 1.3 for SOD1 ALS population vs overall ALS population is removed. HRs between 1 and 0.1 are explored in JNHB's analyses. With a declining hazard ratio, median and mean survival in the SoC arm increases (Table 23).
- Treatment effect of tofersen is varied. For progression, JNHB presents HRs ranging from 0.61 to 0.69 representing crossover-adjusted analysis and ITT analysis, respectively. For survival, respective HRs ranging from 0.12 to 0.66 based on the newest VALOR+OLE datacut are used.
- Health state utility source is changed from the Moore et al publication to VALOR+ OLE. To eliminate implausible increase in the utility value from MiToS stage 2 to 3, a weighted average utility was used for those stages.
- Caregiver utilities are excluded.
- Transportation cost and patient time is included.

Table 23: Relationship between the modelled hazard ratio of SOD1 ALS and median/mean survival in the SoC arm in the model.

HR SOD1 ALS vs overall ALS	Median survival in the SoC arm (years)	Mean survival in the SoC arm (years)
1	1.31	1.56
0.8	1.54	1.84
0.6	1.85	2.33
0.4	2.54	3.36
0.2	5.08	6.94
0.1	11.15	15.28

The grid below represents a range of possible base case scenarios and reflects uncertainty around the treatment effect of tofersen, and the survival of the control group in the Nordic clinical practice. The ICER ranges from NOK 11.5 mln/QALY to NOK 29.5 mln/QALY in the grid, see Table 24. Table 25 and Table 26 show the corresponding grid for incremental costs and incremental QALYs. These values range from NOK 6.1 mln to 19.8 mln and 0.21 to 1.64 QALYs, respectively.

Table 24: JNHB base case results for tofersen + SoC vs SoC, NOK. ICER. The columns of the grid represent HR for effect (progression based on MiToS and survival) ranging from the lowest HRs (crossover-adjusted) to highest HRs (ITT analysis) in 25% intervals. The rows represent HRs for SOD1 ALS population vs overall ALS population.

HR progression HR mortality	0.61 0.12	0.63 0.26	0.65 0.39	0.67 0.53	0.69 0.66
HR SOD1 ALS	ICER				
1	kr 15,130,992	kr 17,648,847	kr 20,687,344	kr 24,697,987	kr 30,029,943
0.8	kr 14,143,336	kr 16,530,892	kr 19,407,579	kr 23,250,967	kr 28,445,623
0.6	kr 13,100,922	kr 15,332,482	kr 18,014,973	kr 21,647,522	kr 26,654,193
0.4	kr 12,104,518	kr 14,156,853	kr 16,629,301	kr 20,035,952	kr 24,851,895
0.2	kr 11,732,737	kr 13,658,535	kr 16,027,939	kr 19,398,515	kr 24,373,174
0.1	kr 13,523,358	kr 15,715,979	kr 18,487,635	kr 22,575,595	kr 28,915,122

Table 25: JNHB base case results for tofersen + SoC vs SoC, NOK. Incremental costs. The columns of the grid represent HR for effect (progression based on MiToS and survival) ranging from the lowest HRs (cross-over-adjusted) to highest HRs (ITT analysis) in 25% intervals. The rows represent HRs for SOD1 ALS population vs overall ALS population.

HR progression HR mortality	0.61 0.12	0.63 0.26	0.65 0.39	0.67 0.53	0.69 0.66
HR SOD1 ALS	**Incremental cost**				
1	kr 11,812,901	kr 8,862,227	kr 7,543,668	kr 6,698,840	kr 6,115,818
0.8	kr 13,191,473	kr 10,100,730	kr 8,628,893	kr 7,659,344	kr 6,980,001
0.6	kr 14,897,498	kr 11,806,493	kr 10,190,362	kr 9,076,402	kr 8,274,203
0.4	kr 16,941,374	kr 14,202,803	kr 12,552,758	kr 11,322,707	kr 10,389,897
0.2	kr 19,109,659	kr 17,432,326	kr 16,181,855	kr 15,107,951	kr 14,203,003
0.1	kr 19,985,286	kr 19,144,384	kr 18,432,781	kr 17,755,996	kr 17,133,965

Table 26: JNHB base case results for tofersen + SoC vs SoC. Incremental QALYs. The columns of the grid represent HR for effect (progression based on MiToS and survival) ranging from the lowest HRs (crossover-adjusted) to highest HRs (ITT analysis) in 25% intervals. The rows represent HRs for SOD1 ALS population vs overall ALS population.

HR progression HR mortality	0.61 0.12	0.63 0.26	0.65 0.39	0.67 0.53	0.69 0.66
HR SOD1 ALS	**Incremental QALY**				
1	0.78	0.50	0.36	0.27	0.20
0.8	0.93	0.61	0.44	0.33	0.25
0.6	1.14	0.77	0.57	0.42	0.31
0.4	1.40	1.00	0.75	0.57	0.42
0.2	1.63	1.28	1.01	0.78	0.58
0.1*	1.48	1.22	1.00	0.79	0.59

**The survival (and QALYs) more than doubles when changing HR from 0,2 to 0,1, and the increase affects SoC slightly more. Relatively, patients in SoC spend more time in better health states.*

5.2.2 JNHB sensitivity analyses

JNHB sensitivity analyses are presented in Table 27 below. The middle ICER value from the JNHB base case grid is used as a reference for the scenarios. This middle ICER value is based on a HR 0.4 for SOD1 ALS population vs overall ALS, HR for progression of 0.65, and HR for survival of 0.39. This middle value does not represent the most plausible scenario but rather was chosen from pragmatic reasons to show sensitivity of the main results to alternative scenarios. A summary of justification for the sensitivity analyses can be found below the table.

Table 27: JNHB sensitivity analyses for tofersen +SoC vs SoC, NOK

Sensitivity analyses		Incr. costs	Incr. QALYs	Cost/QALY
Base case (BC) middle scenario value		**12,552,758**	**0.75**	**16,629,301**
Discounting (BC: 4% and 3%)	0%	14,052,284	0.94	14,919,890
	5%	12,240,093	0.72	17,057,833
Age at model entry (BC: 49 years)	39 years	12,552,758	0.76	16,422,880
	59 years	12,552,758	0.76	16,613,464
Backward transitions to a lower MiToS stage (BC: allowed)	Excluded	11,207,084	0.50	22,260,008
Use of staging system (BC:MiToS)	King's staging system	13,339,584	0.65	20,648,730

Utility weights (BC: sourced from VALOR, VALOR OLE and adjusted: 0.6 for stage 0, 0.4 for stage 1, 0.20 for stage 2 and 3, 0.15 for stage 4)	Sourced from Moore et al: 0.71 for stage 0, 0.48 for stage 1, 0.36 for stage 2, 0.33 for stage 3, 0.25 for stage 4	12,552,758	0.92	13,653,639
	Alternative adjustment of utilities from VALOR, VALOR+OLE: 0.6 for stage 0, 0.4 for stage 1, 0.18 for stage 2, 3, and 4	12,552,758	0.75	16,675,446
Adverse event utility decrements (BC: -0.0072, 7 days)	Increased to -0.0144	12,552,758	0.74	16,908,090
Stopping rule (BC: no treatment stop)	Treatment stop in MiToS stage 4	12,228,378	0.74	16,518,598
	Treatment stop in MiToS stage 3/4	11,634,723	0.70	16,513,324
Discontinuation probability per 4 weeks (*BC:1.02%)*	Increased to 1.5% in all stages	10,550,321	0.62	17,151,375
	Increased to 2% in all stages	9,035,304	0.51	17,716,324
Health care resource use in MiToS stages (BC: Moore et al 2019)	10% more resource use	12,576,750	0.75	16,661,084
	10% less resource use	12,528,766	0.75	16,597,517
Cost of genetic testing *(BC:excluded)*	Cost of genetic testing included (4.3.3)	12,662,208	0.75	16,774,295
Transportation and patient time cost	Transportation and patient time cost excluded	12,457,985	0.75	16,503,750

Age at model entry. Since ALS age onset varies between 40-60 years old, age at model entry of 49 years old +/- 10 years is tested but has a minor impact on the ICER.

Backward transitions to a lower MiToS stage. Backward transitions are accepted in JNHB's base case given the improvement in ALSFRS-R observed in VALOR+OLE and some improvements in MiToS staging observed in the tofersen group in VALOR Part C. However, Biogen has not presented empirical evidence that supports improvement in MiToS/King's staging in the SoC arm. Exclusion of backward transitions substantially increases the ICER (+5.5 mln NOK).

Use of staging system. In agreement with Biogen's main scenario, JNHB uses MiToS staging in the base case and test King's staging in a scenario. The two staging systems are complementary and there is no clear superiority of one over another. However, the impact of the classification system on the results is substantial (+4 mln NOK increase in the ICER with King's). Note that Biogen's model automatically selected the Moore et al publication as a source of utilities when King's staging was selected. JNHB overwrote the utility values with values from VALOR+OLE.

Utility weights. JNHB changed the source of utility value from the Moore et al publication (preferred by Biogen) to VALOR+OLE as this is the source of efficacy data in the model. To account for implausibility of increased utilities in Stage 3 compared to Stage 2, JNHB used one weighted utility of 0.20 in both stages. An alternative value of 0.18 for Stages 2, 3 and 4 does not affect the ICER much. This shows that JNHB arbitrary adjustment of utility values has a minimal impact on the results. It is rather the choice of the utility source that has the largest impact. The use of the Moore publication in a scenario shows a decrease in the ICER of -3 mln.

Stopping rule. In the base case JNHB agreed to exclude stopping rules for treatment with tofersen due to a lack of guidelines on treatment in the Nordics. There is a consensus among

the clinical experts consulted in all the Nordic countries that it is meaningful to have a stopping-criteria, and that this may be at later stages in the disease. Stopping rules of 100% in MiToS stage 4 and 100% in stages 3 and 4 were tested. Both the incremental costs and the incremental QALY decrease when adding stopping rules, and the ICER is reduced by around 110,000 NOK in both scenarios.

Discontinuation probability. In the base case JNHB used Biogens treatment discontinuation probabilities from VALOR. Based on comments from clinical experts, there are reasons to believe that the discontinuation probability is higher. When increasing the discontinuation probability to 1.5% and 2% the ICER is increased by 0.5 mln NOK and 1 mln NOK respectively.

Health care resource use. JNHB accepted the health state resource use from Moore et al, but the resource use is uncertain since it is derived from a UK perspective. Sensitivity analysis was performed to explore increased and decreased resource use. Adjusting the resource use by 10% in either direction results in a change of 30,000 NOK in the ICER.

Genetic testing. JNHB accepted the exclusion of genetic testing in the base case as the practice for testing patients varies and Norwegian ALS patients are offered testing as part of the GAIN study currently. Usually, only patients with familial ALS would be routinely tested, therefore a scenario with the costs of testing patients with sporadic ALS was explored. Routine testing of all patients, as opposed to only familiar ALS patients, increases the ICER with around 145,000 NOK.

Transportation and patient time cost. Introduction of tofersen would require patients to travel for the administration of the pharmaceutical. Sweden and Finland do not include this cost in their analysis. A sensitivity analysis has been conducted to explore the effect these costs have in the model. The ICER is reduced by around 130,000 NOK, which is a relatively small change at this level.

5.3 Patient numbers

Biogen used country specific references for the prevalence of ALS and SOD1 ALS (Table 28) to calculate the estimated number of patients with SOD1-ALS expected to be eligible for tofersen treatment. The prevalence of ALS varied from 0.006% in Sweden to 0.0119% in Finland. The proportion of SOD1 ALS varied from 2% in Denmark to assumed 20% in Iceland. Market share of tofersen varied between 11% in Finland and 100% in Iceland. The total number of patients treated with tofersen in the Nordics in 2029 was estimated to be 31 (Table 29).

Table 28: Epidemiology of ALS and SOD1-ALS in the Nordic countries

Input parameter	Value	Source
FINLAND		
Prevalence of ALS	0.0119% (11.9/100,000)	Hanhisuanto et al. (2023) (70)
Prevalence of FALS	NR	
Prevalence of SALS	NR	
Prevalence of *SOD1* ALS	7%	Laaksovirta, H. (2023) (26)
NORWAY		
Prevalence of ALS	0.008% (7.6/100,000)	Olsen et al. (2022) (71)
Prevalence of FALS	12%	Olsen et al. (2022) (71)
Prevalence of SALS	88%	Olsen et al. (2022) (71)
Prevalence of *SOD1* ALS	4%	Olsen et al. (2022) (71)
SWEDEN		
Prevalence of ALS	0.006% (6.23/100,000)	Brown et al. (2021) (5)
Prevalence of FALS	NR	
Prevalence of SALS	NR	
Prevalence of *SOD1* ALS	4-5%	Socialstyrelsen (2022) (72)
DENMARK		
Prevalence of ALS	0.007% (6.8/100,000)	RehabiliteringsCenter for Muskelsvind (n.d.) (73)
Prevalence of FALS	15-20%	Lindquist et al. (2014) (74)
Prevalence of SALS	90-95%	Lindquist et al. (2014) (74)
Prevalence of *SOD1* ALS	2%	Lindquist et al. (2014) (74)
ICELAND		
Prevalence of ALS	0.009% (27/270,000)	Icelandic MND association (75)
Prevalence of FALS	NR	
Prevalence of SALS	NR	
Prevalence of *SOD1* ALS	20%	Based on assumed ALS prevalence and actual number of ALS SOD1 patients

Table 29: Estimated number of patients with SOD1-ALS who are expected to be eligible for treatment and also treated with tofersen

Country	2025	2026	2027	2028	2029
Finland: total eligible	38	38	38	39	39
Treated with tofersen, n (11%)	**4.19**	**4.21**	**4.22**	**4.24**	**4.25**
Norway: total eligible	14	15	15	15	15
Treated with tofersen, n (35%)	**5.03**	**5.08**	**5.12**	**5.16**	**5.20**
Sweden: total eligible	25	26	26	26	26
Treated with tofersen, n (48%)	**12.20**	**12.27**	**12.34**	**12.42**	**12.48**
Denmark: total eligible	7	7	7	7	7
Treated with tofersen, n (61%)	**4.02**	**4.01**	**4.03**	**4.05**	**4.06**
Iceland: total eligible	**5**	**5**	**5**	**5**	**5**

Treated with tofersen, n (100%)	5	5	5	5	5

JNHB discussion

JNHB has validated the calculated numbers of SOD1 ALS patients and the market share of tofersen with the clinical experts. Experts from Norway and Denmark agree that approximately 5 and 4 patients, respectively, will be treated with tofersen per year. In Finland, the calculated 4 patients per year may be an overestimation as patients with homozygous D91A and heterozygous A90V who are slow progressors may not be eligible for tofersen. The Finish experts suggested that in slow progressors the AEs will likely override the benefits of tofersen in the long run. In contrast, the estimated 12 patients of tofersen treated patients per year in Sweden may be an underestimation. Sweden has one of the highest incidence numbers of ALS in the world (76), and the Swedish clinical expert believes that based on prevalence of 7-8/100 000, and 4-5% of SOD1 ALS, there are 40 patients yearly, of which 24 will be potentially treated with tofersen. The Swedish expert does not anticipate that slow progressive variants would preclude patients from the tofersen treatment.

In addition, as the mean survival of SOD1 ALS patients is expected to be longer in the Nordics, JNHB estimates that the number of patients will increase over the years.

JNHB conclusion:
The estimated number of 31 patients treated with tofersen per year in the Nordics may be underestimated. Specifically, Swedish experts believe that the number of tofersen-treated patients in Sweden will be twice the number estimated by Biogen. In addition, the constant number of patients per year is unlikely to be representative due to the longer expected survival of SOD1 ALS patients in the Nordics.

6 Post launch evidence generation

6.1 Regulatory perspective

The Committee for Human Medicinal Products adopted a list of specific obligations for continued data generation, which is mandatory for a marketing authorisation under exceptional circumstances. Specific obligations are described in Figure 12.

Description	Due Date
To further investigate the long-term efficacy and safety of tofersen in the treatment of SOD1-ALS, the MAH shall submit the final results of the long-term extension study (Study 233AS102).	by 30 September 2025
-To further investigate if initiation of tofersen in presymptomatic SOD1ALS patients can delay or even prevent emergence of clinically manifested ALS (CMALS), the MAH shall submit the final results of the phase 3 study in patients with clinically presymptomatic SOD1-ALS (Study ATLAS 233AS303).	by 31 December 2028
To further characterise variant-specific survival, the MAH will provide the final results of the descriptive integrated analyses of disease duration (survival) by SOD1 variant-type in tofersen-treated (Studies 101/102; disease registries) vs. patients untreated with tofersen (disease registries, natural history datasets/literature).	by 30 June 2027
To further evaluate the long-term safety of tofersen in patients with SOD1-ALS, the MAH shall conduct and submit the results of an observational registry-based study 233AS401 according to the agreed protocol.	Annually (with annual reassessment)
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.	Annually (with annual reassessment)

Figure 12 Specific Obligation to complete post-authorisation measures for the marketing authorization (10).

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Appendix 1. Transition probabilities based on Thakore et al (2018) and the calibration exercise

Transition probabilities for SOC used in the economic model are presented in Table 30Table 30 and Table 31.

Table 30: 4-Weekly Transition Probabilities, Baseline to Month 12, SoC – Thakore et al. (2018) [PRO-ACT] [MiToS] (49)

From/to	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	Death
Thakore, Lapin (49), converted to 4-weekly transitions						
Stage 0	0.905	0.078	0.012	0.002	0.000	0.002
Stage 1	0.030	0.872	0.066	0.013	0.003	0.016
Stage 2	0.004	0.054	0.816	0.058	0.021	0.047
Stage 3	0.000	0.008	0.041	0.775	0.092	0.084
Stage 4	0.000	0.001	0.006	0.032	0.856	0.106

MiToS = Milano-Torino functional staging system; PRO-ACT = Pooled Resource Open-Access ALS Clinical Trials; SoC = standard of care; TP = transition probability.

Note: Transitions between stages in the above table may sum to greater than 1 due to rounding.

Source: Derived based on data reported by Thakore et al (2018)

Table 31: 4-Weekly Transition Probabilities, 12 months+, SoC – Calibrated Thakore, Lapin (49) et al, 4-weekly calibrated [PRO-ACT] [MiToS] (49)

From/to	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	Death
Stage 0	0.884	0.076	0.012	0.002	0.000	0.026
Stage 1	0.027	0.788	0.059	0.012	0.003	0.111
Stage 2	0.004	0.047	0.730	0.051	0.018	0.149
Stage 3	0.000	0.007	0.036	0.694	0.081	0.181
Stage 4	0.000	0.001	0.005	0.028	0.754	0.213

MiToS = Milano-Torino functional staging system; PRO-ACT = Pooled Resource Open-Access ALS Clinical Trials; SoC = standard of care; TP = transition probability.

Note: Transitions between stages in the above table may sum to greater than 1 due to rounding.

Source: Derived based on data reported by Thakore et al (2018)

The calibration exercise for 12 months + was initiated as follows:

1. 3-months transition probabilities from Thakore et al were converted to 1-month transition probabilities (Table 32).

Table 32: One-monthly Transition Probabilities, SoC – Thakore et al. (2018) [PRO-ACT] [MiToS] (49)

From/to	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	Death
Stage 0	0.898	0.084	0.014	0.002	0.000	0.002 (pd_{HS0})
Stage 1	0.032	0.862	0.071	0.014	0.003	0.017 (pd_{HS1})
Stage 2	0.004	0.058	0.801	0.063	0.023	0.051 (pd_{HS2})
Stage 3	0.000	0.008	0.044	0.757	0.099	0.091 (pd_{HS3})
Stage 4	0.000	0.001	0.006	0.035	0.844	0.114 (pd_{HS4})

MiToS = Milano-Torino functional staging system; PRO-ACT = Pooled Resource Open-Access ALS Clinical Trials; SoC = standard of care; TP = transition probability.

Note: Probabilities of death are henceforth labelled as pd_{HS0}, pd_{HS1}, pd_{HS2}, pd_{HS3}, and pd_{HS4}, corresponding to the probability of death for Stage 0, Stage 1, Stage 2, Stage 3, and Stage 4, respectively.

Source: Derived based on data reported by Thakore et al (2018)

2. Excel solver was used to adjust the transition probability of death from each health state. It was decided to vary the transition probability of death in the calibration exercise because this was the outcome most significantly underestimated by the modeled prevalences in Thakore et al. To do this, death was factored out of the transition probability matrix by dividing the transition probabilities in each 'from' row in Table 32 by 1–the probability of death for each health state. It is noted that this step implicitly implies that the probability of death is uniform across health states. The resultant transition probability matrix with death factored out is outlined in Table 33, with each calculation shown in brackets.

Table 33: One-monthly Transition Probabilities With Death Removed, SoC – Thakore et al. (2018) [PRO-ACT] [MiToS] (49)

From/to	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
Stage 0	0.8997 (= 0.898/[1−pd_{HS0}])	0.0844 (= 0.084/[1−pd_{HS0}])	0.0135 (= 0.014/[1−pd_{HS0}])	0.0020 (= 0.002/[1−pd_{HS0}])	0.0003 (= 0.000/[1−pd_{HS0}])
Stage 1	0.0329 (= 0.032/[1−pd_{HS1}])	0.8768 (= 0.862/[1−pd_{HS1}])	0.0724 (= 0.071/[1−pd_{HS1}])	0.0144 (= 0.014/[1−pd_{HS1}])	0.0034 (= 0.003/[1−pd_{HS1}])
Stage 2	0.0046 (= 0.004/[1−pd_{HS2}])	0.0611 (= 0.058/[1−pd_{HS2}])	0.8444 (= 0.801/[1−pd_{HS2}])	0.0662 (= 0.063/[1−pd_{HS2}])	0.0237 (= 0.023/[1−pd_{HS2}])
Stage 3	0.0004 (= 0.000/[1−pd_{HS3}])	0.0092 (= 0.008/[1−pd_{HS3}])	0.0483 (= 0.044/[1−pd_{HS3}])	0.8330 (= 0.757/[1−pd_{HS3}])	0.1091 (= 0.099/[1−pd_{HS3}])
Stage 4	0.0000 (= 0.000/[1−pd_{HS4}])	0.0008 (= 0.001/[1−pd_{HS4}])	0.0068 (= 0.006/[1−pd_{HS4}])	0.0393 (= 0.035/[1−pd_{HS4}])	0.9531 (= 0.844/[1−pd_{HS4}])

MiToS = Milano-Torino functional staging system; PRO-ACT = Pooled Resource Open-Access ALS Clinical Trials; SoC = standard of care; TP = transition probability.

Source: Derived based on data reported by Thakore et al (2018)

3. Then, death was reintroduced by multiplying the resultant transition probabilities in Table 34 by 1-the probability of death for each health state, which numerically returned the original SoC transition probability matrix except each transition probability was linked to the probability of death by use of an Excel formula.

Table 34: One-monthly Transition Probabilities Linked to Death, SoC – Thakore et al. (2018) [PRO-ACT] [MiToS] (49)

From/to	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	Death
Stage 0	0.8997 × (1−pd_{HS0}) = 0.8976	0.0844 × (1−pd_{HS0}) = 0.0842	0.0135 × (1−pd_{HS0}) = 0.0135	0.0020 × (1−pd_{HS0}) = 0.0020	0.0003 × (1−pd_{HS0}) = 0.0003	pd_{HS0} = 0.0023
Stage 1	0.0329 × (1−pd_{HS1}) = 0.0323	0.8768 × (1−pd_{HS1}) = 0.8620	0.0724 × (1−pd_{HS1}) = 0.0712	0.0144 × (1−pd_{HS1}) = 0.0142	0.0034 × (1−pd_{HS1}) = 0.0033	Pd_{HS1} = 0.0169
Stage 2	0.0046 × (1−pd_{HS2}) = 0.0044	0.0611 × (1−pd_{HS2}) = 0.0580	0.8444 × (1−pd_{HS2}) = 0.8014	0.0662 × (1−pd_{HS2}) = 0.0629	0.0237 × (1−pd_{HS2}) = 0.0225	Pd_{HS2} = 0.0509
Stage 3	0.0004 × (1−pd_{HS3}) = 0.0003	0.0092 × (1−pd_{HS3}) = 0.0084	0.0483 × (1−pd_{HS3}) = 0.0439	0.8330 × (1−pd_{HS3}) = 0.7572	0.1091 × (1−pd_{HS3}) = 0.0992	Pd_{HS3} = 0.0910
Stage 4	0.0000 × (1−pd_{HS4}) = 0.0000	0.0008 × (1−pd_{HS4}) = 0.0007	0.0068 × (1−pd_{HS4}) = 0.0060	0.0393 × (1−pd_{HS4}) = 0.0348	0.9531 × (1−pd_{HS4}) = 0.8444	Pd_{HS4} = 0.1141

MiToS = Milano-Torino functional staging system; PRO-ACT = Pooled Resource Open-Access ALS Clinical Trials; SoC = standard of care; TP = transition probability.

Source: Derived based on data reported by Thakore et al (2018)

4. Next, constraints were added into Excel's solver function to ensure the calibration exercise returned outcomes that were logical and were aligned with data from the PRO-ACT database. Transition probabilities of death were set as the 'changing variable' cells (i.e., pdHS0 pdHS1, pdHS2, pdHS3, and pdHS4 were varied), which were varied so that outcomes from the Markov trace at month 14, 16, 18, 20, 22, and 24 matched the corresponding absolute prevalences from the digitized PRO-ACT data. The sum of transitions from each health state to other health states being equal to 1 and the probability of death increasing for increasing disease severity were additional constraints that were included in Excel solver. The object solved was the sum of transition probabilities from Stage 4 to other stages, which was set to equal 1; it is noted that this could have been replaced with any of the other constraints. Unconstrained variables were also set to be non-negative, and the Generalized Reduced Gradient (GRG) nonlinear solving method was used. The resultant transition probability matrix is shown below in Table 35.

Table 35. One-monthly Transition Probabilities Linked to Death, SoC – Thakore et al. (2018) [PRO-ACT] [MiToS] (49)

From/to	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	Death
Stage 0	0.8741	0.0820	0.0132	0.0020	0.0003	0.0284
Stage 1	0.0289	0.7715	0.0637	0.0127	0.0030	0.1202
Stage 2	0.0039	0.0513	0.7092	0.0556	0.0199	0.1601
Stage 3	0.0003	0.0074	0.0389	0.6707	0.0879	0.1948
Stage 4	0.0000	0.0006	0.0053	0.0303	0.7353	0.2285

MiToS = Milano-Torino functional staging system; PRO-ACT = Pooled Resource Open-Access ALS Clinical Trials; SoC = standard of care; TP = transition probability.
Source: Derived based on data reported by Thakore, Lapin (49)

Appendix 2. Crossover-adjustment methodology

From company's submission

RPSFTM uses a causal model to produce counterfactual survival times in order to estimate a causal treatment effect if treatment had not occurred: counterfactual event times = $T_i^{off} + T_i^{on}\exp(\psi)$, where T_i^{off} *and* T_i^{on} represent the time spent off and on treatment, and ψ represents the treatment effect (77, 78). The treatment effect, ψ, is estimated by balancing average counterfactual event times between treatment groups. A g-estimation procedure (grid search) is used to find ψ. Once ψ has been identified, survival times under no treatment can be calculated for the control group. We can then obtain an estimate of the treatment effect adjusted for treatment switching by comparing the observed experimental treatment group survival times with the counterfactual survival times for the control group.

The results from the ITT analysis, RPSFTM and a supplemental iterative parameter estimation (IPE) analysis are presented in the table below.

Table 36 Hazard ratios adjusted for baseline plasma NfL and riluzole or edaravone use for the associa-tion between tofersen and time to death from VALOR baseline and time to transition to later MITOS and King's stages using ITT analyses, RPSFTM, and IPE to address treatment switching

	ITT	RPSFTM	IPE
Time to death using original baseline, hazard ratio (tofersen vs placebo to tofersen), 95% CI	0.27 (0.08, 0.89)	0.1 (0.01, 0.81)	0.1 (0.01, 0.81)
Time to transition from original baseline to later MITOS stages (excluding death) hazard ratio (tofersen vs placebo to tofersen), 95% CI	0.69 (0.4, 1.2)	0.61 (0.29, 1.27)	0.65 (0.32, 1.47)
Time to transition from original baseline to later King's stages (excluding death) hazard ratio (tofersen vs placebo to tofersen), 95% CI	0.98 (0.56, 1.71)	0.98 (0.51, 1.87)	0.97 (0.52, 2.15)

Table 37 Number of overall subjects, subjects with an event, and subjects who were censored from VALOR + OLE baseline

	Number of subjects in placebo + delayed start tofersen	Number of subjects in early-start tofersen 100mg group	Number of subjects with an event in placebo + delayed start tofersen	Number of subjects with an event in early-start tofersen	Number of subjects who were censored in placebo + delayed start tofersen	Number of subjects who were censored in early-start tofersen

	100mg group		100mg group (%)	100mg group (%)	100mg group (%)	100mg group (%)
Time to death	36	72	6 (16.7)	8 (11.1)	30 (83.3)	64 (88.9)
Time to transition from original baseline to later MITOS stages	36	72	21 (58.3)	34 (47.2)	15 (41.7)	38 (52.8)
Time to transition from original baseline to later King's stages	36	72	19 (52.8)	40 (55.6)	17 (47.2)	32 (44.4)

Table 38 Assessment of the RPSFTM common treatment effect assumption

Outcome	Ratio of the treatment effect in the delayed-start group vs the early-start group	Multiplicative factor	RPSFTM hazard ratio (early-start group vs delayed-start group), 95% CI
Time to death			
Time to death	100%	-0.9454	0.0983 (0.0119, 0.8118)
Time to death	90%	-0.9408	0.0983 (0.0119, 0.8118)
Time to death	80%	-0.8996	0.1127 (0.0154, 0.8218)
Time to death	70%	-0.8752	0.1165 (0.0165, 0.8243)
Time to death	60%	-0.8304	0.1235 (0.0184, 0.8286)
Time to death	50%	-0.7891	0.1336 (0.0214, 0.8345)
Time to later MITOS stages			
Time to transition to later MITOS stages	100%	-0.9356	0.6105 (0.2943, 1.2665)
Time to transition to later MITOS stages	90%	-0.9144	0.6097 (0.2954, 1.2584)
Time to transition to later MITOS stages	80%	-0.8828	0.6105 (0.2964, 1.2576)

Time to transition to later MITOS stages	70%	-0.8573	0.6114 (0.2975, 1.2567)
Time to transition to later MITOS stages	60%	-0.8310	0.6114 (0.2975, 1.2567)
Time to transition to later MITOS stages	50%	-0.8072	0.6114 (0.2975, 1.2567)
Time to later King's stages			
Time to transition to later King's stages	100%	-0.0352	0.9779 (0.5107, 1.8722)
Time to transition to later King's stages	90%	-0.0352	0.9777 (0.5109, 1.8710)
Time to transition to later King's stages	80%	-0.0352	0.9777 (0.5109, 1.8710)
Time to transition to later King's stages	70%	-0.0349	0.9777 (0.5109, 1.8710)
Time to transition to later King's stages	60%	-0.0350	0.9777 (0.5109, 1.8710)
Time to transition to later King's stages	50%	-0.0350	0.9777 (0.5109, 1.8710)

From company's response to the list of questions on RPSFTM

RPSFTM were not pre-specified in the protocol, but were pre-specified as part of the integrated efficacy statistical analysis plan based on 28 February 2023 data cut. ITT analyses were conducted first, ignoring treatment switching, to be able to compare with the effect estimates adjusted for treatment switching after implementing RPSFTM. The ITT analyses examined the data according to the arms to which patients were randomized, regardless of whether they switched onto tofersen in the open-label extension. RPSFTM was then used to estimate counterfactual survival times in order to estimate a causal treatment effect if treatment had not occurred: counterfactual event times = (time off treatment) + (time on treatment) exp (treatment effect). The treatment effect is estimated by balancing average counterfactual event times between treatment groups. A g-estimation procedure (grid search) is used to find treatment effect. Once this has been identified, survival times under no treatment can be calculated for the control group. An estimate of the treatment effect adjusted for treatment switching can then be obtained by comparing the observed experimental treatment group survival times with the counterfactual survival times for the control group.

Justification for the common treatment effect assumption

We do not believe it is practically possible to test the common treatment effect assumption for two reasons. First, testing the common treatment effect would require knowledge of "predictive patient characteristics" that can potentially separate those with higher treatment effect from those with lower treatment effect. At this point, we do not know which patient characteristics have this capability. It would need substantial efforts and data to better understand this topic. Second, testing heterogeneity of treatment effect would require large sample size to achieve adequate statistical power. With around 100 subjects we are underpowered.

Re-censoring

We did not perform re-censoring in the analyses. Re-censoring is usually performed to address informative censoring due to the existence of control group non-switchers. Adjusting survival times for control group switchers but not control group non-switchers can induce informative censoring. As discussed in White et al. (79) re-censoring of counterfactual survival time under the RPSFTM model is necessary only if the treatment duration is related to prognostic factors. The duration of treatment is determined by the time to switch to treatment and the cutoff date of the open-label extension study, both are set by the VALOR study design. Out of 36 subjects initially assigned to the placebo arm, 32 (89%) participated in the open-label extension study following the study design. Therefore, the vast majority of the control arm patients switched to treatment following study design, a process not related to their prognostic factors. Therefore, there is minimum bias due to informative censoring. Re-censoring may actually induce a loss of longer-term survival information which can be problematic when long-term survival effects are required for HTA decision making.

The grid range searched

The range of the grid search is [-2,2] with a grid resolution of 0.0001.

The estimated treatment effect parameter (with 95% CI), and g-estimation output

The following graphs show the Z statistic of a log-rank test of the equality of the counterfactor survival curves under no treatment between the two arms as a function of the value of the treatment effect parameter. Point estimate is the value of the parameter corresponding to Z=0. The 95% CI of the treatment effect parameter include all values of the treatment effect parameter corresponding to a $|Z| \leq 1.96$.

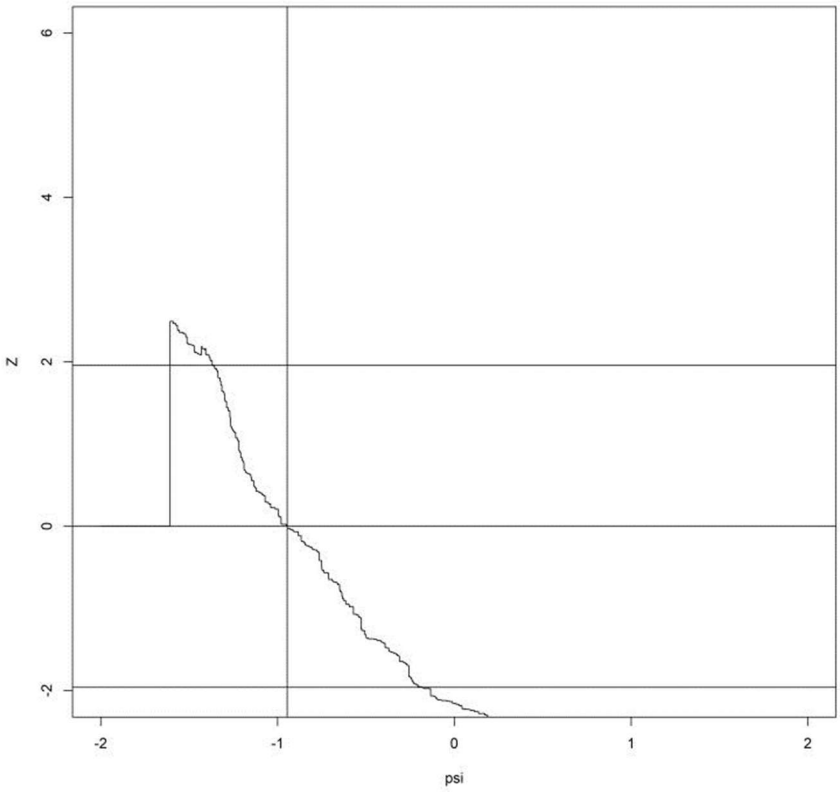

Figure 13 Z Graph plotting the z test statistic against the value of the multiplicative factor identified using RPSFTM for time to death from original baseline in overall ITT population.

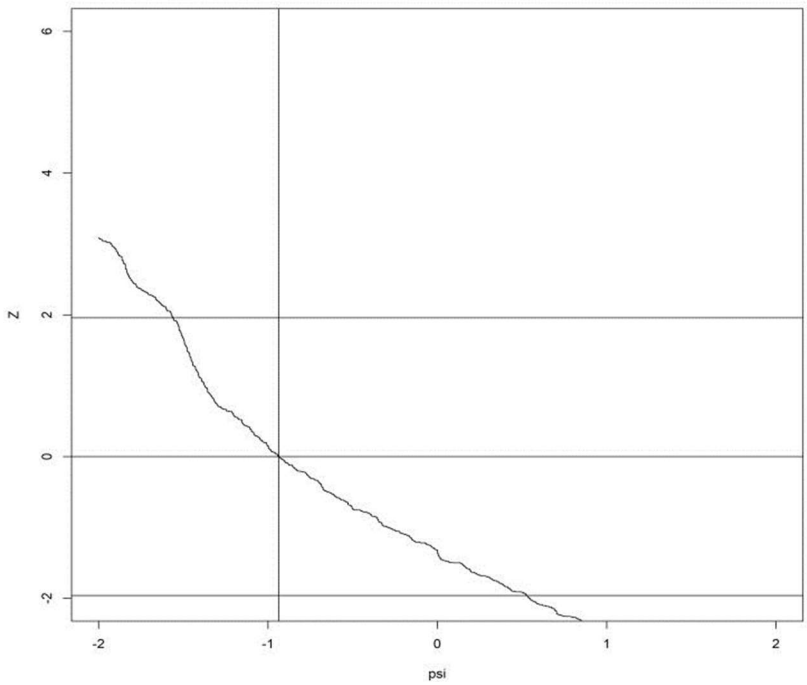

Figure 14 Z Graph plotting the z test statistic against the value of the multiplicative factor identified using RPSFTM for time to later MITOS stages from original baseline in overall ITT population.

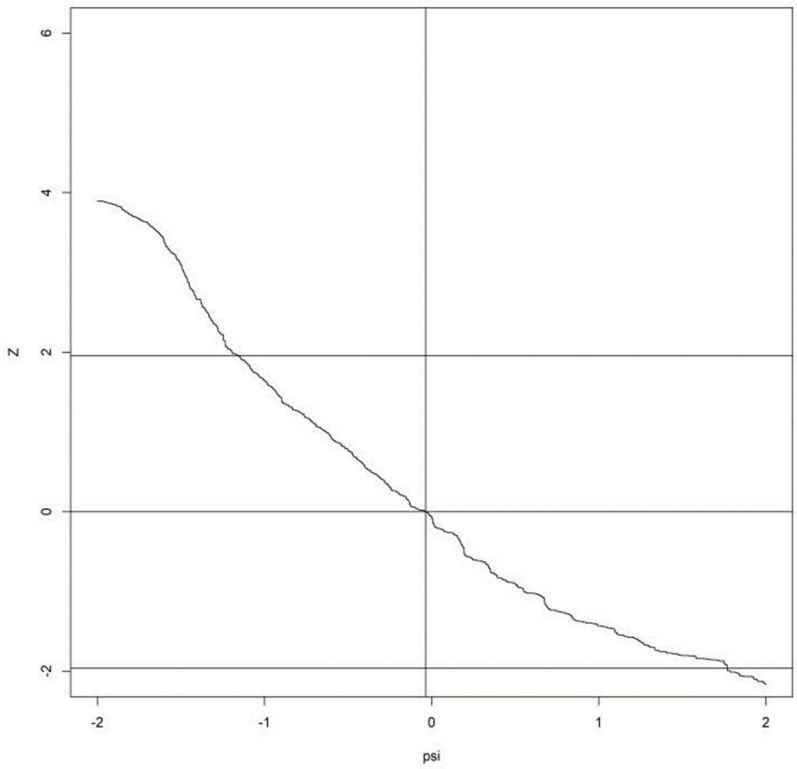

Figure 15 Z Graph plotting the z test statistic against the value of the multiplicative factor identified using RPSFTM for time to later King's stages from original baseline in overall ITT population.

Counterfactual survival times between randomized groups

The following graphs show the counterfactual survival curves under no treatment for both arms for the estimated value of the treatment effect.

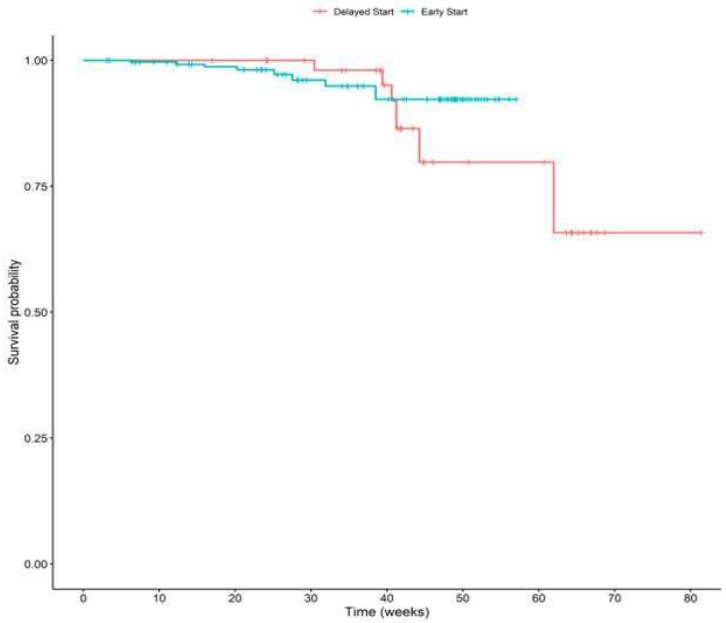

Figure 16 Counterfactual survival curves for time from baseline to death

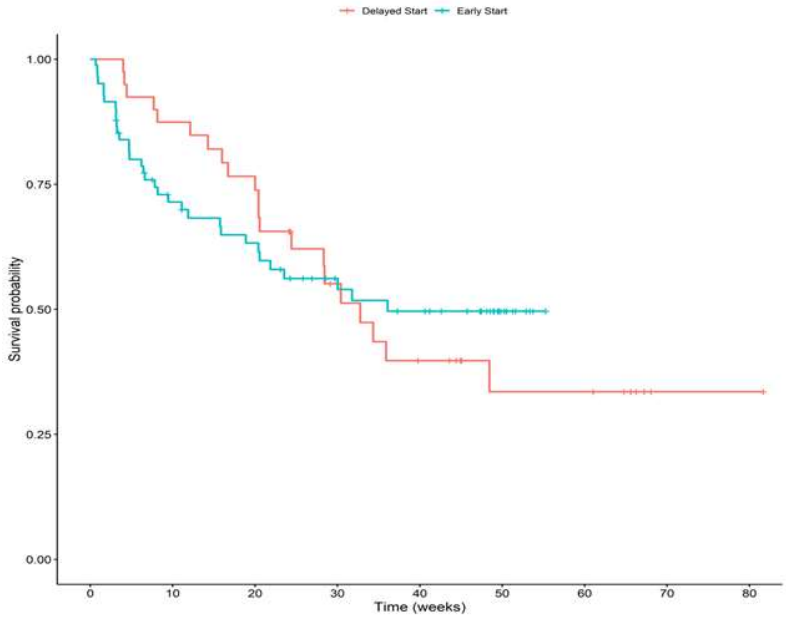

Figure 17 Counterfactual survival curves for time from baseline to later MITOS stages

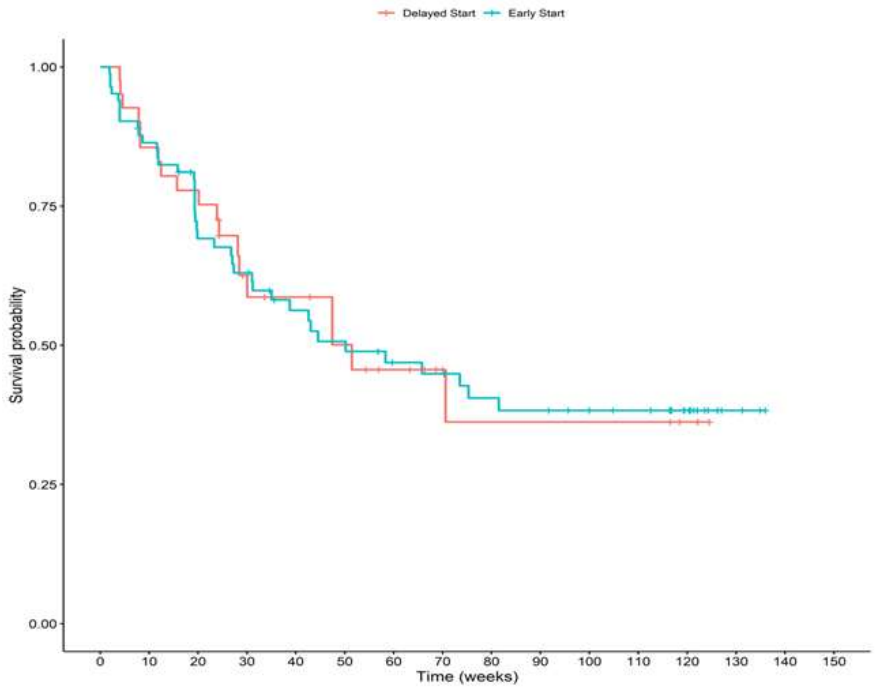

Figure 18 Counterfactual survival curves for time from baseline to later King's stages

The limitations of the RPSFTM and the impact on the study's conclusions

One limitation of the RPSFTM is that it relies on the rank preservation assumption, which states that the ranking of participants' potential outcomes under treatment is the same as the ranking of their potential outcomes under no treatment – the reasonableness of analyses based on this assumption remains to be determined since the effect of treatment often depends on participants' behaviours and characteristics. RPSFTM also depends on the assumption that the treatment effect is multiplicative on time (extends survival time by a fixed factor), every day on treatment leads to an immediate extension of survival (mortality decreases constantly during the study period), and that the benefit of treatment is the same for all patients at all times – violations of these assumptions may lead to biased counterfactual survival times.

A second limitation of RPSFTM is that in the study, there was some non-overlap in the counterfactual even curves under no treatment for the early-start and delayed-start participants for time to death, which suggests that there may be residual confounding of the association between tofersen and death in the RPSFTM analysis. Although the baseline covariates of plasma NfL and edaravone or riluzole use were adjusted for, there may be remaining imbalances between the treatment groups that were not controlled for.

A further limitation is potential violation of the common treatment effect assumption, which may not hold when the treatment effect in participants who switch is different from the effect in participants originally randomised to the experimental treatment. In the sensitivity analysis, the overall hazard ratios comparing the early-start group to the delayed-start group if the delayed-start group had remained on placebo in open-label extension for all outcomes remained similar when the magnitude of the ratio of the treatment effect in the early-start group vs delayed-start group was varied.

However, the counterfactual event curves for the treatment groups were non-overlapping for time to death and time to later MiToS stages when assessing the common treatment effect assumption. Therefore, residual confounding and model specification for the counterfactual

survival times are also potential concerns in the sensitivity analyses for the common treatment effect assumption. The analyses were also limited by the small size of the trial and the small number of deaths that were observed which reduced the precision of effect estimates.

Appendix 3. Utility studies identified via an SLR (span 1999-August 2023)

		Utility instrument					Data source	
Reference and country	Population and intervention	EQ-5D-3L	EQ-5D-5L	SG	Other instruments	Utilities by severity	RCT	Observational
Moore et al. (2018) UK	MND patients (used synonymously with ALS) (n = 595)		✓		ALSUI		✓	
McDermott et al. (2016) UK (HTA)	ALS patients: NIV and NIV + DPS (n = 74)	✓					✓	
Jones et al. (2014) UK	ALS patients on lithium carbonate (n = 214)	✓				✓ (King's CSS)	✓	
Winter et al. (2010) Germany	ALS patients (n = 37)	✓				✓ (ALSSS)		✓
López-Bastida et al. (2009) Spain	ALS patients (n = 63)	✓				✓ (High/low severity)		✓
Beusterein et al. (2005) US	ALS patients (n = 1,356)			✓		✓ ALS HSCS		✓
Green et al. (2003) UK	MND patients (n = 77)	✓		✓		✓ ALS HSS		✓
Kiebert et al. (2001) UK	ALS patients (n = 77)[c]			✓		✓ ALS HSS		✓
Meininger et al. (2017) 11 countries	ALS patients (n = 307)		✓				✓	
Kim et al. (2017)[b] South Korea	ALS patients (n = 202)	✓		✓		✓ ALS HSS		✓
Lapin et al. (2022) US	ALS patients (N = 578)	✓				✓ (early/late stage)		✓

Reference and country	Population and intervention	Utility instrument				Utilities by severity	Data source	
		EQ-5D-3L	EQ-5D-5L	SG	Other instruments		RCT	Observational
Stenson et al. (2022)[b], UK	142 neurologists reported data on 880 ALS patients; complete EQ-5D-5L data were provided by 163 patients (or caregiver proxy).		✓			✓ (King's CSS & MiToS FCS)		✓
Wei et al. (2021) China	▪ ALS patients (N = 547)		✓			✓ (King's CSS)		✓
Lapin and Thakore (2021)[b] NR	ALS patients (N = 578)	✓				✓ (early/late disease)		✓
Hagan et al. (2021b)[b] US	Caregivers of ALS patients: n = 19		✓					✓
Schischlevskij et al. (2021) Germany	Caregivers of ALS patients (N = 249)		✓					✓
Peseschkian et al. (2021) Germany	▪ ALS patients (N = 325)		✓			✓ (King's CSS)		✓
Gebrehiwet and Sarocco (2020a)[b], multicountry	Patients with ALS (N not reported)	✓[d]				✓ (MiToS FCS)	✓	
Schönfelder et al. (2020) Germany	ALS patients (N = 156)		✓			✓ (King's CSS)		✓
Moore et al. (2019) UK	Patients with MND (used synonymously with ALS) (N = 595)		✓		ALSUI	✓ (King's CSS & MiToS FCS)		✓
Calvert et al. (2013) (5153), UK	MND patients (The definition of MND in relation to ALS was unclear) (N = 59)	✓						✓

Reference and country	Population and intervention	Utility instrument				Utilities by severity	Data source	
		EQ-5D-3L	EQ-5D-5L	SG	Other instruments		RCT	Observational
Peters et al. (2021) Canada	ALS patients (N = 52)		✓					✓
NICE (2017) UK	ALS patients (N = 74), active and sham stimulation (RespiStimALS) groups	✓					✓	
Gebrehiwet et al. (2023), multicountry	Patients with ALS (N = 456) who received at least 1 dose of the double-blind study drug, and had ALSFRS-R assessed at baseline and at least 1 post-baseline assessment. Reldesemtiv and placebo		✓				✓	
Gould et al. (2023), UK	MND/ALS (N = 29) patients diagnosed based on using the El Escorial criteria, and caregivers of patients with MND/ALS Acceptance and commitment therapy		✓					✓
Caballero-Eraso et al. (2023), Spain	Adults with ALS (N = 23) according to El Escorial criteria		✓					✓
Total		11	13	4			7	19

ALS = amyotrophic lateral sclerosis; ALSSS = Amyotrophic Lateral Sclerosis Severity Scale; ALSUI = ALS Utility Index; CSS = clinical staging system; DPS = diaphragm pacing stimulator; HSCS = Health State Classification System; HSS = Health State Scale; HTA = health technology assessment; MND = motor neurone disease; NIV = noninvasive ventilation; RCT = randomized controlled trial; SG = standard gamble; UK = United Kingdom; US = United States.

[a] Detailed data extractions for economic evaluations are reported in Table C-2.

[b] Abstract only.

[c] The same study population/sample as Green et al. (2003).

[d] The version of EQ-5D is not clarified in the source. As the use of the term "EQ-5D" often refers to EQ-5D-3L. There was no need to clarify in absence of EQ-5D-5L. An assumption was made that the instrument used was EQ-5D-3L.

Biogen's review of the preliminary Joint Nordic HTA Bodies HTA report on Qalsody (tofersen).

Factual inaccuracies identified

Page 4, Table 2: "233AS102, OLE, NCT03070119, Extension study to 233AS101 (16), Ongoing"	**Comment:** The OLE study was completed during 2024 **Suggested change:** Please change "Ongoing" to "Completed"
Page 28: "Interestingly, a similar analysis for edaravone showed no treatment effect beyond King's stage 2 (44)."	**Comment:** This observation concerning another pharmaceutical, with a different mechanism of action, is irrelevant for the current assessment and thus misleading. **Suggested change:** Please remove this sentence.
Page 29: "The effect of tofersen on survival has not been tested inferentially in VALOR Part C or VALOR+OLE. At week 52, 8/72 (11.1%) deaths were observed in the early-start tofersen group vs 6/36 (16.7%) in the late-start tofersen group (data cut-off 28 february 2022). At week 104, the number of deaths increased to 11/72 (15.3%) in the early-start tofersen vs 7/36 (19.4%) late-start tofersen groups (the latest data cut off, 28 february 2023) (7)."	**Comment:** Please note that 52 and 104 weeks are the minimum follow-up times at these data cut-offs (DCO). At the week 52 DCO (2022 DCO), the time on study for patients alive ranged from 52 to ~156 weeks (median 88.6 weeks). At the week 104 DCO (2023 DCO), the time on study for patients alive ranged from 104 to ~208 weeks. The numbers of deaths reported here for each data cut-off (DCO) include deaths occurring at later timepoints than 52 and 104 weeks, respectively. **Suggested change:** "The effect of tofersen on survival has not been tested inferentially in VALOR Part C or VALOR+OLE. At the **52-week data cut-off**, 8/72 (11.1%) deaths were observed in the early-start tofersen group vs 6/36 (16.7%) in the late-start tofersen group (data cut-off 28 february 2022). At the **104-week data cut-off**, the number of deaths increased to 11/72 (15.3%) in the early-start tofersen vs 7/36 (19.4%) late-start tofersen groups (the latest data cut off, 28 february 2023) (7)."

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20.02.2025

MBA/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	26.03.2025
Leverandør	Biogen
Lægemiddel	Qalsody (tofersen)
Ansøgt indikation	Behandling af amyotrofisk lateral sklerose (ALS) med SOD1 mutation
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Qalsody (tofersen):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Qalsody	100 mg (1 stk.)	150.095,52	[redacted]	[redacted]

Prisen er ikke betinget af Medicinrådets anbefaling.

Informationer fra forhandlingen

[redacted]

[redacted]

Aftaleforhold

[redacted] Leverandøren har mulighed for at sætte prisen ned i hele aftaleperioden.

Konkurrencesituationen

Den årlige lægemiddeludgift for Qalsody samt Glentek (riluzol) fremgår af tabel 2.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandling/år (SAIP, DKK)
Qalsody	100 mg (1 stk.)	Opstart: 100 mg 3 gange med 14 dages mellemrum. Herefter 100 mgen gang hver 28. dag, intratekal	[redacted]	[redacted]
Glentek*	50 mg (56 stk.)	50 mg 2 gange dagligt, oral	[redacted]	[redacted]

* [redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Kommentar	Link
Norge	Under vurdering	JNHB rapport	Link til vurdering
England	Under vurdering		Link til vurdering
Sverige	Under vurdering	JNHB rapport	Link til vurdering

Opsummering

[redacted]

09 August 2024

JNHB – Joint Nordic HTA-Bodies

JNHB Submission Dossier

For Health Technology Assessment of tofersen (QALSODY™)

Version 1 – August 2024

Company	Biogen
Medicinal Product (INN, Brand®)	*Tofersen, QALSODY™*
Relevant therapeutic indication	The treatment of adults with amyotrophic lateral sclerosis (ALS), associated with a mutation in the superoxide dismutase 1 (*SOD1*) gene
Company contact	*mikko.fernstrom@biogen.com*
Date of submission	9.8.2024

Document history

Version	Date	Description of key changes
1.0		First published version of a submission template by JNHB.

Contents

List of Tables

List of figures

List of Abbreviations

Abbreviation	Definition
ALS	Amyotrophic lateral sclerosis
MND	Motor neuron disease
AE	Adverse event
ALSAQ-5	ALS Assessment Questionnaire short-form
ALSFRS-R	The Amyotrophic Lateral Sclerosis Functional Rating Scale Revised
ANCOVA	Analysis of covariance
BIA	Budget impact analysis
cALS	Care partners of people with ALS
CEA	Cost-effectiveness analysis
CEM	Cost-effectiveness model
CHMP	The Committee for Medicinal Products for Human Use
CI	Confidence interval
CNS	Central nervous system
CSF	Cerebrospinal fluid
cSLR	Clinical systematic literature review
DSP	Disease-specific programme
EAN	The European Academy of Neurology
EFNS	The European Federation of Neurological Societies
EMA	European Medicines Agency
EMG	Electromyography
EQ-5D-5L	5-level EQ-5D
fALS	Familial ALS
FDA	Food and Drug Administration
FSS	Fatigue severity score
FVC	Forced vital capacity
HHD	Hand-held dynamometry
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IPE	Iterative parameter estimation
IQR	Interquartile range
ITT	Intent-to-treat
JRT	Joint Rank Test

LY	Life year
MiToS	The Milano-Torino Staging System
mITT	Modified intent-to-treat
MUNIX	Motor Unit Number Index
NfL	Neurofilament triplet protein
NIV	Non-invasive ventilation
NSAIDs	Nonsteroidal anti-inflammatory drugs
OLE	Open-label extension
OWSA	One-way sensitivity analysis
pALS	People with ALS
PEG	Percutaneous endoscopic gastronomy
PLS	Primary lateral sclerosis
PMA	Progressive muscular atrophy
PRO-ACT	Pooled Resource Open-Access ALS Clinical Trials
PSA	Probabilistic sensitivity analysis
PV	Permanent assisted ventilation
QALY	Quality-adjusted life year
QoL	Quality of life
RCND	Rehabilitation Centre for Neuromuscular Diseases
RPSFTM	Rank preserving structural failure time model
SAE	Serious AE
sALS	Sporadic ALS
SD	Standard deviation
SMNDQR	The Swedish Motor Neuron Disease Quality Registry
SmPC	Summary of Product Characteristics
SoC	Standard of care
SOD1	Superoxide dismutase 1
SVC	Slow vital capacity

1. Background

1.1. Overview

Table 1. Overview of intervention and submission

Medicinal product	*Tofersen (QALSODY™)*	
ATC-code	*N07XX22*	
Pharmaceutical class	*Other nervous system drugs*	
	For the indication relevant for the submission, state:	
Indication approved by EMA	*Qalsody is indicated for the treatment of adults with amyotrophic lateral sclerosis (ALS), associated with a mutation in the superoxide dismutase 1 (SOD1) gene.*	
Patient population relevant for assessment (if different from indication)	*Same as indication.*	
Posology	*Posology: Recommended dose is 100 mg of tofersen per treatment.* *Loading doses: 3 loading doses administered at 14-day intervals.* *Maintenance doses: Once every 28 days thereafter.*	
Route of administration	*Method of administration: Intrathecal, by lumbar puncture. Performed or under the direction of, healthcare professionals experienced in performing the procedure.*	
Conditional approval	If applicable, specify: N/A	
Does treatment require prior biomarker testing, companion diagnostics etc.?	*Genetic testing and screening for the SOD1 mutation is necessary to identify the patients who can benefit from tofersen.*	
	Information on the clinical documentation:	
Pivotal/main studies for the indication under review	VALOR study *NCT02623699*	Multicenter, Phase 3, double-blind, randomized, placebo-controlled study. Participants were adults with weakness attributed to ALS and a confirmed *SOD1* mutation. Patients were randomized 2:1 to tofersen 100mg (n=72) or placebo (n=36) for ~6 months; each participant received a 15 mL intrathecal bolus of study treatment or placebo, which was administered alongside standard of care (riluzole and/or edaravone), which was permitted at stable dose. VALOR completed: 2021-07-16.
	VALOR Open-label extension (OLE) study *NCT02623699*	Open-label extension study to assess the long-term effects of 100 mg tofersen in participants who previously completed VALOR and SAD/MAD studies. All participants had the opportunity to receive tofersen

		100 mg and be followed for approx. 3-7 years (n=95). OLE data cuts: 2021-07-16, 2022-01-16, 2023-02-18.
Type of economic model: e.g., paritioned survival model, Markov model, or other (please specify) Result of economic model using country-specific setting of Health Technology Developer (HTD) choice	The model uses a **Markov model structure**, capturing the expected *SOD1*-ALS patient experience from treatment initiation to death. The model structure reflects the treatment pathway and captures the expected clinically important differences in costs and outcomes between patients receiving alternative comparators.	
	LY-gained	2.07
	QALY-gained	2.47
	Incremental costs	10,619,031 SEK
	Cost pr. LY	5,132,726 SEK
	Cost pr. QALY	4,306,571 SEK

Please state the name of clinical experts consulted for preparation of this submission.

Table 2. Clinical experts contacted for preparation of the submission package

Name	Place of employment

Note: No clinical experts were contacted for preparation of the submission package.

1.2. Description of the disease and patient population

1.2.1. The disease: Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disorder characterized by spontaneous [1] and progressive degeneration of motor neurons [2]. It is the most common form of motor neuron disease (MND), making up approximately 90% of cases, and has both sporadic (sALS) and familial (fALS) forms. Other forms of MND include progressive muscular atrophy (PMA), which represents 5% of MND cases[3], and primary lateral sclerosis (PLS), which represents between 2-5% of MND cases, depending on the population[4]. In PMA, only the lower motor neurones are affected, whilst in PLS, only the upper motor neurones are affected. In contrast, both upper and lower motor neurones are affected in ALS[5].

The age of onset of ALS ranges, on average, from 40 to 70 years, although disease onset may be earlier or later [6]. ALS symptom onset typically begins in the limbs, but bulbar onset is present in approximately 20%-30% of cases, affecting speech and swallowing [2]. In rare cases, the respiratory muscles are involved at onset, [1, 2]. ALS causes progressive disability and most patients die from respiratory failure within 3 to 5 years of symptom onset [2, 7]. There is heterogeneity in survival of affected patients depending on the genetic variant. For example, for patients with the *SOD1*-A5V genetic variant of ALS (discussed further below), the expected survival is closer to 1 year [8].

ALS aetiology is multifactorial but the end result is always axonal injury and neurodegeneration [7, 9]. Mutations in key cellular genes result in the accumulation of toxic proteins and RNA aggregates, which in turn disrupts cellular processing [7, 9-12]. The aggregation of proteins disrupts axonal transport, resulting in axonal instability [9]. Mitochondrial dysfunctions, glutamate excitotoxicity, impaired axonal structure, transport defects, and oxidative stress all result in cell damage [9]. The end result of this process is loss of neuromuscular junction viability and motor neuron dysfunction and death [13].

Classified genetic mutations occur in approximately 10% of ALS patients of European descent [6], and nearly 72% of these patients do not have a family history [14]. The most common mutated genes found in ALS patients are C9orf72, *SOD1*, TDP-43 and FUS [14-17].

The *SOD1* (superoxide dismutase 1) gene is responsible for encoding of the *SOD1* protein [18], an antioxidant enzyme that protects the cell from reactive oxygen species toxicity [7]. In *SOD1*-ALS, the *SOD1* protein gains an unknown toxic function which causes axonal injury and subsequent neurodegeneration [7, 18]. As a consequence of axonal injury, neurofilaments – the core structures of axons – are released into the cerebral spinal fluid (CSF) and serum of ALS patients. The light subunit of the neurofilament triplet protein (NfL) is the main component of the neurofilament and is particularly abundant in axons, where its main function is to maintain their shape, calibre and size [19, 20]. NfL is considered an important marker of axonal injury and neurodegeneration in ALS [19, 20]; it is highly elevated in ALS and correlates with and predicts disease progression rate [21]. These high levels have been detected prior to symptom and clinical sign onset of ALS, and seem to continue rising for approximately 6 -20 months after symptom onset [22].

1.2.2. Epidemiology

ALS can be divided into familial (fALS) and sporadic (sALS) cases [9, 23]. Patients with sALS (no family history of ALS) account for 90%-95% of cases [9] and classified genetic mutations are present in approximately 10% of cases [23]. Familial ALS cases account for the remaining 5%-10% of cases and genetic mutations are found in approximately 70% of these cases [9, 23]. Symptom onset in patients with fALS typically occurs earlier (40s or early 50s) than in patients with sALS (late 50s or early 60s) [9]. Symptom onset during childhood or teenage years (juvenile ALS) is rare.

A genetic cause must be investigated in every suspect case of ALS so as not to miss possible genetic variants that can be present in both fALS and sALS cases, such as *C9ORF72, SOD1, FUS etc..* Restricting genetic testing to only patients with fALS would miss more than 40% of those with a disease-causing genetic varian[24].

The *SOD1* gene accounts for approximately 2% of the total ALS cases [14]. Among patients with a *SOD1* mutation, approximately 61% do not present with fALS [14]. S*OD1* mutations have been described to be associated with all clinical ALS subtypes, but is most commonly associated with limb onset and overall cognitive impairment is relatively rare. Moreover, patients with *SOD1*-ALS have on average an earlier onset of disease in the range of 40-50 years old [8, 24].

Most known *SOD1* mutations are associated with autosomal dominantly inherited ALS, but in Scandinavian populations there is a relatively frequent p.Asp90Ala mutation, which is associated with autosomal recessively inherited ALS[25]. p.Asp90Ala homozygous patients are clinically characterized by a slowly progressive classic motor phenotype.

Epidemiological data on the incidence and prevalence of ALS in the Nordic countries is somewhat scarce and often outdated, with a particular lack of clear data on *SOD1*-ALS patients.

Finland

The prevalence of ALS (all types) was earlier reported in Finland (in 1973) [26] as 3.6/100,000 and during 1976-1981 in Central Finland as 6.4/100,000 [27]. In a study from 2023 on the epidemiology of ALS in two regions[28], the overall crude incidence of ALS was 4.2/100,000 person-years in Southwestern Finland and 5.6/100,000 person-years in North Karelia, while crude prevalences were 11.9/100,000 and 10.9/100,000, respectively. The number of patients living with ALS in Finland has been estimated to be between 300-600 patients [29]. Mean age at diagnosis has been estimated to be 65.5-71.6 years in women (higher in Southwestern Finland compared to North Karelia, $p = 0.003$) and 64.7-67.3 years in men (no difference between provinces, $p = 0.39$) [28]. The estimated prevalence of *SOD1*-ALS among ALS patients in Finland is 7%, corresponding to an estimated 20-40 patients [30].

Norway

A 2021 meta-analysis [31] estimated the incidence of ALS in Norway as 2.06 per 100,000 (range: 2.00-2.13). The prevalence has been estimated as 7.6 per 100,000 [24], corresponding to an estimated 300-400 patients with ALS in Norway at any given time [24].

Olsen et al. (2022) [24] analysed the genetic epidemiology of 279 ALS patients in Norway and found that 88.5% of ALS cases were sporadic and the remaining 11.5% of cases were familial. In the same study, *SOD1* mutations were the second most frequent genetic cause of ALS and were present in approximately 4% of the study population (n=279). There are an estimated 10-20 *SOD1*-ALS patients in Norway. In the study by Olsen et al. (2022) [24], 28% of fALS cases were caused by a *SOD1* mutation, in contrast with just 0.4% of sporadic cases. Genetic variant distribution was found to vary according to the geographic region: *SOD1*-ALS was more frequent in familial cases in the South-Eastern region which can partly explain the high number of fALS cases in this region [24].

The mean age of patients with *SOD1*-ALS was 45 years old, close to 20 years younger than the age of onset of 62 years old in the general ALS population. These findings align with those found by Opie-Martin et al. (2022) [8] where the reported mean age of onset in a *SOD1*-ALS dataset was 48.9 (SD 12.8) compared to 61 (SD 12) in the ALS dataset with no recorded *SOD1* variant ($p<0.001$).

There are certain *SOD1* variants associated with atypical disease progression [8] depending on which protein is affected by the mutation. For example, the p.A5V variant is associated with shorter survival while the p.D91A variant is associated with longer survival [8]. In Norway, the most frequent variant is p.H47 as reported by Olsen et al. (2022) and is associated with a younger age of onset [8].

Sweden

The 2021 meta-analysis estimated the incidence of ALS in Sweden as 2.31 per 100,000 (95% CI: 2.08-2.55) [31]. A difficulty with Swedish epidemiological reports is that the terms ALS and MND are often used interchangeably. The Swedish Motor Neuron Disease Quality Registry (SMNDQR) was created in 2015 as part of the Neuro-registry already existing in Sweden, and today is estimated that 85% of all Swedish ALS/MND patients are registered in the SMNDQR. However, the registry does not discriminate between patients with different forms of ALS/MND, which makes it difficult to present clear epidemiological data for *SOD1*-ALS patients.

The prevalence of patients with ALS in Sweden has been estimated to approximately 6.23/100,000 (i.e., 500 patients), with 4-5% of these patients expected to have *SOD1*-ALS (i.e., 20-30 patients) [31].

Denmark

In Denmark, the incidence of ALS is 1-3 per 100,000 [32] and the prevalence is approximately 6.8 per 100,000 [33]. The mean age of onset is 58-63 years[34]. There are an estimated 300-400 patients living in Denmark with ALS, and it has been estimated that approximately 5-10% of ALS cases are familial and the remaining 90-95% are sporadic[35]. Further, an estimated 15-20% of fALS cases and 2-7% of sALS cases are *SOD1*-ALS resulting in an overall estimated 2% (i.e., 7-8 patients) prevalence of *SOD1*-ALS in Denmark [35].

Iceland

There are three known families in Iceland where MND is familial. All the families have SOD1 gene mutation. It is also considered likely that these three families here can be traced together, implying some degree of kinship.

1.2.3. Risk factors

Risk factors that may be associated with ALS include: 1) genetic mutations, including the intermediate CAG repeat expansion in ATXN2; 2) previous exposure to heavy metals such as lead and mercury; 3) previous exposure to organic chemicals, such as pesticides and solvents; 4) history of electric shock; 5) history of physical trauma/injury (including head trauma/injury); 6) smoking (a weak risk factor for ALS in women); and 7) other risk factors, such as participating in professional sports, lower body mass index, lower educational attainment, or occupations requiring repetitive/strenuous work, military service, exposure to Beta-N-methylamino-l-alanine and viral infections [36-38].

Risk factors that may be associated with ALS progression rate include: 1) nutritional status, including vitamin D deficiency; 2) comorbidities; 3) ethnicity and genetic factors; 4) lack of supportive care; and 5) smoking [36-38].

1.2.4. Clinical presentation

ALS is a differential diagnosis with other conditions (e.g. tumours, multiple sclerosis, herniated disks, Lyme disease, HIV, spinal muscular atrophy, etc.). As no single investigation is specific for ALS, and there is no sensitive and specific disease biomarker, diagnosis is based on symptoms, clinical examination findings and the results of electrodiagnostic, neuroimaging and laboratory studies[39].

Clinical features supporting ALS diagnosis include [40, 41]:

- Abnormal tests in the following categories, not explained by other causes:
    - Pulmonary function tests
    - Speech studies

- Swallowing studies

- Abnormal strength tests in clinically uninvolved muscles
- Abnormal muscle biopsy with evidence of denervation

Signs and symptoms of ALS can involve both upper and lower motor neuron pathways [2]:

- Upper motor neuron: minimum wasting, weakness, stiffness, slowness, spasticity, hyperreflexia, presence of primitive reflexes (Babinski sign), imbalance, excessive yawning, increase jaw jerk, and spastic dysarthria (slow, labored and distorted speech [2, 9, 42-45]).
- Lower motor neuron: wasting, weakness, low or normal tone (flaccidity), fasciculations (low threshold for irritation of the motor neuron), cramping, hyporeflexia or areflexia, nasal dysarthria, or nasal regurgitation [2, 9, 45, 46].

1.2.5. Diagnosis

For research purposes, different diagnostic criteria have been proposed over time [47, 48] (Table 1):

Table 1. ALS diagnostic criteria

Criteria	Description
Original El Escorial Criteria (1994) [47]	Initial published criteria Developed to capture wide variety of ALS clinical features and improve certainty of diagnosis
Revised El Escorial (Airlie House) Criteria (2000)[49]	Revised to increase diagnostic sensitivity. Laboratory-supported probable ALS category was introduced, which allowed the use of EMG instead of clinical findings
Awaji Criteria (2008) [50]	Developed to further integrate electrophysiological criteria with clinical examinations findings
Gold Coast Criteria (2020) [48]	Recommendations to simplify how the diagnosis can be established. Inclusion of nonmotor symptoms (cognitive, behavioural, and psychiatric disturbances) Establishing a single clinical diagnostic entity rather than different disease categories

Abbreviations: ALS = amyotrophic lateral sclerosis; EMG = electromyography.

Nevertheless, delay of ALS diagnosis is common, and patients often experience an array of symptoms before a diagnosis can be reached [51, 52]. This delay in diagnosis may be a consequence of the heterogeneity in ALS presentation which also results in delays in treatment access [51]. In a recent systematic literature review, median diagnostic delay was reported to be 11 months (interquartile ratio [IQR]: 9.1-12.0), with studies reporting median delays of 7 to 22 months [51]. ALS patients often consult a general practitioner and/or other specialists (e.g., orthopaedist, neurosurgeon, otolaryngologist) in the first 6-12 months after symptom onset [53]. Patients are then referred to a general neurologist for clinical examination, sensory and motor nerve conduction tests, imaging studies, and electromyography [54]. It is at this stage of their clinical journey that patients

tend to be referred to a neuromuscular disease/ALS specialist for further examination and a clinical diagnosis [55]. On average, ALS patients visit at least 3 different physicians before receiving an ALS diagnosis [53].

1.2.6. Disease progression

ALS patients experience progressive motor weakness leading to a loss of independence, eventually resulting in paralysis [2]. Independence progression in ALS can be categorized into 3 groups: early stage, middle stage and late stage [41-44, 56, 57]. Symptoms in the early stage include fatigue, reduced exercise capacity, slurred speech, difficulty swallowing, weakness in the limbs, loss of motor skills and muscle cramping or twitching [41, 42, 44, 57]. Middle stage symptoms include falls, contractures, weight loss, malnutrition, widespread muscle paralysis, weakness in swallowing and breathing muscles, pseudobulbar affect (uncontrolled laughing or crying), excessive salivation, breathlessness lying down and dyspnoea [42, 56, 57]. Late-stage symptoms include paralysis of most voluntary muscles resulting in limited mobility, difficulty communicating, and respiratory failure [42, 56, 57].

ALS is heterogenous [58] and symptoms in each progression stage can be grouped in 6 categories based on the most common observations by independence level [58]: 1) Lower motor function, 2) Upper motor function, 3) Fatigue, 4) Eating/Swallowing, 5) Communicating, and 6) Respiratory function (Table 2).

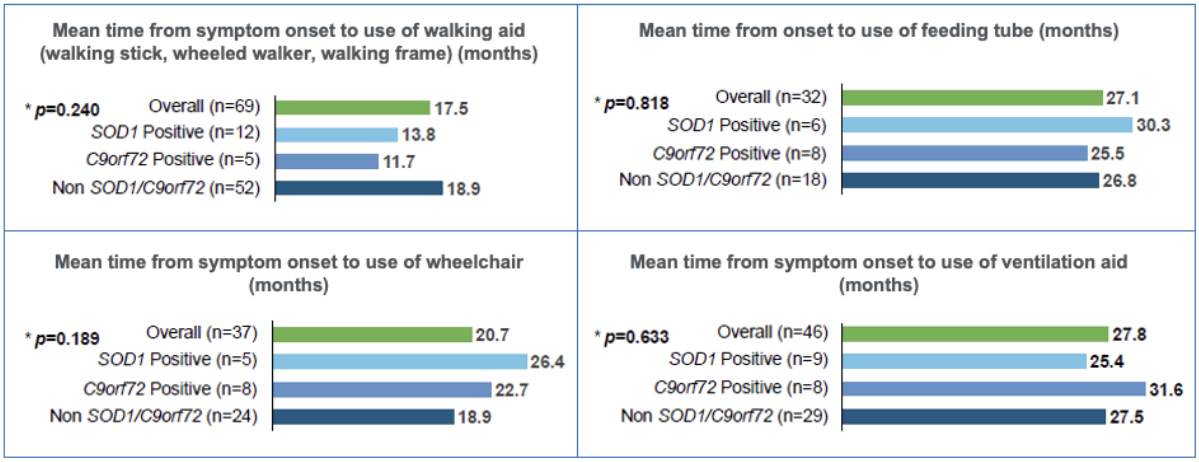
Table 2. ALS independence progression characterized by early, middle, and late stages

	Early Stage	Middle Stage		Late Stage
Lower Motor Function	Ability to walk declines; assistive devices are needed later in this stage	Progresses from walking with an assistive device to requiring a wheelchair most of the time	Require a wheelchair all of the time; unable to bear weight for transfers	Become incontinent; no remaining function in legs
Upper Motor Function	Grip strength and finger dexterity weaken; limited range of motion in shoulders	Increasingly difficult to lift arms to shoulders; Grip becomes very weak	Lose ability to raise arms and move hands and fingers	No remaining function in arms, hands, or fingers
Fatigue	Limited in the number of activities they can do in a day; they must do them more slowly	Need to rest frequently throughout the day; leaving the house is exhausting	Difficult to sit up for long periods, spend more time in bed during the day; rarely leave home	Bedridden; Do not leave the house
Eating / Swallowing	Chewing becomes slower; certain textures may be avoided	Begin to choke and aspirate; must eat softer foods cut into small pieces	Complications due to swallowing difficulty lead to feeding tube placement	Rely on a feeding tube for all nutritional intake
Communi-cating	Speech is still clear for most; some have a change in the sound of their voice start to speak slower	Speech begins to slur, may only be understood by family	Speech may become incomprehensible or lost completely	Unable to speak (due to tracheostomy or lack of lung strength)
Respiratory Function	Minimal issues for most; may have difficulty breathing when reclined	Require non-invasive ventilation when sleeping	Require non-invasive ventilation for part of the day	Require constant non-invasive ventilation or permanent ventilation

Source: Athanasakis K. et al. 2015.[55]

Progression rate is heterogeneous but average times to key milestones are similar across genetic variants [59]. ALS patients reach key disease milestones within approximately 17 to 28 months from symptom onset [60], and the timing is similar across genetic mutations (Figure 1).. Approximately 10% of ALS patients may survive for up to 10 years, however, the majority of people living with ALS (plwALS) experience death from respiratory failure within three to five years of symptom onset [2, 7, 41, 61, 62].

Figure 1. Time taken for ALS patients to reach disease milestones



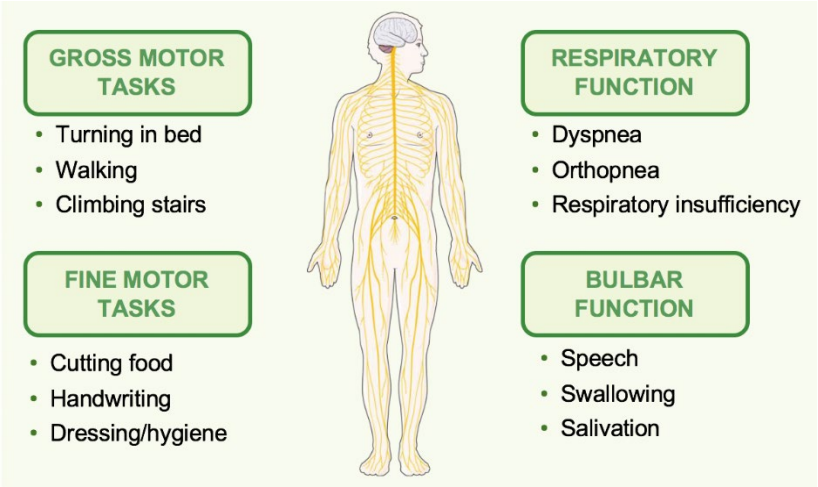
** p-values demonstrate lack of statistical differences between mutation groups.*
Abbreviations: ALS = amyotrophic lateral sclerosis.
Source: Stenson et al., 2021 [60]

1.2.7. Clinical outcome measures in ALS

1.2.7.1. Clinical function: ALSFRS-R

The Amyotrophic Lateral Sclerosis Functional Rating Scale Revised (ALSFRS-R) has been widely used in clinical trials and practice to assess disease status and progression over time [63]. The ALSFRS-R consists of 12 questions that assess overall disability within 4 distinct domains [18, 64]. There are 4 sub-scores with 12 points within each domain. Each function is scored from 0 (absent function) to 4 (normal function) with the maximum score being 48. Figure 2 illustrates the domains and sub-categories of the ALSFRS-R.

Figure 2. Amyotrophic Lateral Sclerosis Functional Rating Scale Revised



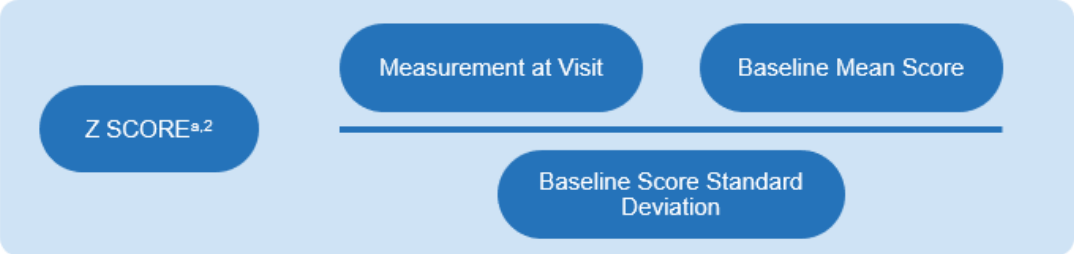
As ALS patients progress, their functional ability decreases rapidly requiring the addition of substantial care to survive [41]. Many ALS patients will eventually require enteral feedings, ventilation support, and other invasive interventions. The ALSFRS-R decline rate varies widely but averages approximately 1 point per month [65, 66]. The monthly decline rate of ALSFRS-R is largely similar across genetic mutations (overall: 0.80 points, *SOD1* positive: 0.77 points, non-*SOD1*/C9orf72: 0.74 points) [60].

Staging systems are further described in Sections 3.3.2 and 3.3.3.

1.2.7.2. Muscle strength: HHD

Strength is most frequently measured by hand-held dynamometry (HDD), a device that can be placed between the hand of the practitioner and the patient's tested body part, similar to how a manual muscle test is performed [67]. Unlike manual muscle testing, HHD provides a quantified measurement of force through an examination of 16 muscle groups in both upper and lower extremities to derive the overall HHD megascore [18].To calculate the HHD megascore, individual muscle strength values are normalized to Z scores and are standardized to baseline. Individual Z scores are then averaged to produce a megascore for a single extremity, both upper extremities, and both lower extremities, and a global megascore including all muscle groups [68].

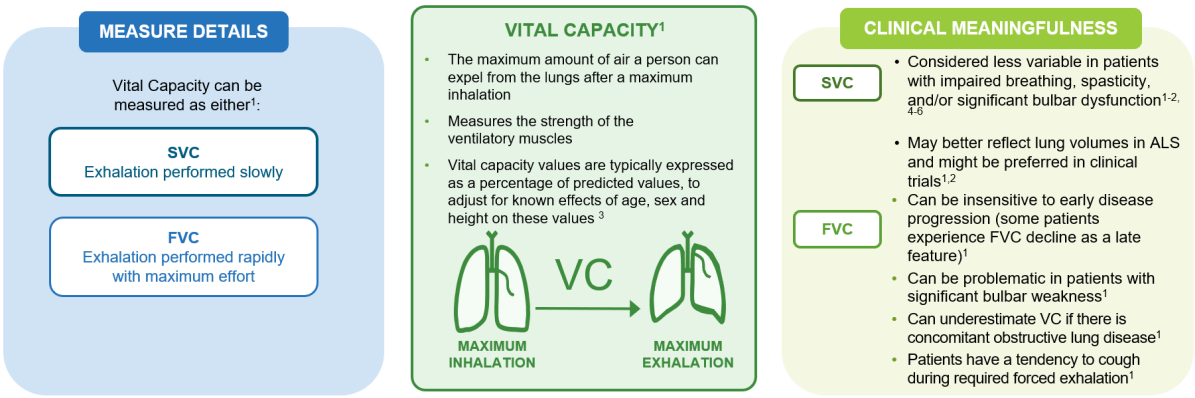
Figure 3: HHD Score calculation



1.2.7.3. Respiratory strength: SVC & FVC

The decline in respiratory function results from ALS pathophysiology [69]. Respiratory function is measured by vital capacity (VC), which is the amount of air expelled from lungs after a maximum inhalation, and reflects the strength of the ventilatory muscles [64]. VC can be measured as either slow VC (SVC), exhalation performed slowly, or forced VC (FVC), exhalation performed rapidly with maximum effort; SVC may better reflect lung volumes in ALS and is preferred in clinical trials [64, 70]. See also Figure 4. The average decline of slow vital capacity (SVC) from baseline through 1.5-year follow-up is -2.7% predicted per month. The measure is therefore associated with meaningful clinical events [71] such as use of assisted ventilation, tracheostomy, and ultimately, death.

Figure 4: SVC & FVC



Source:*1: [64] ; 2: [70] ; 3: [18] ; 4: [71] ; 5: [72] ; 6: [73]*
Abbreviation: *ALS = amyotrophic lateral sclerosis; FVC = forced vital capacity; SVC = slow vital capacity; VC = vital capacity*

1.2.7.4. Biomarkers: Total CSF-SOD1, NfL & MUNIX

Cerebrospinal fluid (CSF) superoxide dismutase 1 (SOD1) is a measure of total SOD1 protein concentration in CSF (a marker of target engagement). Lowering mutant SOD1 protein concentration in CSF is recognized as a potential therapeutic target [13]. Elevated concentration of neurofilament levels have been described in a variety of neurological conditions characterized by axonal injury and neurodegeneration [74].

Neurofilaments (NFs) are intermediate filaments uniquely expressed in neurons. Following axonal injury and neurodegeneration, NF light chains (NfLs) leak into extracellular fluid and then penetrate into blood [75, 76]. Elevated NfL levels have been described in a variety of neurological conditions characterized by neuroaxonal damage [77] NfL is a marker of disease activity in ALS as it has been shown to reflect the rate of disability progression. Both serum and CSF NfL levels correlate with ALS progression rate [78, 79]. NfL levels were also found a prognostic factor for longitudinal change in function and survival in ALS [22].

1.2.7.5. Survival

Overall survival (OS) is defined as the length of time from either the date of diagnosis or start of treatment that patients diagnosed with a disease are still alive [82]. Another measure of survival is the time to death or permanent assisted ventilation (PV), defined as the time to the earliest occurrence of one of the following events: death or PV (VALOR trial defined as ≥22 hours of mechanical ventilation [invasive or non-invasive] per day for ≥21 consecutive days) [18]. It may be directly measured or a compositecan be utilized ,which ranks patients' clinical outcomes based on survival time and change in ALSFRS-R score.[82, 83]. The Joint Rank Test (JRT) combines ALSFRS-R total score and time to death into a composite score, with death treated as the worst outcome [18]. Increased survival, especially increased ventilator assistance-free survival (VAFS), is important to ALS patients who have a life-expectancy of only 3–5 years [2, 7, 61].

1.2.8. Patient and caregiver reported outcomes

In addition, evaluating patient reported outcomes (e.g. EQ-5D-5L; Amyotrophic Lateral Sclerosis Assessment Questionnaire [ALSAQ-5]; Fatigue Severity Scale [FSS]) and caregiver reported outcomes (e.g., Zarit Burden Interview [ZBI]) is critical among patients with ALS as it allows for the incorporation of the patient voice into drug development (Table 3) [84-89]. Due to the lack of consensus regarding the best instrument for measuring quality of life in patients with ALS, use of a variety of measures is needed [89]. Instruments such as the SF-36 and ALSAQ-5 focus on function which naturally declines as disease progresses. Symptom specific measures should be considered, as ALS symptoms such as fatigue are common [90]. In addition, impacts to paid and unpaid work and activities and increased reliance on caregivers have been reported in patients with ALS and therefore is important to capture through the use of WPAI and ZBI, respectively [86-88, 91].

Table 3: Patient and caregiver outcomes

ALS Impacts	Measures Used	Description	Scoring	Clinically Meaningful Change in ALS Population
HRQoL	EQ-5D-5L	Assesses decline in health status in various conditions.[92, 93] 5-question generic visual analogue scale recording self-rated mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[92, 94]	The self-rated health on a visual analogue scale ranges from 0 (the worst health you can imagine) to 100 (the best health you can imagine). By applying a set of preference weights, responses to the EQ-5D-5L questionnaire can be converted to health state utility values on 0-1 scale. ↑ score = ↑ HRQoL	*No data available on meaningful change thresholds derived for patients with ALS*
	ALSAQ-5; ALSAQ-40	Assesses impairment and severity in ALS.[97] The ALSAQ-5 and ALSAQ-40 contains 5 and 40 questions, respectively, corresponding to the 5 health-related dimensions: physical mobility, activities of daily living, eating and drinking abilities, communication, and emotional functioning. Among patients with ALS, physical impairment and progression rate of physical deterioration has a significant impact on emotional well-being.[98]	**ALSAQ-5 and ALSAQ-40** Scores are calculated for each dimension on a standard scale of 0 (best possible health state) to 100 (worst possible health state). ↑ score = ↓ HRQoL	**ALSAQ-5** *No data available on meaningful change thresholds derived for patients with ALS* **ALSAQ-40** The smallest level of deterioration that might be regarded by patients as subjectively important: mean change scores 3.35 (SD=14.10) for mobility, 5.67 (13.28) for activities of daily living, 6.40 (20.46) for eating and drinking, 6.67 (16.52) for communication, and 2.67 (15.45) for emotional functioning[99]
Symptom Impact	FSS	Consists of 9 questions assessing 3 domains (life participation, sleep, and daily	The domains are scored on a 7-point scale with 1	FSS ≥4 *[105]

		activities) with a 7-point Likert scale ranging from "strongly disagree" to "strongly agree".[101] Fatigue is frequent and persistent among patients with ALS.[102] ALS/NMD patients often experience fatigue leading to distress and poor quality of life.[103, 104]	representing strongly disagree and 7 representing strongly agree; the total scores range from 9 (lower fatigue severity) to 63 (higher fatigue severity). ↑ score = ↑ fatigue = ↓ HRQoL	
Caregiver Burden	ZBI	Assesses burden to caregivers of patients with ALS.[106] Consists of 12 questions about the impacts of the patient's disability on caregivers' lives. Up to 48% of caregivers of ALS patients report high levels of burden due to the patients' abnormal behavior rather than physical disability. Caregiver burden seems to increase parallel to the disease severity of the patient.[107]	The ZBI items are rated on a 5-point Likert scale that ranges from 0 (never) to 4 (nearly always) with the sum of scores ranging between 0–48. A score of 17 or more was considered high burden. ↑ score = ↑ burden = ↓ HRQoL	*No data available on meaningful change thresholds derived for patients with ALS*

1.2.9. Disease burden and influence on quality of life

SOD1-ALS is a relentless, progressively debilitating disease with a median survival time of 2.7 years [108]. As the disease progresses, it impacts the person's independence, including walking, eating, and speaking. Functional decline leads to an "inevitable change in work status, likely loss of income, and a momentous shift in future hopes and plans" [109]. Unsurprisingly, quality of life (QoL) is lower in people with ALS compared to the general population [110-115].

Disease progression has also been shown to have an adverse impact on the QoL of people with ALS when assessed by King's and Milano-Torino (MiToS) staging systems [116] (see Section 3.3.2 for further information on staging systems). Across King's staging, the steepest decline in QoL was observed between stages 3 and 4; this coincides with the introduction of feeding and/or ventilation assistance due to nutritional and respiratory failure. In contrast, across MiToS staging, the steepest decline in QoL was observed between stages 1 and 2, following loss of independent function in two domains. From this stage onwards, the EQ-5D index scores indicated a QoL state close to or worse than death.

The loss of independence associated with disease progression greatly impact patient and caregiver QoL, and up to 49% of caregivers reported high level of burden (physical, depression, anxiety and stress) associated with caring for an ALS patient [86, 117, 118]. A recent EU5/US survey of people with ALS (pALS) and their care partners (cALS) reports the burden across the disease course [119].

Patient burden

Aa point-in-time survey of de-identified neurologists in France, Germany, Italy, Spain, the UK, and the USA finds that 46% of pALS reported changing their working arrangements due to ALS, with 42% of these pALS either having reduced hours or stopping work entirely [120]. Their neurologists reported that changes in employment status occurred on average 16.1 months after symptom

onset; the most frequently cited reasons were impaired mobility (74%), increased muscle weakness (36%), and impaired communication (27%)[120].

Functional changes result in many pALS (68%) requiring home modifications to accommodate their current capabilities, with 14% of pALS moving to a more ALS-friendly house. These modifications, professional caregiving support, and other out-of-pocket expenses result in 73% of neurologists outlining that pALS often express concerns to them about the financial burden of ALS [120].

People with late-stage ALS require professional caregiver support more frequently as a result of their ALS (early: 7%, mid: 30%, late: 68%), and those with a professional caregiver also utilize a greater number of hours of care per week (early: 17.8, mid: 18.4, late: 46.4) [121]. The wider economic burden associated with ALS is substantial, with an annual predicted out of pocket costs increasing with the level of care needed ($0 where care is not needed to-$21,600 [2018 USD] for 16–24 hours of daily care) [122].This does not include the financial strain attributed to loss of income from reduction in employment [55]. In Germany, the mean annual total cost associated with ALS was €78,256 (in 2018 EUR) per patient per year (€82,325 inflated to 2021 EUR), and the total yearly burden was over €500 million (inflated to €526 million to 2021 EUR) [88]

Caregiver Burden

The Burden or stress levels in bereaved caregivers was considered high or maximum in over 60% of surveyed respondents [86, 117, 118]. Most caregivers indicated that their current health was much worse (12% of caregivers and 17% of bereaved caregivers) or somewhat worse (43% of caregivers and 38% of bereaved caregivers) than before they began caring for the person with ALS/MND [119].

Furthermore, according to the data from France, Germany, Italy, Spain, the UK, and the USA, 51% of people with ALS report receiving no formal care, thereby increasing the caregiver burden by relying on family members and friends for informal care [123]. Caregiving accounts for more than half of total ALS costs, with typical hours devoted to caregiving reaching up to 130 hours per week (depending on the stage of the disease) [124, 125]. Overall, 37% of cALS reported a change to their working arrangements to care for the pALS, with 18% of these cALS having either reduced hours or stopping work entirely. The support activities cALS most reported were “preparing meals/cooking” (72%), “shopping” (68%), and “cleaning/housework” (68%) [120].

1.3. Patient population relevant for the assessment

The target patient population for treatment with tofersen aligns with the therapeutic indication i.e., “adults with amyotrophic lateral sclerosis (ALS), associated with a mutation in the superoxide dismutase 1 (*SOD1*) gene” [126].

1.3.1. Patient characteristics

As mentioned in Section 1.2.2, data on patients with *SOD1*-ALS is relatively scarce in the Nordic countries. Characteristics for patients with ALS (and, where possible, *SOD1*-ALS) are presented in this section. Overall, there are not expected to be any significant differences in patient characteristics between countries.

1.3.1.1. Age and gender

There are always about 300-600 ALS patients in Finland at any given time. The corresponding number of *SOD1*-ALS patients is approximately 20-40 [30]. The disease usually leads to death in 3–5 years. The patients are usually 40–60 years old at disease onset, but the youngest are under 25 and the oldest are over 85 [29]. One paper describing 36 Finnish patients with the Asp90Ala variant of the *SOD1* mutation found that mean age of *SOD1*-ALS onset was 44 years [127]. Data on gender characteristics of ALS patients is lacking.

In Norway there are approximately 500 patients living with ALS at any given time [128, 129]. Men are more affected than women at a 1.6:1 ratio, however, this difference equalizes in familial cases indicating that gender does not affect genetic variants [24]. Furthermore, in Norway, spinal onset is most frequent in both sporadic and familial ALS [24]. The mean age of onset is 62 years but younger patients can also be affected by ALS [24, 129]. The prevalence of *SOD1*-ALS is approximately 10-20 patients in Norway. The mean age of patients with *SOD1*-ALS in Norway has been reported as 45 years old, close to 20 years younger than the age of onset of 62 years old in the general ALS population [24]. These findings align with those found by Opie-Martin et al. (2022) [8] where the reported mean age of onset in a *SOD1*-ALS dataset was 48.9 (SD 12.8) compared to 61 (SD 12) in the ALS dataset with no recorded *SOD1* variant ($p<0.001$).

In Sweden, there are an estimated 800 patients with ALS, of which 20-30 have *SOD1*-ALS[31]. One retrospective study on individuals diagnosed with MND[1] in Sweden between 2002-2021 (of which approximately 90% of cases were ALS) identified 7,805 cases, of which 4,477 (57.4%) were men and 3,328 (42.6%) were women [130]. Patients had a median age at diagnosis of 70 years (61-77): 69 (60-76) for men and 71 (62-78) for women. Although there is scarce data on the characteristics of *SOD1*-ALS patients, it is reported that the age at diagnosis is generally younger than for general ALS [131] [132].

In Denmark, there are approximately 300 ALS patients and 7-8 *SOD1*-ALS patients at any time. The mean age of overall ALS onset has been estimated as 58-63 years [34]. The ratio between male and female patients is approximately 1.5:1 [133]. Although there is little information available on the characteristics of patients with *SOD1*-ALS in Denmark, it is expected that they are likely to be younger at diagnosis than the overall ALS population.

1.3.2. Relevant patient subgroups

In line with the marketing authorisation and therapeutic indication, tofersen is indicated as treatment for the entire *SOD1*-ALS population, for whom there is a clear unmet need for effective treatments. Therefore, subgroup analyses are not presented in the current submission.

1.3.3. Number of patients eligible for treatment with tofersen

The estimated number of patients expected to be eligible for treatment with tofersen, based on epidemiological data presented in Section 1.2.2, are presented in Table 4 below.

As outlined in section 1.3.2, the patients who are eligible for treatment with tofersen are patients with *SOD1*-ALS. Please refer to Section 5.1.2 for additional details.

[1] MND patients were identified using the ICD-10 code G12.2 with ALS expected to account for most, approximately 90%, of cases.

Table 4. Estimate of SOD1-ALS patient numbers

Country	Prevalence (per 100,000) of ALS	Yearly incidence (per 100,000) of ALS	Percentage of ALS patients with *SOD1*-ALS	Number of ALS patients with *SOD1*-ALS	Patients who are expected to be eligible for treatment with tofersen
Finland	10.9-11.9 [28]	4-6 [28]	7% [30]	38-39	4-5
Norway	7.6 [24]	2.06 [31]	4% [24]	14-15	5-6
Sweden	6.23 [31]	2.31 [31]	4-5% [134]	20-25	12-13
Denmark	6.8 [33]	1-3 [32]	2% [35]	7-8	3-4

1.4. Current treatment practice

The European Federation of Neurological Societies (EFNS) have published guidelines of the diagnoses and management of ALS [39]. The EFNS guidelines are used to guide the treatment guidelines in the Nordic countries.

According to the latest version of the guidelines, riluzole is the only drug to date that has been shown to slow the course of ALS in four Class I studies [55-58]; a Cochrane review has also been published [59]. Oral administration of 100 mg riluzole daily improved the 1-year survival by 15% and prolonged survival by ≈3 months after 18 months' treatment. There was a clear dose effect. Eleven people needed to be treated with riluzole to delay one death for 12 months. These studies did not include patients with early disease. Later, retrospective Phase IV studies from five clinical databases indicate that the overall gain in survival (i.e. over the whole extent of the disease course) may extend from 6 (Class III) [60], 10 (Class IV) [61], 12 (Class IV) [62], 14 (Class IV) [63] or 21 (Class IV) [64] months, although these estimates are almost certainly subject to statistical biases. The drug is safe, with few serious side effects. Fatigue was a side effect in 26% of patients taking riluzole compared with 13% receiving placebo (number needed to harm = 8) [55]. Although patients with progressive muscular atrophy or primary lateral sclerosis were not included in the riluzole trials, pathological and genetic studies show that some patients with progressive muscular atrophy and primary lateral sclerosis fall within the ALS syndrome, so may benefit from the drug [16,65] (Class IV).

Riluzole is thought to exert neuroprotective effects by preventing the accumulation of toxic concentrations of glutamic acid in the central nervous system (CNS) of ALS patients [135, 136] and is well tolerated by patients but its efficacy is modest as it increases the median ventilation-free survival by approximately 2-3 months [136] without noticeable improvement in strength or disability [137]; it is not a genetically targeted treatment. Adverse effects are relatively rare and mostly reversible after discontinuation of riluzole [136], however, riluzole is not recommended for use in patients with impaired renal function and should be prescribed with care in patients with a history of abnormal liver function, due to the risk of increased alanine aminotransferase levels which can be associated with jaundice. Cases of interstitial lung disease have also been reported in patients treated with riluzole, with some of them being severe [136].

Riluzole may have little effect in late-stage ALS, and it is not clear whether and when treatment should be terminated. A large number of other drugs have been tested in ALS, unfortunately with negative results.

It is in this desolate treatment landscape for ALS-patients, that the European Academy of Neurology (EAN) - in the newly published guideline on the management of ALS from March 2024 - has strongly recommended the novel treatment with Tofersen as a first-line treatment in patients with progressive ALS. See Section 1.6.

In summary, the magnitudes of slowing in progression of clinical and PRO endpoints when compared with the natural history of ALS/SOD1-ALS, for tofersen treatment, is at odds with this natural disease history and shows clinically relevant advantage due to improved efficacy [138].

Finland

The treatment and rehabilitation of ALS should be interdisciplinary and involve cooperation of doctors, nurses, physical, occupational, speech and nutrition therapists, as well as social workers and rehabilitation instructors. Early rehabilitation the patient to preserve and maintain their functional capacity for as long as possible. Physiotherapy aims to prevent incorrect posture, reduce muscle spasticity and support functional capacity and independence for as long as possible. Physiotherapists and occupational therapists also help with planning home renovations and purchasing and using aids [140]. A speech therapist monitors speech output and communication ability and provides guidance on the use of various communication aids. If necessary, a nutritionist may be employed to enhance nutrition and energy intake with supplements. If swallowing problems worsen, it is worth considering installing a percutaneous endoscopic gastronomy (PEG) tube to secure nutrition.

ALS also causes the respiratory muscles to weaken, so breathing functions should be monitored regularly. Symptoms of respiratory deficiency include poor nighttime sleep, daytime fatigue and morning headaches. When respiratory failure occurs, different forms of treatment should be discussed, preferably well in advance. The goal of respiratory support treatment is to relieve shortness of breath and improve the quality of life. In order to support breathing, continuous support measures may be implemented e.g., a nasal or face mask or invasive ventilator therapy, which requires a tracheostomy. Due to the progressive nature of the disease, the needs must be reassessed from time to time.

In Finland, the treatment recommendation for ALS is riluzole 50 mg every 12 hours [29]. Currently, there are two basic replacement riluzole preparations available in Finland, one of which is in capsule form (Rilutek) and the other is a liquid oral suspension preparation (Teglutik). In some patients, the drug slows down the progression of the disease, thus slightly increasing life expectancy. Approximately 15% of users experience side effects from the use of the drug, the most common of which is mild nausea, which, if persistent, may prevent the use of the drug. In some cases, riluzole may also increase the main symptom of ALS, i.e. muscle weakness. If exceptional muscle weakness occurs during use, the medication should be stopped. The use of the medicine requires infrequent but regular monitoring of blood and liver values [140].

Other medical treatment for ALS aims to treat symptoms (e.g., diazepam to treat muscle cramps and spasms) or ease discomfort in the terminal phase (e.g., morphine).

Norway

When an ALS diagnosis is made, the diagnosing hospital should offer a coordinator for the patient and those who provide the healthcare services, in order to ensure that plans are made in line with the patient’s wishes, how serious the patient’s situation is, and the degree of urgency. A municipal coordinator is also appointed, and a municipal interdisciplinary team is established to oversee treatment and follow-up of the patient. The ALS team in the hospital and the municipal coordinator should together ensure that facilitation, aids, and various support schemes are assessed and discussed with the patient in advance of their functional decline [141].

The patient's contact doctor and professionals in the ALS team in the hospital should make plans for carrying out the diagnostic interview and follow-up of the patient and relatives in the following days

after the diagnosis has been given. The interdisciplinary follow-up of patients with ALS should focus on mental health, coping, physical function, activity and participation, in addition to mapping disease development and functional decline [141].

In Norway the standard of care for ALS patients is treatment with riluzole [136].

Patients are offered other supportive treatment such as percutaneous endoscopic gastrotomy, ventilation support/BiPAP or botulinum toxin.

Sweden

When a patient exhibits symptoms indicative of ALS, the patient must be investigated as soon as possible by an experienced neurologist. The aim is to make an early diagnosis and that is why it is important that the investigations, including the neurophysiological examination, are prioritized. The diagnosis is made by a doctor with a good understanding of the patient's illness and the disease. The patients are also informed about and registered in the ALS register (www.neuroreg.se).

After diagnosis, the patient is connected to a multidisciplinary team (ALS team). Most major hospitals in Sweden have ALS teams that work together to provide the best possible care and support to people with ALS and their close relations. The ALS teams include various professional categories, and the interventions take place in the medical, psychological, social and technical fields. The efforts consist of, among other things, treatment, and conversation support, testing of aids and advice for possible adaptation of the home. As needs change over time, it is important that interventions are planned and adapted to the individual. A prerequisite for this is regular contact with the ALS team. A recommendation is return visits every three months and telephone contact, if necessary, between visits.

According to Swedish guidelines, which build upon the EFNS guidelines [142], medication with riluzole 50 mg twice per day should be started as soon as possible. The medical treatment focuses on relieving symptoms such as hypersalivation, abundant mucus production, emotional lability, anxiety, depression, muscle cramps, spasticity, and pain. Nutrient supply via PEG improves nutrition and quality of life and should be instituted before respiratory failure develops or the patient is lost to much of the body weight. Non-invasive ventilation (NIV) also improves survival and quality of life and should be offered. Preserving the patient's ability to communicate is important.

Denmark

Ninety-five percent of all people diagnosed with ALS in Denmark accept referral from their hospital to the national Rehabilitation Centre for Neuromuscular Diseases (RCND), which develops and supports multidisciplinary approaches in rehabilitation and palliation, at a personal, family and community level [143].

From the moment the diagnosis of ALS is made, it is recommended to receive physiotherapeutic guidance, training and possibly manual treatment. Physiotherapy cannot slow down the disease, but the physiotherapist can, through guidance and treatment, help the person with ALS to utilize their strengths and maintain their activity level as best as possible. A speech therapist may also be employed to support the patient with exercises to train their speech and suggest different communication aids. Other aids for ALS patients – such as walking/mobility aids, wheelchairs, and other assistive devices – are granted by the municipal assistive devices department [33].

It is recommended that palliative care specialists are involved as the disease progresses, and even earlier, to ensure that the patient and their family have appropriate end-of-life plans.

Riluzole is the only medical treatment recommended for treatment of ALS in Denmark. Riluzole is approved as a disease-modifying medication for patients with ALS, but there is no evidence of efficacy in isolated first neuron loss (in PLS) or isolated second neuron loss (in PMA). Riluzole can prolong the initial phase of the disease but seems to have an effect only in the first six months of

treatment. This postpones the time to death or ventilator by approx. 3 to 6 months, but no effect on the disability has been shown. Discontinuation can be considered in case of side effects, late in the course and if a ventilator is needed. The dosage is 50 mg twice per day. Treatment should be initiated by a specialist in neurology. Liver counts must be taken before starting and checked for side effects, every 3 months for the remainder of the first year of treatment and occasionally thereafter [144].

1.5. Description of the intervention, anticipated place in the treatment pathway

Pharmaceutical form: tofersen 100mg solution for intrathecal injection; 15 ml vial containing 100 mg of tofersen. Each ml contains 6.7 mg of tofersen.

Please refer to the Summary of Product Characteristics (SmPC) for further information on tofersen [126].

1.5.1. Indication

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

1.5.2. Posology and method of administration

Posology: Recommended dose is 100 mg of tofersen per treatment.

Loading doses: 3 loading doses administered at 14-day intervals.

Maintenance doses: Once every 28 days thereafter.

Method of administration: Intrathecal, by lumbar puncture. Performed or under the direction of, healthcare professionals experienced in performing the procedure.

Should the pharmaceutical be administered with other medicines? No

Treatment duration / Criteria for end 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.

Necessary monitoring, both during administration and during the treatment period: Additional monitoring or guided lumbar puncture might be required by the individual patient.

Need for diagnostic or other test: Genetic testing and screening for the *SOD1* mutation is necessary to identify the patients who can benefit from tofersen.

Mode of action

QALSODY™ (tofersen) is an antisense oligonucleotide (ASO) designed to bind to *SOD1* mRNA to reduce *SOD1* protein production. Tofersen causes degradation of *SOD1* mRNA through binding to *SOD1* mRNA, which results in a reduction of *SOD1* protein synthesis.

1.5.3. Anticipated placement in treatment pathway

It is expected that initial treatment with tofersen will follow EAN guidelines [139] and be the first option for ALS patients with an identified *SOD1* mutation. Tofersen is expected to be given in combination with riluzole given that the latter has proven to exert a modest effect on survival. Current clinical trials [18] included participants who used tofersen alone, tofersen with riluzole,

tofersen with edaravone, and tofersen with riluzole and edavaravone. As edaravone is not EMA approved, we have based this documentation on the concomitant use of riluzole and tofersen.

1.5.4. Comparator (Standard of care)

In the clinical setting, the current standard of care (SoC) in Finland, Norway, Sweden, and Denmark for adult ALS patients is treatment with riluzole.

In the Nordic countries, there is not a standardized routine for genetic testing and/or screening of ALS, and the disease is diagnosed by clinical assessment of signs and symptoms. Therefore, riluzole is offered to all patients diagnosed with ALS irrespective of the underlying disease mechanism i.e., all *SOD1*-ALS patients are currently offered riluzole as standard of care.

According to Nordic clinical experts, concomitant treatment with riluzole is anticipated in clinical practice [145] for *SOD1*-ALS patients also upon introduction of tofersen.

1.5.4.1. Description of riluzole (SoC in the Nordic countries)

Pharmaceutical form: Oral tablet or oral suspension

Posology: 50 mg twice a day every 12 hours. Should be taken at the same time every day (e.g. morning and evening)

Method of administration: Oral

Should the pharmaceutical (or other method) be administered with other medicines?: No

Treatment duration / Criteria for end of treatment: Lifetime

Necessary monitoring, both during administration and during the treatment period: Regular monitoring with specialist.

Need for diagnostic or other test: No

1.6. European treatment guidelines and recommendations

The newly published EAN guideline on the management of ALS from March 2024 - has *strongly recommended* the novel treatment with tofersen as a first-line treatment in patients with progressive ALS caused by pathogenic mutations in *SOD1*. The guideline is published in collaboration with the European Reference Network for Neuromuscular Diseases (ERN EURO-NMD) [139] and in it, riluzole is the only strongly recommended treatment for *all* patients with ALS at a dosage of 50 mg twice daily. Other therapies (edaravone, cell-based therapies) were not recommended.

2. Clinical evidence

2.1. Overview of literature

A clinical systematic literature review (cSLR) was performed to identify relevant clinical and safety studies of disease modifying therapies for ALS. The report of this cSLR is included as a separate file with the name “cSLR of tofersen in ALS”. Please refer to this document for a full overview of the literature review, search strategy, study selection and quality assessment.

2.1.1. Key outcome measures in ALS trials

Measuring diverse outcomes is important as ALS impacts multiple aspects of patient and caregiver life. Below is a summary table of outcome measures recommended by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidance for ALS clinical trials.

See also Section 1.2.7 and above for a more detailed explanation of the different measures.

Table 5. Summary of ALS trial outcome measures

ALS impacts	FDA/EMA recommended endpoint type [146, 147]	Measures used	Clinically meaningful change in ALS population
Function	Primary; Secondary	ALSFRS-R	90% and 100% of clinicians endorsed a 20% and 25% or higher change in the ALSFRS-R score as being at least somewhat clinically meaningful, respectively[65] 2-point change in ALSFRS-R scores on the gross motor, bulbar and respiratory domains was considered moderately or very clinically meaningful by >50% of the experts, while a 2-point change on the fine motor domain was considered moderately or very clinically meaningful by 42% of experts. Three-point changes (but not two-point changes) were rated as moderately or very clinically meaningful by the majority of experts when the changes involved multiple functional domains [148] A 2-point change in single domains was also perceived to be clinically meaningful by most respondents, except for the fine motor domain, where a 3-point change was believed to be clinically meaningful [149]
Strength	Primary, Secondary, or Exploratory	HHD	No data available on meaningful change thresholds derived for patients with ALS
Survival	Primary or Secondary	Time to death or PV; JRT	No data available on meaningful change thresholds derived for patients with ALS
Respiratory	Secondary	SVC; FVC	No data available on meaningful change thresholds derived for patients with ALS
Biomarkers	-	Plasma NfL; Total CSF *SOD1*; MUNIX	No data available on meaningful change thresholds derived for patients with ALS

Abbreviations: ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS Functional Rating Scale Revised; CSF, cerebrospinal fluid; EMA, European Medicines Agency; FDA, Food and Drug Administration; FVC, forced vital capacity; HHD, hand-held dynamometry; JRT, Joint Rank Test; MUNIX, Motor Unit Number Index; NfL, neurofilament; PV, permanent assisted ventilation; SVC, allow vital capacity.

2.2. Summary of clinical evidence

2.2.1. Clinical evidence for the intervention: tofersen

Table 6. Summary of clinical efficacy studies for intervention (tofersen)

VALOR + OLE	
Study ID (NCT number)	VALOR study and open-label extension (OLE) (NCT02623699)
Study design	Multicenter*, Phase 3, double-blind, randomized, placebo-controlled **Locations: Belgium, Canada, Denmark, France, Germany, Italy, Japan, United Kingdom and United States [18, 150].*
Intervention	Tofersen
Comparator	Placebo (riluzole or Edaravone)
Primary endpoint	Change from baseline in ALSFRS-R total score (included in the model). Statistical significance was not achieved on the primary analysis in VALOR (faster-progressing population) at Week 28. Over the longer-term in the overall (ITT) population, the early-start participants experienced a nominally statistically significant slower decline from baseline to Week 52 on the ALSFRS-R than the placebo/delayed-start participants, with an adjusted mean difference of 3.5 (95% CI: 0.4–6.7, p=0.0272). This slower decline in early-start patients persisted at Week 104, wherecompared to placebo/delayed-start participants, the early-start participants demonstrated an adjusted mean difference of 3.7 (95% CI: -0.7, 8.2, ANCOVA+MI p=0.1004).
Secondary and safety endpoint(s)	The secondary endpoints were tested sequentially in the following rank order: • Change from baseline (ratio) to Week 28 in total *SOD1* concentration in CSF • Change from baseline (ratio) to Week 28 in NfL concentration in plasma • Change from baseline (ratio) to Week 28 in percent predicted SVC • Change from baseline (ratio) to Week 28 in HHD megascore • Ventilation assistance-free survival (time to earliest occurrence of either death or permanent ventilation) • Overall survival (time to death) - *SOD1 concentration in CSF:* Reductions in total CSF SOD1 were apparent by 8 to 12 weeks of tofersen use and were sustained over time. At Week 52, the percent reduction (geometric mean ratio) from baseline was 21% (95% CI: 4–35) and 33% (95% CI: 21–42) for the delayed- and early-start tofersen groups, respectively. -*NfL:* Plasma NfL declined through approximately Week 16, and the reductions were sustained over time, suggesting that tofersen administration reduced axonal injury and neurodegeneration. At Week 52, the percent reduction (geometric mean ratio) from baseline was 41% (95% CI: 26–54) and 51% (95% CI: 42–60) for the delayed- and early-start tofersen groups, respectively.

	-*Respiratory Function:* Over the longer-term in the ITT population, the early-start participants experienced a nominally statistically significant slower decline from baseline to Week 52 on percent-predicted SVC than the placebo/delayed-start participants. At Week 52, the percent-predicted SVC adjusted mean difference was 9.2 (95% CI: 1.7–16.6, p=0.0159). - *Muscle Strength:* Early-start participants experienced a nominally statistically significant less decline from baseline to Week 52 in HHD megascore than the placebo/delayed-start participants. Although the placebo/delayed-start group declined more than the early-start group over the 52-week period, they did experience an apparent stabilization in decline across measures of function and strength beginning around Week 40. - *Ventilation free-survival:* Though the median time to death or permanent ventilation and median time to death were still not estimable due to the limited number of events observed, available data provides early evidence of a prolongation of event-free survival with earlier tofersen initiation. That the median wasn't reached suggests that mortality is reduced with tofersen (in comparison to natural history). -*Time to death:* The short survival of *SOD*1-ALS patients makes it imperative to capture the effect of tofersen on time to death and time to death or permanent ventilation. There was an apparent reduction in the risk of death or permanent ventilation (PV) (HR: 0.36, 95% CI: 0.137-0.941) and the risk of death (HR: 0.27, 95% CI: 0.084-0.890) in the early-start compared with the delayed-start group. Safety endpoint (not included in the model): -*Weight*: Weight was collected as part of the safety battery in VALOR. Weight loss has been found to be a strong independent predictor of survival in ALS. The average weight increased in the tofersen group (mean change from baseline at Week 28 [±SD]: 0.5 kg [±4.4]) and decreased in the placebo group (mean change from baseline at Week 28 [±SD]: -1.6 kg [±5.4]) (Figure 19)
Exploratory endpoints	Patient reported outcomes captured by the EQ-5D-5L utility score are used for enrichment of the health economic analysis. Additional outcomes as ALSAQ-5 and FSS The early-start tofersen group had nominally statistically significant less worsening of QoL at week 52 as measures by the ALSAQ-5 total score (adjusted mean difference: -10.3, 95% CI: -17.3 to -3.2, p=0.0044). For both EQ-5D-5L utility score (included in the model) (adjusted mean difference: 0.2, 95% CI: 0.13 to 0.32, p<0.0001) and FSS (-3.8, 95% CI: -9.0 to 1.38, p=0.1493), trends consistently favored early tofersen administration.
Observation time	104 weeks; note: some results above are presented at 52 weeks. OLE is still continuing past 104 weeks (due to end late Sept 2024)
Data cuts *primary analysis and later planned analyses*	VALOR completed: 2021-07-16 OLE data cuts: 2021-07-16, 2022-01-16, 2023-02-18.
Proportion of patients with stabilization or improvement in outcomes	A subset of tofersen-treated participants experienced sustained stabilization or improvement in function and strength. In the early-start

	tofersen group the proportion of patients that experienced improvements or stabilization over 104 weeks are: - *ALSFRS-R:* 23.5% - *percent-predicted SVC*: 21.1% - *HHD megascore*: 20.2%

Note: All the function, strength, survival, and respiratory primary and secondary endpoints incorporated into tofersen's VALOR trial are recommended by the FDA and EMA guidance (Table 5) [146, 147].

Table 7. Summary of relevant supportive studies used in health economic modelling for intervention (tofersen)

SAD (Phase 1) and MAD (Phase 1/2) trials (NCT02623699)	
Study ID (NCT number)	These trials were included in the three-part trial (NCT02623699) that also included VALOR as a part C. Part A: Single Ascending Dose (SAD) Part B: Multiple Ascending Dose (MAD)
Study design	Phase 1-2, randomized, double-blind, placebo-controlled trial
Population	Adults with ALS due to *SOD1* mutations
Intervention	Tofersen in ascending doses of 20, 40, 60 or 100mg administered intrathecally for 12 weeks
Comparator	Placebo administered intrathecally for 12 weeks
Observation time	Participants were followed for up to 31 weeks, which comprised a screening period of up to 7 weeks followed by a 12-week intervention period and 12-week follow-up.
Study completion date *primary analysis and later planned analyses*	The study completed on 16 July 2021.
How is the data from this study used in the assessment?	This was an early phase study to assess the safety and pharmacokinetics (PK) of tofersen in order to find the adequate dose for further efficacy studies. It is directly not used in the assessment but is included for information.

Table 8. Summary of relevant ongoing studies used in health economic modelling for intervention (tofersen)

ATLAS	
Title of the study and RCT (clinical-trials.gov)	A Phase 3 Randomized, Placebo-Controlled Trial With a Longitudinal Natural History Run-In and Open-Label Extension to Evaluate BIIB067 Initiated in Clinically Presymptomatic Adults With a Confirmed Superoxide Dismutase 1 Mutation- The ATLAS Study (**NCT04856982)**
Objective of the study (Patient pop., etc.)	**Primary objective:** evaluate the efficacy of tofersen in presymptomatic adult carriers of a *SOD1* mutation with elevated neurofilament. **Secondary objective:** evaluate the safety and tolerability of tofersen and to evaluate the effect of tofersen on pharmacodynamics/treatment response

	biomarkers when initiated prior to versus at the time of emergence of clinically manifest ALS. **Population:** presymptomatic adult carriers of a *SOD1* mutation.
Intervention	Tofersen 100mg via intrathecal injection
Comparator	Placebo via intrathecal injection
Outcome	**Primary outcome:** percentage of participants with emergence of clinically manifest ALS within 12 months **Secondary outcomes:** Percentage of participants with emergence of clinically manifest ALS within 24 months [Time Frame: Up to 24 months] Time to emergence of clinically manifest ALS [Time Frame: Up to 2 years] Change in ALS Functional Rating Scale (ALSFRS-R) total score [Time Frame: Up to 2 years] Change from baseline in percent Predicted Slow Vital Capacity (SVC) [Time Frame: Up to 2 years] Percentage of participants with outcome as Death or Permanent Ventilation Based on Time to Death or Permanent Ventilation Analysis [Time Frame: Up to 2 years] Permanent ventilation is defined as ≥22 hours of invasive or non-invasive mechanical ventilation per day for ≥21 consecutive days. Percentage of participants with outcome as Deaths Based on Time to Death Analysis [Time Frame: Up to 2 years] Number of participants with Adverse Events (AEs) and Serious Adverse Events (SAEs) during the treatment period [Time Frame: Up to 2 years] Change from baseline in plasma NfL concentrations [Time Frame: Up to 2 years] Change in total cerebrospinal fluid (CSF) *SOD1* concentrations [Time Frame: Up to 2 years]
Starting date	April 23, 2021
Expected end date	August, 2027

2.2.2. Clinical evidence for the comparator: SoC

A cSLR was performed to identify relevant studies reporting the efficacy and safety of SoC (riluzole and edaravone) for ALS patients; please refer to Appendix E. Clinical Systematic Literature Review). However, none of these studies were directly used in the cost-effectiveness model and are therefore not described in this section.

In the cost-effectiveness model, natural history data from PRO-ACT was used to inform the inputs for SoC (see Section 3.8.1-3.8.2).).

The PRO-ACT database is a multinational registry of prospective clinical trials and includes merged, deidentified data from over 10,700 patients with ALS who participated in 23 phase 2/3 clinical trials [151]. More than 3,500 of those patients have longitudinal records of ALSFRS-R, a subjective functional assessment commonly used as a primary endpoint in ALS clinical trials [63]. A summary of the results of an SLR exploring studies that report natural history and/or prognostic outcomes is provided in Appendix D.

2.3. Efficacy results per study (intervention and comparator)

2.3.1. Intervention studies: VALOR + OLE

2.3.1.1. Study design and methodology

VALOR study

VALOR was a randomized, multicentre, double-blind, placebo-controlled Phase 3 study of tofersen administered to 108 adults participants (intent to treat (ITT) population) with weakness attributed to ALS and a confirmed *SOD1* mutation (locations: Belgium, Canada, Denmark, France, Germany, Italy, Japan, United Kingdom and United States) [18, 150]. Participants were randomized 2:1 to tofersen 100mg (n=72) or placebo (n=36) for ~6 months; each participant received a 15 mL intrathecal bolus of study treatment or placebo, which was administered alongside standard of care (riluzole and/or edaravone), which was permitted at stable dose [18, 150]. Three loading doses were administered approximately once every 2 weeks, followed by 5 maintenance doses administered approximately once every 4 weeks. The prespecified primary analysis population (i.e. modified intent-to-treat [mITT], "enriched", "faster-progressing/faster progressor") comprised participants who met the prognostic enrichment criteria for rapid disease progression defined according to *SOD1* mutation type and prerandomization ALSFRS-R slope (n=60). All other participants were classified as the non-mITT (i.e. "other", "slower-progressing") population (n=48) (Table 9).

Table 9. Study enrichment

	Protocol-defined disease progression subgroups		
	Enriched primary analysis cohort "Faster-progressing" (mITT[a], n=60)		"Slower-progressing" (non-mITT[a], n=48)
***SOD1* mutation**	***SOD1* mutation historically associated with shorter survival[b]**	**Another *SOD1* mutation**	**Another *SOD1* mutation**
Pre-randomization ALSFRS-R slope decline	**≥ 0.2 points/month[c]**	**≥ 0.9 points/month[c]**	**No requirement**
SVC cutoff	**≥ 65% predicted**		**≥ 50% predicted**

[a]The study-defined mITT population was the subset of this cohort that was randomized and received at least one dose of study treatment; all other participants comprise the non-mITT population; formal statistical testing of primary endpoint and key secondary endpoints (plasma NfL, SVC, HHD, time to death, time to death or PV) performed in enriched primary analysis population (mITT) only. bp.Ala5Val, p.Ala5Thr, p.Gly42Ser, p.His44Arg, p.Gly94Ala, p.Leu107Val, p.Leu39Val, p.Val149Gly, p.Leu85Val. cPre-randomization ALSFRS-R slope was calculated as [(48 – baseline score) / (time since symptom onset)]; Abbreviations: SVC= slow vital capacity.

Open-label extension

An ongoing open-label extension (OLE) assesses the long-term effects of 100 mg tofersen in participants who previously completed VALOR and SAD/MAD [18]. All participants in the OLE had the opportunity to receive tofersen 100 mg and have been followed up for approximately 3-7 years, depending on timing of enrolment. Of the 108 randomized and dosed ITT population in VALOR, 63 participants from the tofersen arm (88%) and 32 participants from the placebo arm (89%) enrolled in the OLE study. Interim data cuts of the OLE were performed on 16 July 2021 (at the time that VALOR was completed), on 16 January 2022 (when all participants from VALOR had the opportunity for at

least 12 months follow-up), and on 28 February 2023 (as requested by the Committee for Medicinal Products for Human Use (CHMP), to offer an additional > 12 months of follow-up).

To enable longer follow-up, the tofersen development program was prospectively designed to evaluate crossover from VALOR to the OLE via an integrated analysis plan. This integration enables comparison of early-start tofersen (participants who initiated tofersen in VALOR and continued tofersen in OLE) versus delayed-start tofersen (participants who received placebo in VALOR and initiated tofersen in the OLE approximately 6 months later) (Figure 5). The participant disposition for the VALOR + OLE studies as of February 28th, 2023, is shown in Figure 6**.** By this date, all participants enrolled in VALOR had the opportunity for at least 2 years of follow-up, with a median opportunity for follow-up if 3.4 years (range: 2.2-3.9 years).

Figure 5. VALOR and OLE study design

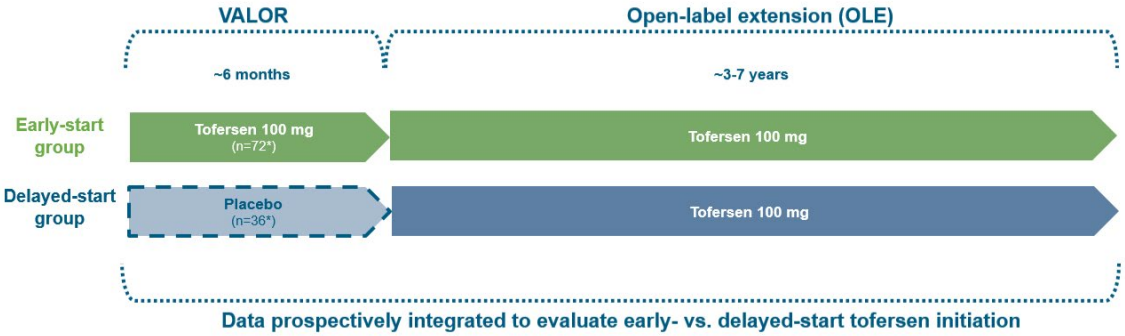
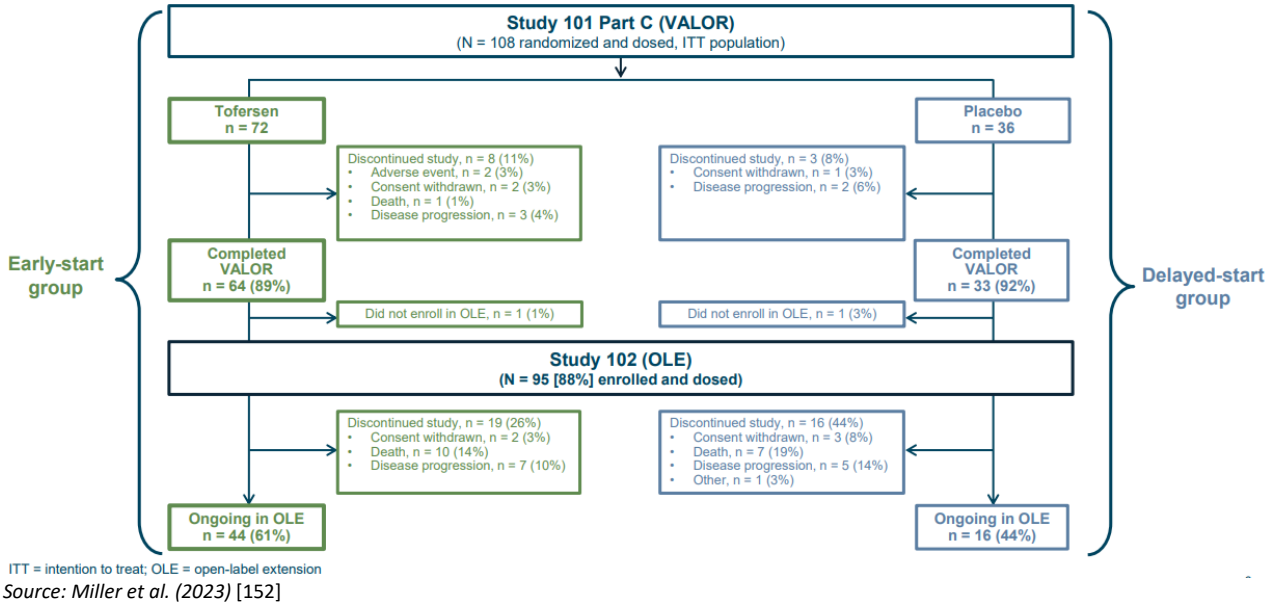


Figure 6. VALOR/OLE participant disposition (Feb 2023)



ITT = intention to treat; OLE = open-label extension

Source: Miller et al. (2023) [152]

VALOR + OLE

When VALOR was designed, *SOD1* mutation type and pre-randomization ALSFRS-R slope were thought to be appropriate tools to control for disease heterogeneity and were used to create study population subgroups (mITT and non-mITT)[18]:

- *SOD1* mutation type was incorporated as it can, in some cases, differentiate between very quickly progressing and slowly progressing phenotypes. However, between individuals carrying the same mutation, there is significant variability in disease progression (i.e., intra-mutation variability), limiting its prognostic utility over a relatively short study period. Even a single individual with *SOD1*-ALS exhibits variability in the rate of disease progression over time as measured by clinical outcome scores (e.g., periods of faster/slower progression).
- Pre-randomization ALSFRS-R slope was incorporated based on previous clinical experience[18]. However, this approach is limited by nonlinear progression of the ALSFRS-R, with periods of stable disease preceded or followed by periods of rapid decline [153, 154]. The utility of ALSFRS-R slope is therefore limited as a marker of active disease progression at a specific point in time (e.g., baseline) and conveys limited prognostic value.

Inclusion of Plasma neurofilament as control for heterogeneity

Reliance on these enrichment criteria led to imbalances in key baseline disease characteristics between treatment groups such that baseline NfL levels were higher in the tofersen group, and ALSFRS-R run-in slope (from Screening to Day 15) was faster in the tofersen group. These imbalances suggest that participants in the tofersen group were progressing more quickly than those in the placebo group at baseline.

While the utility of neurofilament as a mechanism to control for heterogeneity was not fully appreciated at the time VALOR was designed, emerging literature illustrating that neurofilament is prognostic for disease progression and survival in ALS led to prespecifying alternative disease progression subgroups defined according to baseline plasma NfL, correcting for key imbalances in baseline characteristics. However, adjustment for baseline NfL level as a continuous variable provides greater precision than a categorical (and semi-arbitrary) subgrouping of the population[155]. Accordingly, prior to the analysis of the VALOR data cut-off of 16 January 2022 and the 12-month OLE data, the integrated statistical analysis plan (SAP) was updated to include covariate adjustment for baseline levels of plasma NfL. Adjusting for baseline NfL as a continuous covariate, accounts more accurately for baseline disease heterogeneity and thus, permitted analyses in the larger ITT population (n=108), increasing power compared to analyses in disease progression subgroups.

A second interim data cut of the OLE was performed on February 28th, 2023, at the request of CHMP, when all participants from VALOR had the opportunity for > 24 months of follow-up.

Since only the first 6 months of this 2+ year follow-up period included a placebo control, after which all participants were offered the opportunity to receive open label tofersen, it was anticipated that both the early and delayed start groups may experience convergence with longer follow-up. While some convergence was seen, separation of the two groups remained at the 2+ year mark, highlighting the continued benefit of early treatment with tofersen.

2.3.1.2. Statistical analyses

An ANCOVA is a type of ANOVA that controls the linear effect of covariate variables by using a regression analysis, allowing for independent analysis of one independent variable at a time without the influence of other covariates [156, 157]. For multiple imputation and ANCOVA (MI+ANCOVA) analyses in VALOR+OLE, the ANCOVA model included covariates of (1) corresponding baseline score for the endpoint (continuous), (2) baseline plasma NfL (not adjusted for when analysing total CSF *SOD1* protein concentration), and (3) riluzole or edaravone use. The model was used to estimate least-square (LS) means for each treatment group with standard errors (SEs), and LS mean

differences between treatment groups with corresponding 95% confidence intervals (CIs). The p-values comparing treatment differences are presented for ITT.

The joint rank test (JRT) allows for a statistical test of the treatment effect on the ALSFRS-R total score while accounting for truncating of data due to deaths. A joint rank score was calculated by comparing each participant with every other participant in the study, resulting in a score of +1 if the outcome was better than the participant being compared, -1 if worse, and 0 if the same. Each participant's score was then calculated by summing their comparison to all the other participants in the study. MI was used to impute the ALSFRS-R score for participants who withdrew for reasons other than death prior to calculating the rank score. Participants who completed the study or withdrew due to reasons other than death were compared against their ALSFRS-R total score in separate analysis (imputed score for those who withdrew). These participants were ranked higher than those who died. Participants who died were compared against each other based on their time to death, with the lowest ranks being given to those who died in the shortest time after first dose. The ranked scores were analysed using an ANCOVA model with treatment included as fixed effect and adjusted for the following covariates: baseline plasma NfL, baseline ALSFRS-R total score, and use of riluzole or edaravone.

2.3.1.3. Study population

The intent-to-treat (ITT) population (n=108) comprised all randomized participants who received at least 1 dose or a part of 1 dose of study treatment (tofersen or placebo).

The mITT population (i.e. "enriched", "faster-progressing/faster progressor") comprised participants who met the prognostic enrichment criteria for rapid disease progression defined according to *SOD1* mutation type and pre-randomization ALSFRS-R slope (n=60) (see Table 9). All other participants were classified as the non-mITT (i.e. "other", "slower-progressing") population (n=48). The primary analysis for VALOR was performed in the mITT population i.e. participants predicted to have faster progression based on mutation type and/or progression rate.

After completion of VALOR, 95 participants (88%) were enrolled in the nonrandomized OLE, with 63 (88%) originally assigned to receive tofersen and 32 (89%) originally assigned to receive placebo. As outlined above, analyses of the integrated VALOR and OLE data (results at 52 weeks and 104 weeks) focused on the ITT population.

2.3.1.4. Important inclusion and exclusion criteria

Inclusion criteria included: adults ($\geq$18 years of age) with weakness attributable to ALS and confirmed *SOD1* mutation at Screening Visit; SVC $\geq$65% of predicted value as adjusted for age, sex, and height from the sitting position (for participants who met prognostic enrichment criteria for rapid disease progression [mITT]) and SVC $\geq$50% of predicted value as adjusted for age, sex, and height from the sitting position (for all other eligible participants, non- mITT). Concomitant use of edaravone and/or riluzole was permitted, assuming the patient was on a stable dose for at least 30 or 60 days prior to Day 1, respectively, and expected to remain on that dose through end of study.

Exclusion criteria included: A history of a positive test for HIV; current hepatitis C or B infection; treatment with another investigational drug or current enrolment in another interventional study; current or recent use of copper or pyrimethamine; or current or anticipated need, in the Investigator's opinion, of a diaphragm pacing system during the study period.

2.3.1.5. Pre-planned subgroups

Owing to the potential for nonlinear progression on the ALSFRS-R score and for intra-mutation variability confounding the prognostic value of these measures, as well as literature supporting the use of neurofilament light chains as a prognostic marker of disease progression, analyses in subgroups that were defined according to baseline concentrations of neurofilament light chains in plasma (above vs. below the median concentration for the trial population) were prespecified before VALOR results were available (see above, "Inclusion of Plasma neurofilament as control for heterogeneity").

Prior to the analysis of the VALOR data cut-off of 16 January 2022 and the 12-month OLE data, the integrated SAP was updated to include covariate adjustment for baseline levels of plasma NfL. Adjusting for baseline NfL as a continuous covariate, accounts more accurately for baseline disease heterogeneity and thus, permitted analyses in the larger ITT population (n=108), increasing power compared to analyses in disease progression subgroups.

2.3.1.6. Treatments

The treatments administered in the VALOR (Part C) trial for the intervention (tofersen) and comparator (placebo) arms are presented in Table 10 below.

Table 10. Treatments administered in the VALOR (Part C) trial

Treatment	Dosage and Regimen
Tofersen	100 mg administered on day 1, 15, and 29 initially and every 4 weeks thereafter by intrathecal injection
Placebo	Matching placebo administered by intrathecal bolus over 1-3 minutes, following the same dosing regimen as tofersen

Source: [158] [VALOR C trial protocol]

Details on the concomitant use of edaravone and riluzole are outlined in Table 11 below.

Table 11. Allowed concomitant therapy- VALOR (Part C) trial

Concomitant Therapy	Requirements
Riluzole	Subjects taking concomitant riluzole at study entry must be receiving a stable dose for ≥ 30 days prior to the first dose of study treatment (Day 1). These subjects should remain on this stable dose of riluzole until the completion of the Week 12 Visit, unless riluzole use must be discontinued in the judgment of the Investigator, in which case it should not be restarted until the completion of the Week 12 Visit. If subjects are not receiving riluzole at Day 1, they should not initiate it until the completion of the Week 12 Visit.
Edaravone	Subjects taking concomitant edaravone at study entry must have initiated edaravone ≥ 60 days (2 treatment cycles) prior to the first dose of study treatment (Day 1). Edaravone may not be administered on dosing days of this study. These subjects should remain on this stable dose of edaravone until the completion of the Week 12 Visit, unless edaravone use must be discontinued in the judgment of the Investigator, in which case it should not be restarted until the completion of the Week 12 Visit. If subjects are not receiving edaravone at Day 1, they should not initiate it until the completion of the Week 12 Visit.

2.3.1.7. Study endpoints

The objective of the study was to evaluate the clinical efficacy and safety of tofersen in adult patients with ALS and a confirmed *SOD1* mutation.

The primary endpoint of VALOR was the change from baseline to Week 28 in total ALSFRS-R score, and was powered based on those who met the prognostic enrichment crietria for faster progression and was only formally tested in this population [18]. In the slower-progressing population, it was not expected to see an adequate decline on clinical function in the placebo arm over 6 months to detect separation between treatment groups. However, given that total CSF *SOD1* protein does not correlate with disease progression, formal testing of this biomarker was perfomed in the slower-progressing population, dictating the sample size of this subgroup.

Secondary endpoints were tested sequentially in the following rank order:

- Change from baseline (ratio) to Week 28 in total *SOD1* concentration in CSF
- Change from baseline (ratio) to Week 28 in NfL concentration in plasma
- Change from baseline (ratio) to Week 28 in percent predicted SVC
- Change from baseline (ratio) to Week 28 in HHD megascore
- Ventilation assistance-free survival (time to earliest occurrence of either death or permanent ventilation)
- Overall survival (time to death)

2.3.1.8. Baseline characteristics

A total of 108 participants were enrolled; 72 were assigned to receive tofersen and 36 to receive placebo [18]. Out of the 108 participants, 60 met the prognostic enrichment criteria for rapid disease progression and made up the faster-progression (mITT) subgroup in which the primary analysis was performed. A total of 42 unique *SOD1* mutations were included in the study, with the most common being p.Ile114Thr (n=20), p.Ala5Val (n=17), p.Gly94Cys (n=6) and p.His47Arg (n=5).

Baseline clinical characteristics were similar in the two groups for use of riluzole, edaravone, or both, time from symptom onset, baseline ALSFRS-R score, and percentage of predicted SVC[18]. However, baseline concentrations of NfL were 15-25% higher in participants who received tofersen than in those who received placebo, and the rate of decline in the ALSFRS-R score from Screening to Day 15 (a period of approximately 42 days) was greater in participants who received tofersen.

Baseline characteristics from VALOR are summarized in Table 12. For key baseline characteristics stratified by NfL refer toAppendix F – Key baseline characteristics stratified by NfL

Table 12. VALOR baseline characteristics

	Faster-progression (mITT) subgroup (N=60)[a]		Slower progression (non mITT) subgroup (N=48)		Overall (ITT) population (N=108)	
	Placebo (n=21)	**Tofersen 100 mg (n=39)**	**Placebo (n=15)**	**Tofersen 100 mg (n=33)**	**Placebo (n=36)**	**Tofersen 100 mg (n=72)**
Riluzole Use n (%)	13 (62)	25 (64)	9 (60)	20 (61)	22 (61)	45 (63)
Edaravone Use n (%)	1 (5)	2 (5)	2 (13)	4 (12)	3 (8)	6 (8)
Time from symptom onset (m)[b]						
Median (Q1, Q3) Range: min, max	8.3 (5.1, 12.1) 2.4, 21.3	8.3 (6.0, 10.4) 1.7, 18.5	39.6 (30.3, 53.6) 11.8, 103.2	35.5 (19.5, 60.9) 3.9, 145.7	14.6 (6.6, 32.0) 2.4, 103.2	11.4 (7.2, 28.9) 1.7, 145.7
Concentration of NfL in plasma (pg/mL)						
Mean (SD) Range: min, max	127.3 (94.4) 9, 370	146.2 (82.6) 12, 329	37 (29.5) 8, 99	47.6 (41.8) 5, 211	89.7 (86.5) 8, 370	100.4 (82.8) 5, 329
ALSFRS-R pre-randomization slope (points per month)[c]						
Mean (SD) Range: min, max	-1.81 (1.2) -4.91, -0.42	-1.74 (1.6) -8.30, -0.39	-0.26 (0.3) -0.84, -0.02	-0.30 (0.2) -0.77, 0.00	-1.16 (1.2) -4.91, -0.02	-1.08 (1.4) -8.30, 0.00
ALSFRS-R run-in slope (points per month)[d]						
Mean (SD) Range: min, max	-1.3 (3.9) -11, 10	-1.8 (2.5) -9, 3	0.1 (1.9) -3, 4	-0.1, 1.3 -3, 4	-0.7 (3.3) -11, 10	-1.0 (2.2) -9, 4
ALSFRS-R baseline total score						
Mean (SD) Range: min, max	35.4 (5.7) 24, 45	36.0 (6.4) 15, 44	39.9 (5.1) 32, 47	38.1 (5.1) 26, 48	37.3 (5.8) 24, 47	36.9 (5.9) 15, 48
% Predicted SVC at baseline						
mean (SD) Range: min, max	83.7 (17.9) 57.4, 120.4	80.3 (14.2) 46.7, 114.8	87.1 (14.8) 54.8, 114.4	84.2 (19.0) 55.4, 134.7	85.1 (16.5) 54.8, 120.4	82.1 (16.6) 46.7, 134.7

[a] NfL subgroups defined as ≥75.60 pg/mL and <75.60 pg/mL, respectively.
[b] Time since ALS symptom onset is calculated in months as (date of baseline minus date of ALS symptom onset)/30.4375.
[c] Pre-randomization ALSFRS-R slope is calculated using ([maximum possible score of 48] minus [ALSFRS-R score at baseline; Day1])/(time since symptom onset).
[d] Run-in ALSFRS-R slope reflects the rate of decline on ALSFRS-R from screening to Day 15 (~42-day "run-in" period).
Abbreviations: ALSFRS-R = The Revised Amyotrophic Lateral Sclerosis Functional Rating Scale; IQR = interquartile range; ITT = intention to treat; mITT = modified intention-to-treat; NfL = neurofilament; SD = standard deviation; SVC = slow vital capacity.

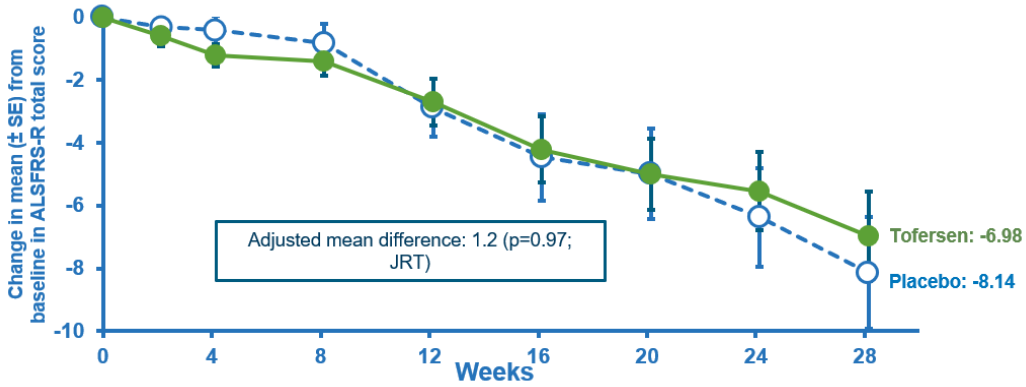
Source: Miller et al. NEJM 2022;387:1099-110 [18].

2.3.1.9. Efficacy results

2.3.1.9.1. Primary endpoint

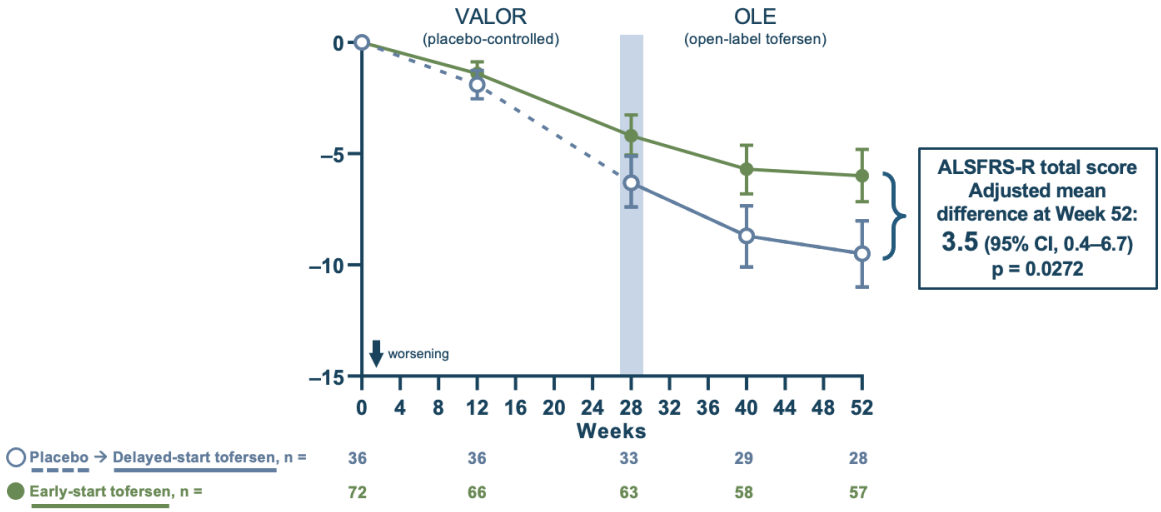
ALSFRS-R [18]: Statistical significance was not achieved in the primary analysis in VALOR (mITT population), where endpoints were measured from baseline to Week 28 (Figure 7). In the OLE, the early-start participants (i.e. patients that received tofersen from the beginning of the VALOR study) experienced a nominally statistically significant slower decline from baseline to Week 52 on the ALSFRS-R than the placebo/delayed-start participants, with an adjusted mean difference of 3.5 (95% CI: 0.4-6.7, p=0.0272) (Figure 8). This slower decline in early-start patients persisted to Week 104. Compared to placebo/delayed-start participants, the early-start participants demonstrated an adjusted mean difference of 3.7 (95% CI: -0.7,8.2, ANCOVA+MI p=0.1004, JRT p=0.0835) (Figure 9).

Figure 7. Tofersen Effect on ALSFRS-R total score at Week 28 (VALOR, mITT population/fast progressors)



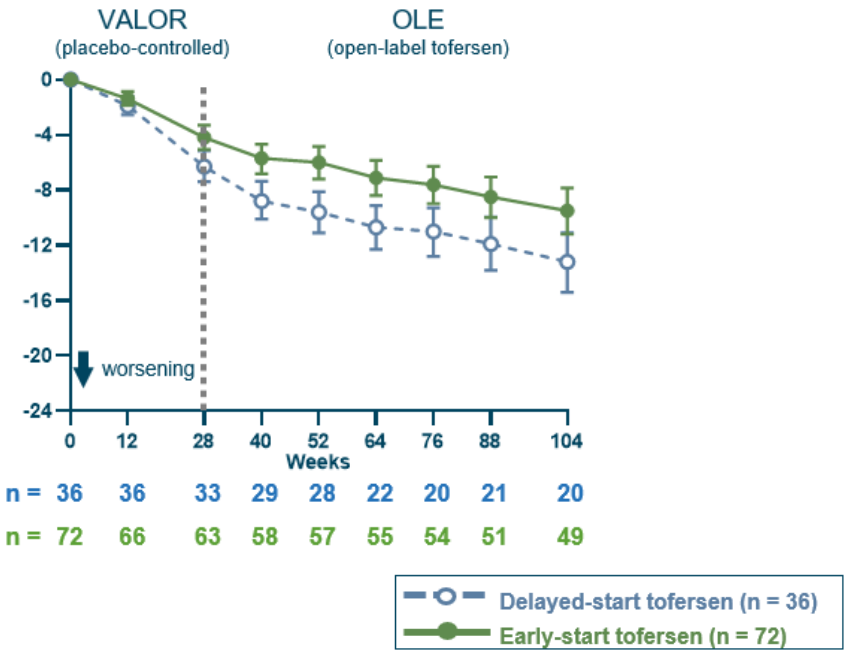
Note: Analysis is based on ANCOVA model in conjunction with multiple imputation for missing data. The model includes covariates for the corresponding baseline value, baseline plasma NfL, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = ALS Functional Rating Scale–Revised; ITT = intent-to-treat; JRT = Joint Rank Test; SE = standard error
Sources: 1. Miller TM et al. ANA 2021; Oct 17-19 2021. 2. Miller TM et al. N Engl J Med 2022;387:1099-110.

Figure 8. Tofersen effect on ALSFRS-R total score at Week 52 (VALOR + OLE, ITT population)



Note: Analysis is based on ANCOVA model in conjunction with multiple imputation for missing data. The model includes covariates for the corresponding baseline value, baseline plasma NfL, and use of riluzole or edaravone.
Abbreviations: ALSFRS-R = ALS Functional Rating Scale–Revised; CI = confidence interval; ITT = intent-to-treat; OLE = open-label extension
Source: Miller et al. N Engl J Med 2022; 387:1099-110

Figure 9. Tofersen effect on ALSFRS-R total score at Week 104 (VALOR + OLE, ITT population)



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

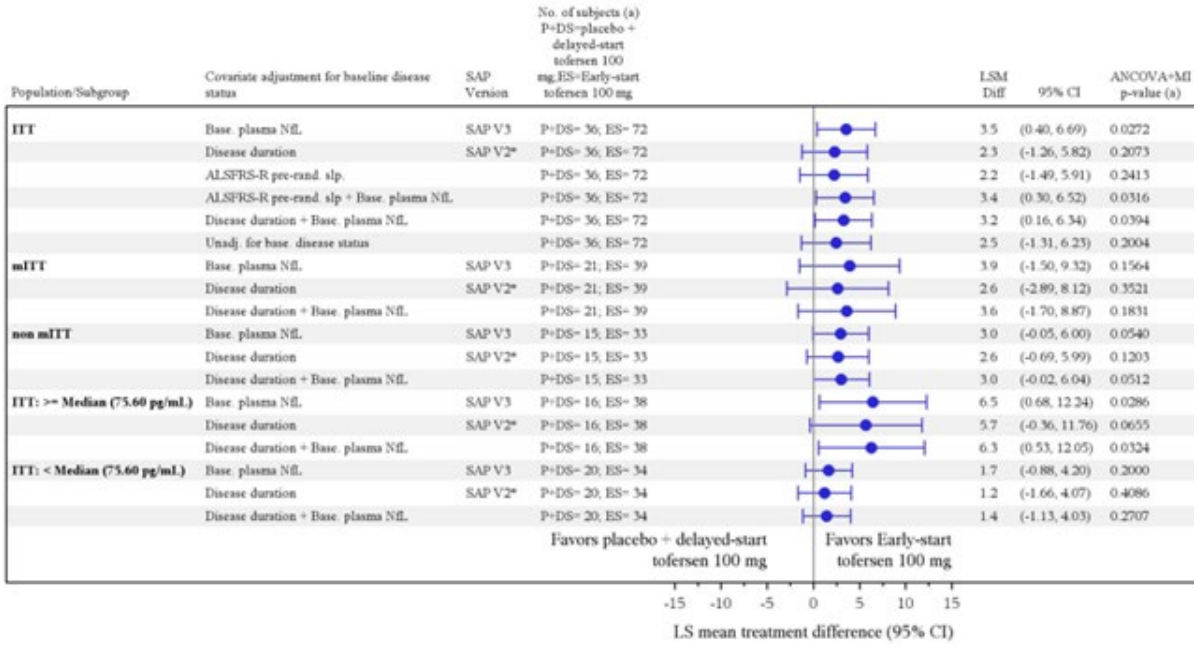
LS means are obtained from the ANCOVA model with treatment included as a fixed effect and adjusted for the following covariates: baseline plasma NfL, baseline ALSFRS-R total score, and use of riluzole or edaravone.

Abbreviations: ALSFRS-R = ALS Functional Rating Scale–Revised; CI = confidence interval; ITT = intent-to-treat; OLE = open-label extension

To further investigate the importance and impact of adjusting for baseline NfL as a continuous covariate, the forest plot in Figure 10 presents the integrated efficacy analyses for the ITT population and disease progression subgroups, adjusting for baseline plasma NfL in the imputation model and analysis model. It is compared with various post-hoc analyses for change from baseline to Week 52 in ALSFRS-R total score that adjust for other covariates for baseline disease status in ANCOVA + MI and JRT + MI (with similar patterns noted in change from baseline to Week 104 in ALSFRS-R total score).

Due to the prognostic value of baseline NfL, analyses in the ITT population adjusting for baseline plasma NfL are the most robust and appropriate analyses to account for baseline disease heterogeneity. Trends in favor of early-start tofersen are consistent across different populations and disease progression subgroups (faster and slower progressors and above/below the median NfL). For key baseline characteristics stratified by NfL refer to Appendix F – Key baseline characteristics stratified by NfL.

Figure 10. ALSFRS-R total score change from baseline to Week 52



Population/Subgroup	Covariate adjustment for baseline disease status	SAP Version	No. of subjects (a) P+DS=placebo + delayed-start tofersen 100 mg,ES=Early-start tofersen 100 mg	LSM Diff	95% CI	ANCOVA+MI p-value (a)
ITT	Base. plasma NfL	SAP V3	P+DS= 36; ES= 72	3.5	(0.40, 6.69)	0.0272
	Disease duration	SAP V2*	P+DS= 36; ES= 72	2.3	(-1.26, 5.82)	0.2073
	ALSFRS-R pre-rand. slp.		P+DS= 36; ES= 72	2.2	(-1.49, 5.91)	0.2413
	ALSFRS-R pre-rand. slp + Base. plasma NfL		P+DS= 36; ES= 72	3.4	(0.30, 6.52)	0.0316
	Disease duration + Base. plasma NfL		P+DS= 36; ES= 72	3.2	(0.16, 6.34)	0.0394
	Unadj. for base. disease status		P+DS= 36; ES= 72	2.5	(-1.31, 6.23)	0.2004
mITT	Base. plasma NfL	SAP V3	P+DS= 21; ES= 39	3.9	(-1.50, 9.32)	0.1564
	Disease duration	SAP V2*	P+DS= 21; ES= 39	2.6	(-2.89, 8.12)	0.3521
	Disease duration + Base. plasma NfL		P+DS= 21; ES= 39	3.6	(-1.70, 8.87)	0.1831
non mITT	Base. plasma NfL	SAP V3	P+DS= 15; ES= 33	3.0	(-0.05, 6.00)	0.0540
	Disease duration	SAP V2*	P+DS= 15; ES= 33	2.6	(-0.69, 5.99)	0.1203
	Disease duration + Base. plasma NfL		P+DS= 15; ES= 33	3.0	(-0.02, 6.04)	0.0512
ITT: >= Median (75.60 pg/mL)	Base. plasma NfL	SAP V3	P+DS= 16; ES= 38	6.5	(0.68, 12.24)	0.0286
	Disease duration	SAP V2*	P+DS= 16; ES= 38	5.7	(-0.36, 11.76)	0.0655
	Disease duration + Base. plasma NfL		P+DS= 16; ES= 38	6.3	(0.53, 12.05)	0.0324
ITT: < Median (75.60 pg/mL)	Base. plasma NfL	SAP V3	P+DS= 20; ES= 34	1.7	(-0.88, 4.20)	0.2000
	Disease duration	SAP V2*	P+DS= 20; ES= 34	1.2	(-1.66, 4.07)	0.4086
	Disease duration + Base. plasma NfL		P+DS= 20; ES= 34	1.4	(-1.13, 4.03)	0.2707

[a] From the listed ANCOVA analysis based on change form baseline. Fast and slow progressors (mutation/slope) are disease progression subgroups based at 28 weeks on mutation type and prerandomization slope (as defined in the protocol) and at 104 weeks on the median baseline plasma NfL (≥ median and <median [75.60 pg/mL], respectively).

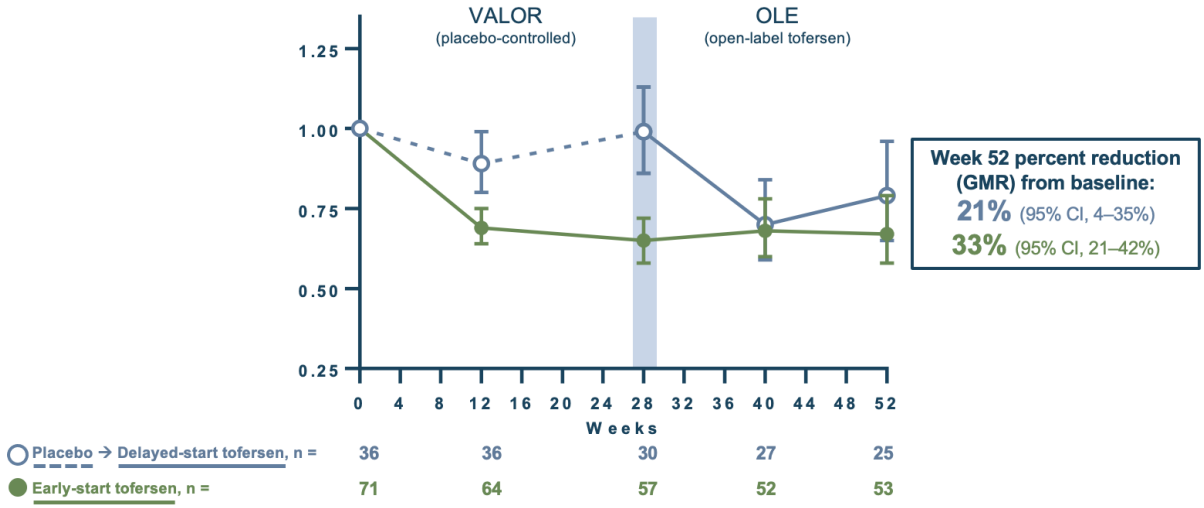
Abbreviations: ALSFRS-R = ALS Functional Rating Scale–Revised; ANCOVA = analysis of covariance; CI= confidence interval; ES = early-start tofersen 100 mg; ITT = intent-to-treat; LS = least square; NfL = neurofilament; P + DS = placebo + delayed-start tofersen 100 mg.

Source: Miller et al. NEALS 2022 [155].

2.3.1.9.2. Secondary endpoints

- **Target engagement [18, 155]**: Reductions in total CSF *SOD1* were apparent by Week 8 of tofersen use and were sustained over time. At Week 52, the percent reduction (geometric mean ratio) from baseline was 21% (95% CI: 4-35) and 33% (95% CI: 21-42) for the delayed- and early-start tofersen groups, respectively (Figure 11). Similar reductions were seen at Week 104, with reductions of 19% (95% CI:0.69-0.97) in the delayed-start group and 27% (95% CI: 0.64-0.83) in the early-start group (Figure 12). Variability in the percent reduction is likely influenced by assay variability, which can vary up to 15.6%.

Figure 11. Tofersen effect on SOD1 concentration in CSF at Week 52 (VALOR + OLE, ITT population)

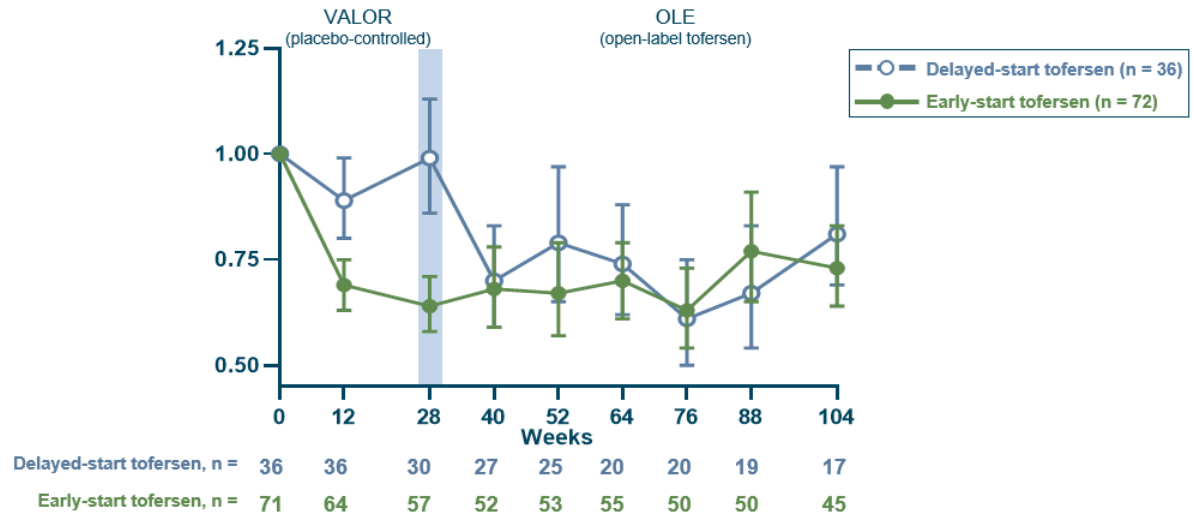


Note: Analysis is based on ANCOVA model in conjunction with multiple imputation for missing data; based on natural log transformed data. The model includes covariates for the corresponding baseline value i.e., log value, and use of riluzole or edaravone.

Abbreviations: CI = confidence interval; CSF = cerebrospinal fluid; GMR = geometric mean ratio; ITT = intent-to-treat; OLE = open-label extension; SOD1 = superoxide dismutase 1

Source: Miller TM et al. ENCALS 2022[155]. Miller et al. N Engl J Med 2022; 387:1099-110[18].

Figure 12. Tofersen effect on SOD1 concentration in CSF at 104 Weeks (VALOR + OLE, ITT population)

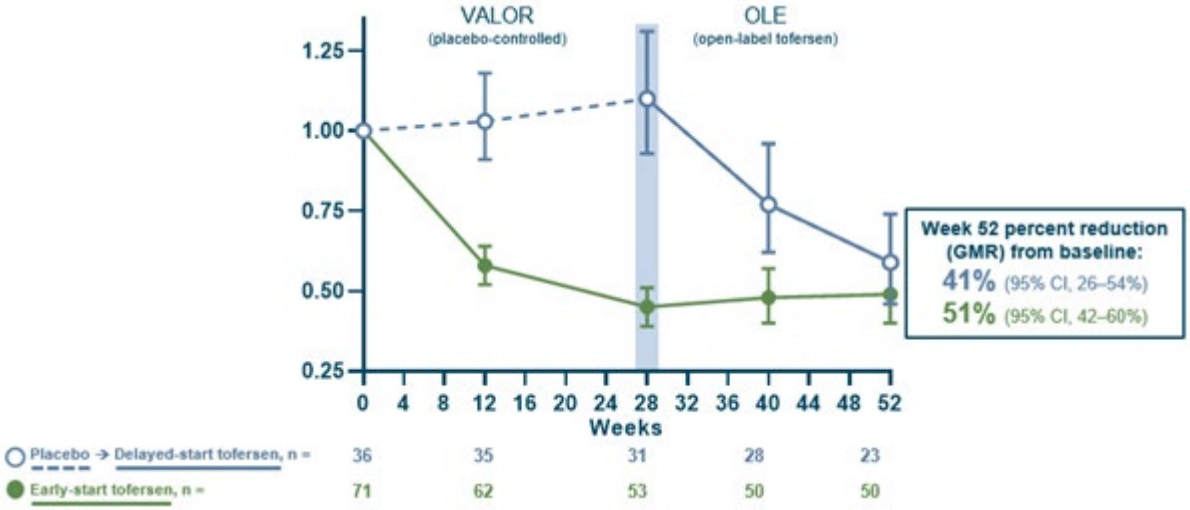


Lower limit of quantitation (LLOQ) is 15.6 ng/mL. Values below limit of quantitation (BLQ) are set to half of LLOQ in calculations.

Multiple imputation including treatment group, use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data. The analysis is based on ANCOVA model with natural log transformed data. The model includes covariates for the corresponding baseline value i.e. log value, and use of riluzole or edaravone. Abbreviations: CSF = cerebrospinal fluid; SOD1 = superoxide dismutase 1; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.

- **Neurofilament[18, 155]:** Plasma NfL declined at approximately Week 16, and reductions were sustained over time, suggesting that tofersen administration reduced axonal injury and neurodegeneration. At Week 52, the percent reduction (geometric mean ratio) from baseline was 41% (95% CI: 26-54) and 51% (95% CI: 42-60) for the delayed- and early-start tofersen groups, respectively (Figure 13). These reductions in plasma NfL persisted and continued to decline at Week 104, with levels of 60% (HR:0.40, 95% CI: 0.30-0.54) and 66% (HR: 0.34, 95% CI: 0.27-0.42) for the delayed- and early-start groups, respectively (Figure 16). Consistent reductions in CSF NfL were observed to 104 weeks, indicating that tofersen robustly reduces axonal injury and neurodegeneration, with no evidence of attenuation of effect over time.

Figure 13. Tofersen effect on NfL in plasma at Week 52 (VALOR + OLE, ITT population)

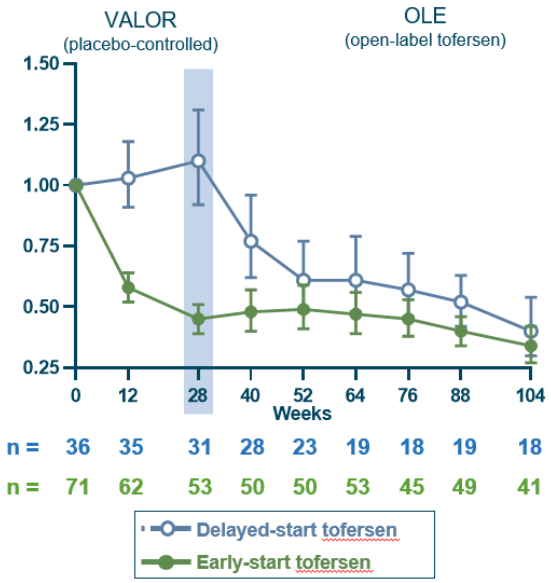


Note: Analysis is based on ANCOVA model in conjunction with multiple imputation for missing data; based on natural log transformed data. The model includes covariates for the corresponding baseline value i.e., log value, and use of riluzole or edaravone.

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; ITT = intent-to-treat; NfL = neurofilament light chain; OLE = open-label extension

Source: *Miller et al. (*2022) [18] and [155]

Figure 14. Tofersen effect on NfL in plasma at Week 104 (VALOR + OLE, ITT population)



Lower limit of quantitation (LLOQ) is 4.9 pg/mL. Values below limit of quantitation (BLQ) are set to half of LLOQ in calculations.

Multiple imputation including treatment group, use of riluzole or edaravone, and the relevant baseline and postbaseline values for the endpoint is used for missing data. An extreme value of >477 pg/mL is set to missing and is imputed with multiple imputation in the ANCOVA analysis.

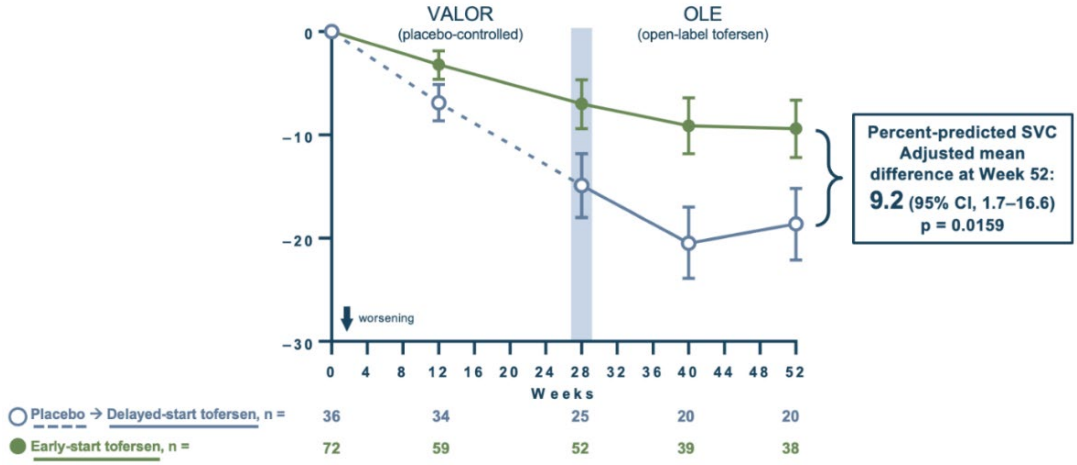
The analysis is based on ANCOVA model with natural log transformed data. The model includes covariates for the corresponding baseline value i.e. log value, and use of riluzole or edaravone. Abbreviations: NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square

Source: Miller et al. (2023) [152]

- **Respiratory function [18]:** In the long-term ITT population, the early-start participants experienced a nominally statistically significant slower decline from baseline to Week 52 on percent-predicted SVC compared to the placebo/delayed-start participants. At Week 52, the percent-predicted SVC adjusted mean difference was 9.2 (95% CI: 1.7-16.6, p=0.0159) (Figure 17). These respiratory effects were sustained at Week 104, with a 9.7 percent-predicted difference in favor of early-start tofersen (95% CI: -0.8- 20.2, p=0.0702) (Figure 18). As reduction in the rate of SVC decline by 1.5 percent-predicted per month is known to reduce the risk of first onset of respiratory insufficiency or death by 22%, these measured effects represent a clinically impactful result for the patient [71].

  Many placebo participants who initiated tofersen in the OLE fell below the initial VALOR SVC inclusion criteria eligibility thresholds during the 6 months of VALOR. Of the 36 participants who were randomized to placebo in VALOR, 32 participants enrolled in the OLE, and two of these had missing baseline assessments for SVC. Twelve of the 30 (40%) participants in the OLE with non-missing baseline assessments had an SVC <65% predicted at baseline of the OLE; 7 (23.3%) had SVC <50% predicted.

Figure 15. Tofersen effect on respiratory function at Week 52 (VALOR + OLE, ITT population)

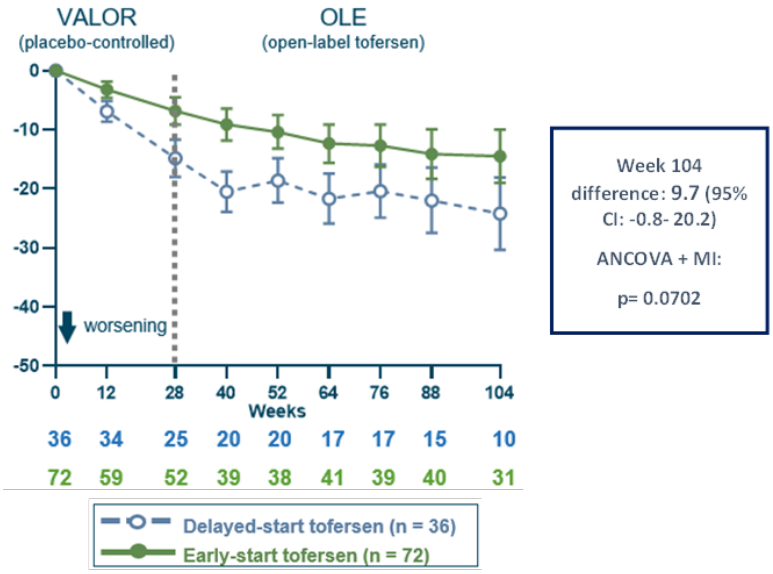


Note: Analysis is based on ANCOVA model in conjunction with multiple imputation for missing data; based on natural log transformed data. The model includes covariates for the corresponding baseline value i.e., log value, and use of riluzole or edaravone.

Abbreviations: CI = confidence interval; ITT = intent-to-treat; OLE = open-label extension; SVC = slow vital capacity

Source: Miller TM et al. ENCALS 2022 [155]. Miller et al. N Engl J Med 2022;387:1099-110[18].

Figure 16. Tofersen effect on respiratory function to Week 104 (VALOR + OLE, ITT population)



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

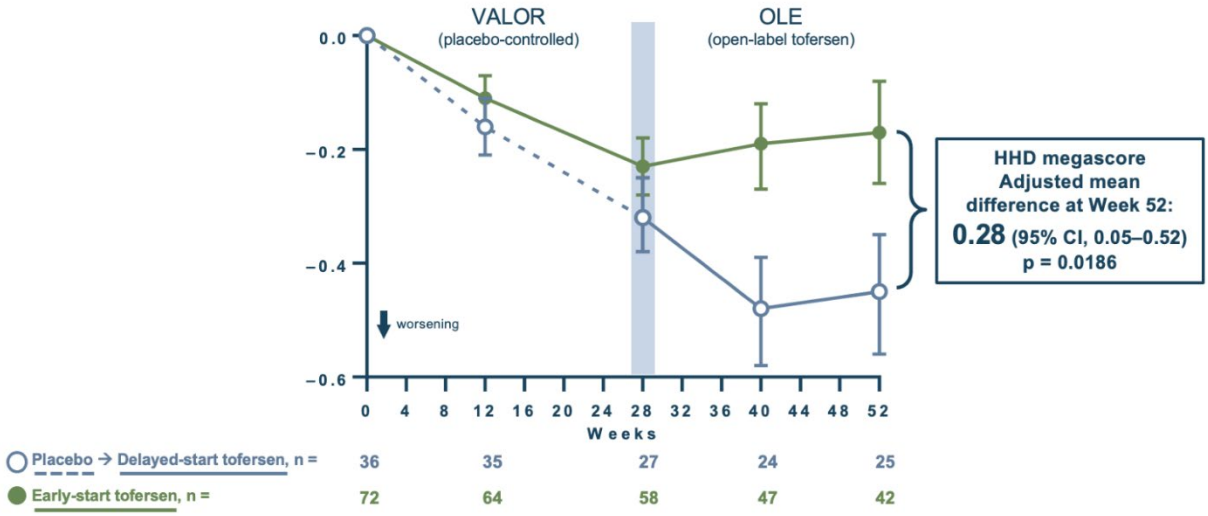
Note 3: The maximum (best effort) acceptable reading is used for analysis. A positive change indicates an improvement.

Note 4: LS means are obtained from the ANCOVA model with treatment included as a fixed effect and adjusted for the following covariates: baseline plasma NfL, baseline percent predicted SVC, and use of riluzole or edaravone. Abbreviations: SVC = slow vital capacity; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square; ATS = the American Thoracic Society.

Source: Miller et al. (2023) [152]

- **Muscle strength [18]:** Early- start participants experienced a nominally statistically significant lower decline from baseline to Week 52 in HHD megascore compared to placebo/delayed-start participants. Although the placebo/delayed-start group declined more than the early-start group over the 52-week period, they did experience an apparent stabilization in decline across measures of function and strength beginning around Week 40 and lasting until Week 88 (Figure 17). At Week 52, the HHD megascore-adjusted mean difference was 0.28 (95% CI: 0.05-0.52, p=0.0186), which is notable considering that any slowing in decline in muscle strength is distinct from the progressive decline typically observed in the natural history of ALS [159, 160]. Despite some convergence, this effect remained consistent at Week 104, with tofersen treatment continuing to favor the early-start group with a 0.19-point difference at Week 104 (95% CI: -0.098-0.474, p=0.1946) (Figure 16).

Figure 17. Tofersen effect on muscle strength to Week 52 (VALOR + OLE, ITT population)

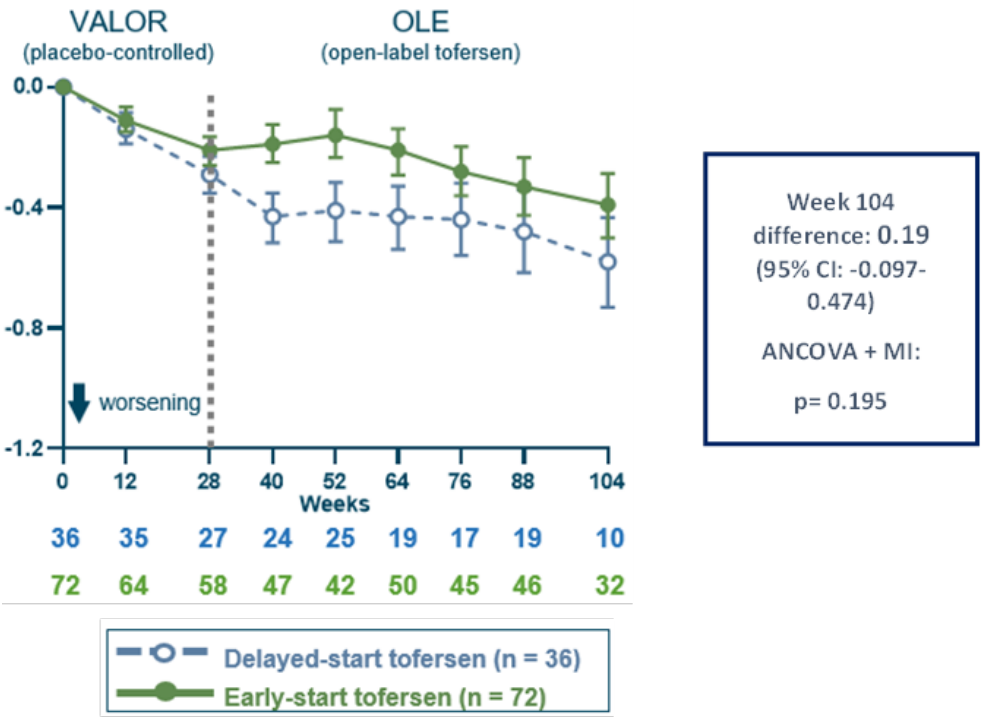


Note: Analysis is based on ANCOVA model in conjunction with multiple imputation for missing data; based on natural log transformed data. The model includes covariates for the corresponding baseline value i.e. log value, and use of riluzole or edaravone.

Abbreviations: CI = confidence interval; HHD = handheld dynamometry; ITT = intent-to-treat; OLE = open-label extension

Source: Miller TM et al. ENCALS 2022 [155]. Miller et al. N Engl J Med 2022;387:1099-110 [18].

Figure 18. Tofersen effect on muscle strength to Week 104 (VALOR + OLE, ITT population)



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

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

Note 4: LS means are obtained from the ANCOVA model with treatment included as a fixed effect and adjusted for the following covariates: baseline plasma NfL, baseline HHD overall megascore, and use of riluzole or edaravone. Abbreviations: HHD = handheld dynamometry; NfL = neurofilament light chain; ANCOVA = analysis of covariance; MI = multiple imputation; LS = least square.

- **Time-to-Event Analysis [18, 155]:** As of 16 January 2022, all participants enrolled in VALOR had the opportunity for at least 1 year of follow-up. There was an apparent reduction in the risk of death or PV (HR: 0.36, 95% CI: 0.137-0.941) and the risk of death (HR: 0.27, 95% CI: 0.084-0.890) in patients who initiated tofersen early compared to those with a delayed start. Although the median time-to-death or PV and median time-to-death were not estimable due to the limited number of events observed, there was a reduction in risk of death or PV (HR: 0.47, 95% CI:0.20- 1.11) and risk of death (HR 0.36, 95% CI: 0.13- 1.02) for the early-start vs. delayed-start group for the Feb 2023 data cut. These data provide early evidence of a prolongation of event-free survival with earlier tofersen initiation in the overall population. In the faster-progressing subgroup (NfL-based), the median time-to-death or PV was reached in both treatment groups, enabling the estimation of the extension of event-free survival associated with early-start tofersen (~1.6 years). Consistently, the median time-to-death, PV, or withdrawal due to disease progression was ~0.9 years longer in the early-start faster-progressing tofersen group than in the delayed-start group.

  As of 28 February 2023, all participants enrolled in VALOR had the opportunity for at least 2 years of follow-up (median opportunity for follow-up: 3.4 years; range 2.2 to 3.9 years). Despite this duration of follow-up, there continues to be a limited number of death-equivalent events because the majority of participants are continuing to survive in the study, thus precluding estimation of the median time-to-death or PV, time-to-death, and time-to-

death, PV, or withdrawal due to disease progression in the full ITT population. While expected natural history data show the median disease duration for a *SOD1*-ALS patient is 2.3 years [8], in the VALOR + OLE data cut from 28 February 2023, the median time from ALS symptom onset to death/censoring was 3.3 years (range 0.7 to 12.2 years) in the placebo/delayed-start group and 3.9 (range: 0.7 to 15.7 years) in the early-start group.

A similar subset analysis was performed on A5V carriers, a group consistently found to be associated with a median disease duration of 1-1.2 years[8, 161], and one of the most common variants in the tofersen VALOR + OLE clinical trials. With three A5V carriers still in the study as of data cut-off, the median duration from ALS symptom onset to death or censoring was 1.9 years (range: 0.9 to 4.8 years) in the early-start group and 1.3 years (range: 0.7 to 2.9) in the delayed-start group.

Additionally, the survival benefit in the early-start participants, relative to the delayed-start participants, is unlikely to be attributed to enrollment of individuals with more slowly progressing disease, especially considering that baseline disease characteristics were generally balanced between these early- and delayed-start groups by way of *SOD1* variant type, use of riluzole and/or edaravone, and characteristics reflective of the stage of disease (time from symptom onset, ALSFRS-R total score, and percent-predicted SVC). Baseline plasma NfL levels were approximately 15%-25% higher in the early-start group than in the placebo/delayed-start group at baseline, which, given NfL is a prognostic biomarker, suggests that the early-start group was likely to experience faster disease progression/shorter survival in the absence of tofersen. Between these baseline imbalances and the opportunity for the placebo/delayed-start group to cross over to active tofersen after 6 months, these are conservative analyses that may underestimate the treatment effect of tofersen.

Rank preserving structural failure time model (RPSFTM) analyses were also performed on measures of survival at Week 104. Although not without limitations, RPSFTM is a method used to adjust for treatment switching in trials with survival outcomes, and uses counterfactual survival to assume, at randomization, the counterfactual survival distribution for the investigational and placebo group are identical. These analyses indicate that, had the delayed-start group remained on placebo, the risk of death or PV would be reduced by 78%, the risk of death by 88%, and the risk of death, PV, or withdrawal due to disease progression by 75% in the early-start group compared with the delayed start group.

2.3.1.9.3. Exploratory endpoints

Patient reported outcomes [18]: At 52 weeks**,** the early-start tofersen group had nominally statistically significant less worsening of QoL as measured by the ALS Assessment Questionnaire short-form (ALSAQ-5) total score (adjusted mean difference: -10.3, 95% CI: -17.3 to -3.2, p=0.0044). For both EQ-5D-5L utility score (adjusted mean difference: 0.2, 95% CI: 0.13 to 0.32, p<0.0001) and FSS (-3.8, 95% CI: -9.0 to 1.38, p=0.1493), trends consistently favored early tofersen administration. Both ALSAQ-5 and EQ-5D-5L scores continued to favor the early tofersen administration group at Week 100, further substantiating the effects observed on measures of function and strength. Consistent with some of the earlier analysis time points, results on the fatigue severity score (FSS) were the one instance in which effects favored the placebo/delayed-start group. Notably, a subset of participants in the placebo/delayed-start group and an even greater proportion of participants in the early-start group experienced improvement or stabilization/improvement in their QoL (across ALSAQ-5, FSS and EQ-5D-5L) (Table 10).

Table 13. Proportion of participants with improvement or stabilization/improvement on QoL measures from baseline to Week 100 (VALOR + OLE, ITT population)

Endpoint		Week 100	
		Placebo/delayed-start (n=36)	**Early-start (n=72)**
ALSAQ-5	Proportion of participants with **improvement**	9.8	12.8
	Proportion of participants with **stabilization or improvement**	20.8	33.9
FSS	Proportion of participants with **improvement**	21.7	24.0
	Proportion of participants with **stabilization or improvement**	33.4	37.1
EQ-5D-5L	Proportion of participants with **improvement**	15.8	26.2
	Proportion of participants with **stabilization or improvement**	21.5	35.9

Note 1*: For ALSAQ-5, FSS, and EQ-5D-5L, results are presented at Week 100. The difference in assessment week is due to assessments been performed at different visits.*

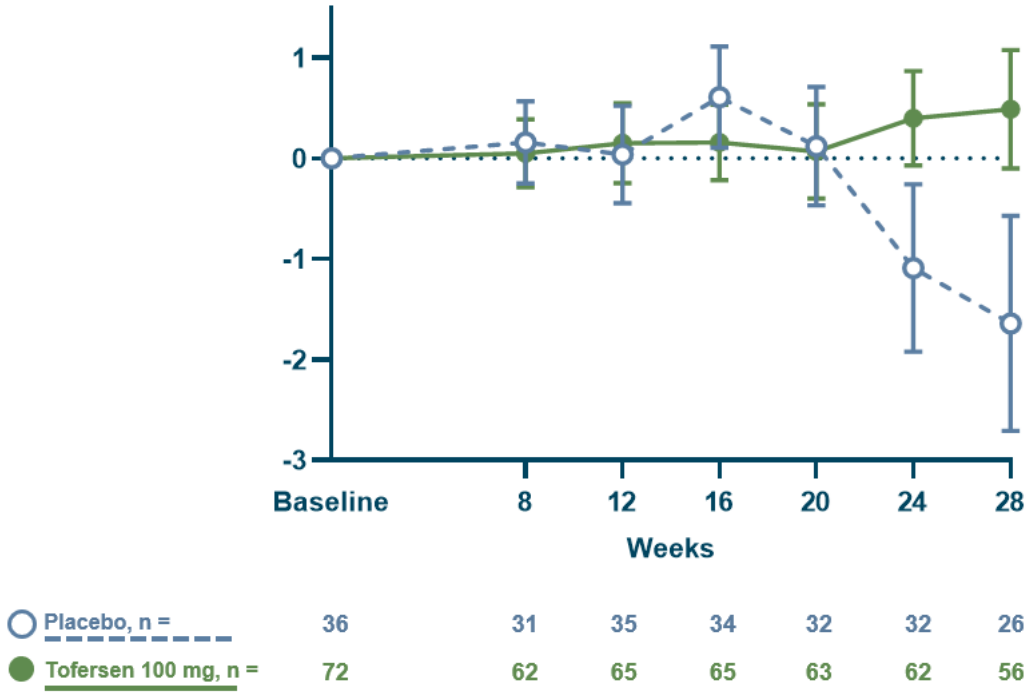
Abbreviations: ALSAQ-5 = ALS Assessment Questionnaire-5; EQ-5D-5L = 5-level EQ-5D; FSS = Fatigue Severity Score; QoL = Quality of Life

Source: Miller et al. 2023 [152]

Weight: Weight was collected as part of the safety battery in VALOR. Weight loss has been found to be a strong independent predictor of survival in ALS. In a large population-based study comprising 2,420 patients, Janse van Mantgem et al. found an adjusted hazard ratio (HR) for absolute weight loss in kg of 1.03 (95% CI: 1.02-1.04, p<0.001), indicating a 3% increase in the risk of death during follow-up with each additional kilogram of weight loss [162].

Given this relationship, an exploratory efficacy analysis of change in weight over time was performed in VALOR[155].

Figure 19. Tofersen effect on body weight (kg) at Week 28 (VALOR, ITT population)



Analysis is based on an analysis of covariance model in conjunction with multiple imputation for missing data. The model includes covariates for the corresponding baseline value, baseline plasma NfL, and use of riluzole or edaravone.

Abbreviations: ITT = intention-to-treat; NfL = neurofilament light chain

Source: Miller et al. NEALS 2022 [155].

2.3.1.9.4. Stabilisation and improvement data

While *SOD1*-ALS is heterogenous, the disease is uniformly associated with progressive decline in function and strength over time[159, 163]. As such, one way to assess treatment effect is by looking for sustained stabilization or improvement in strength and function, which would be highly inconsistent with the usual progressive declines observed in the natural history. A subset of tofersen-treated participants experienced sustained stabilization or improvement in function and strength. In the early-start tofersen group, 19.5% of participants experienced improvement on the ALSFRS-R, 29.3% improvement on percent-predicted SVC, and 25.8% improvement on HHD megascore over 104 weeks. An even larger proportion of tofersen-treated participants experienced stabilization (no loss of function/strength) or improvement over 104 weeks (29.3%, 21.4%, and 25.8% in the early-start tofersen group for ALSFRS-R, SVC, and HHD, respectively) (Table 11).

These data are highly consistent with observations from Study 101 Parts A and B in which disease progression has generally been stabilized for over 3 years of follow-up in the cohort of participants who received at least 1 dose of tofersen in Study 102/OLE (n = 40). These participants experienced a mean change from Study 102 baseline to Week 168 (~3.2 years) of -2.3 points on ALSFRS-R, -2.4 on percent-predicted SVC, and -0.1 on HHD megascore [152].

These observations of stabilization and/or improvements in tofersen-treated participants are particularly notable when compared to the natural history data. Given the limited availability of

natural history data in *SOD1*-ALS patients, data from the Biogen-sponsored dexpramipexole Study 223AS302 (EMPOWER) [n=942] were evaluated to inform the likelihood of observing improvement in an ALS population simply due to biological/measurement variability. Analyses in this dataset were available up to 52 weeks and showed that 1.3% of participants experienced an increase from baseline on ALSFRS-R, ~6% on SVC, and ~5% on HHD. The proportion of improvers would be expected to be even smaller with an additional year of follow-up (e.g., 104 weeks, as is being evaluated in the tofersen analyses). These data suggest that the improvement observed in tofersen-treated participants is not attributable to biological/measurement noise.

Table 14. Proportion of participants with improvement or stabilization/improvement on clinical function and strength measures from baseline to Week 104 (VALOR + OLE, ITT population)

Endpoint		Week 104	
		Placebo/delayed-start (n=36)	Early-start (n=72)
ALSFRS-R	Proportion of participants with **improvement**	11.6%	19.5%
	Proportion of participants with **stabilization or improvement**	22.7%	29.3%
Percent-predicted SVC	Proportion of participants with **improvement**	10.5%	21.4%
	Proportion of participants with **stabilization or improvement**	10.5%	21.4%
HHD Megascore	Proportion of participants with **improvement**	10.1%	25.8%
	Proportion of participants with **stabilization or improvement**	10.1%	25.8%

Abbreviations: ALSFRS-R, Amyotrophic Lateral Sclerosis

Source: Miller et al. (2023) [152]

2.3.1.9.5. Discussion of key efficacy results

Treatment with tofersen demonstrated evidence of biologic effect that preceded evidence of clinical benefit (Figure 20). Specifically, tofersen administration lowers total CSF *SOD1* protein, an indirect marker of target engagement, followed by reductions in neurofilament, a marker of axonal injury and neuronal degeneration. VALOR did not achieve statistical significance on its primary endpoint of chance from baseline in ALSFRS-R total score in the faster progressing group (mITT) population at 6 months; however, trends suggesting slowing of clinical decline in tofersen-treated participants in the faster-progressing subgroup were observed. At week 52, earlier initiation of tofersen was associated with reduction of decline in clinical function, respiratory function, strength, and quality of life. These trends include:

- Nominally statistically significant slower decline from baseline for early-start participants in clinical and respiratory function and muscular strength, measured by ALSFRS-R, SVC, and HHD respectively. The greatest differentiation was observed in faster progressing subgroups (mITT; above the median NfL subgroup)

- Nominally statistically significant less worsening of QoL in the early-start tofersen group, as measured by the ALSAQ-5 total score, with trends consistently favoring early tofersen administration for both EQ-5D-5L and FSS scores.
- Early evidence of a reduction in the risk of death or permanent ventilation and death in the early start group.

Data from the breadth of the clinical trial program support disease-modifying effects of tofersen, most convincingly, through the temporal relationship demonstrated between the observed biological and downstream clinical effects of tofersen. In the VALOR + OLE extension study, tofersen reduced total CSF *SOD1* protein levels after ~8 weeks (indirect marker of target engagement), followed by maximal reductions in plasma NfL, after ~16 weeks, consistent with reduced axonal injury and neurodegeneration. At week 28, while there were trends suggesting a slowing of clinical decline for participants treated with tofersen, these results were not statistically significant. With longer follow-up at 52 weeks however, earlier initiation of tofersen was associated with a reduced decline in clinical and respiratory function, strength, and QoL, despite crossover to tofersen at ~6 months for participants in the placebo/delayed-start group.

The combined data analyses suggest that the CNS might need time to react to treatment and potentially recover from the pathogenic damage. This possibility could explain why clinical effects, following reductions in SOD1 protein and consequently in NfL, were not detected within the 28-week placebo-controlled phase of VALOR Part C [164].

These data suggest that tofersen-mediated impacts on biological processes (reduced *SOD1* protein results in reduced plasma NfL) are necessary before impacts on clinical outcomes can be observed. This is consistent with what would be expected as recovery of muscle force generation would be a finding that lags evidence of reduced axonal injury or neurodegeneration. For a denervated muscle to recover strength, it is believed that several events must occur. First, the injured or degenerating motor neurons that are not contributing to force generation should be stabilized and re-establish neuromuscular transmission with their original myofibers. Such a neuron may then be able to contribute to reinnervation of other denervated myofibers through sprouting of collaterals and formation of new NMJs. As these nascent NMJs mature, the efficiency of neuromuscular transmission may improve. Finally, the reinnervated myofibers need to add myofibrils to contribute additional force to the contraction of a muscle. Only after all of that has occurred would it be expected to potentially observe beneficial impacts on clinical function, respiratory function, strength, and QoL, as has been suggested in the OLE study.

VALOR+OLE at 24 months showed sustained reductions in total CSF *SOD1* protein and NfL in early-start participants and after initiating tofersen, placebo/delayed-start participants achieved biomarker reductions like those seen in early-start participants. With longer follow-up at Week 104, while there is some apparent convergence of effect on clinical and QoL outcomes between treatment groups (as the placebo/delayed-start group had the opportunity to cross over to active tofersen at Week 28), the differences between groups remain highly clinically meaningful. These differences favoring early-start tofersen were seen regardless of which subgroup, statistical methodology, and/or covariates were incorporated.

Clinical effects in function, strength and QoL were noted with longer-term follow-up (24 months) in the OLE study:

- Nominally statistically significant effects favoring the early-start group were observed across clinical outcome measures including ALSFRS-R, SVC, and HHD, despite the lack of placebo control in months 6 through 24.
- An apparent stabilization and in some cases improvement of clinical function, respiratory function and strength were seen in a subset of tofersen-treated participants. These

improvements are also consistent with reports from trial investigators and expanded access program clinicians around the world who indicate that tofersen is slowing disease progression in their patients, and whom, as a result, are shifting expectations for care for people living with *SOD1*-ALS to include changed patient monitoring metrics and new rehabilitation programs (Press Release, Treatment and Research Initiative to Cure ALS [TRICALS], March 2022)[165, 166]. For example, one expanded access program patient with a relatively quickly progressing *SOD1* mutation and a serum NfL level of ~78 pg/mL at treatment initiation maintained a stable score on ALSFRS-R over 1 year of treatment and experienced clinically meaningful improvements on the timed up and go (TUG) and 10-meter walk test (TUG score: 17 seconds at initial evaluation improved to 12.5 seconds at Week 52, and 0.27 m/s at initial evaluation improved to 0.92 m/s at Week 52 in the 10-meter walk test [Data on file from Washington University School of Medicine ALS Center]).

- There continues to be a limited number of death-equivalent events, despite 2 years of follow-up, because the majority of participants are continuing to survive on study, thus precluding estimation of the median time to death or permanent ventilation (PV), time to death, and time to death, PV, or withdrawal due to disease progression in the full ITT population. Importantly, the longer-term data at 104 weeks show the risk of death or PV was reduced by 53%, the risk of death was reduced by 64%, and the risk of death, PV, or withdrawal due to disease progression was reduced by 50% in the early-start group compared with the delayed-start group in the ITT population.
- RPSFTM analyses show that, had the delayed-start group remained on placebo, the risk of death or PV would be reduced by 78%, the risk of death by 88%, and the risk of death, PV, or withdrawal due to disease progression by 75% in the early-start group compared with the delayed-start group.
- In the group comprising the fastest progressing individuals (based on median plasma NfL), a ~1.6-year extension of event-free survival was estimated in the early-start group compared to the placebo/delayed-start group.

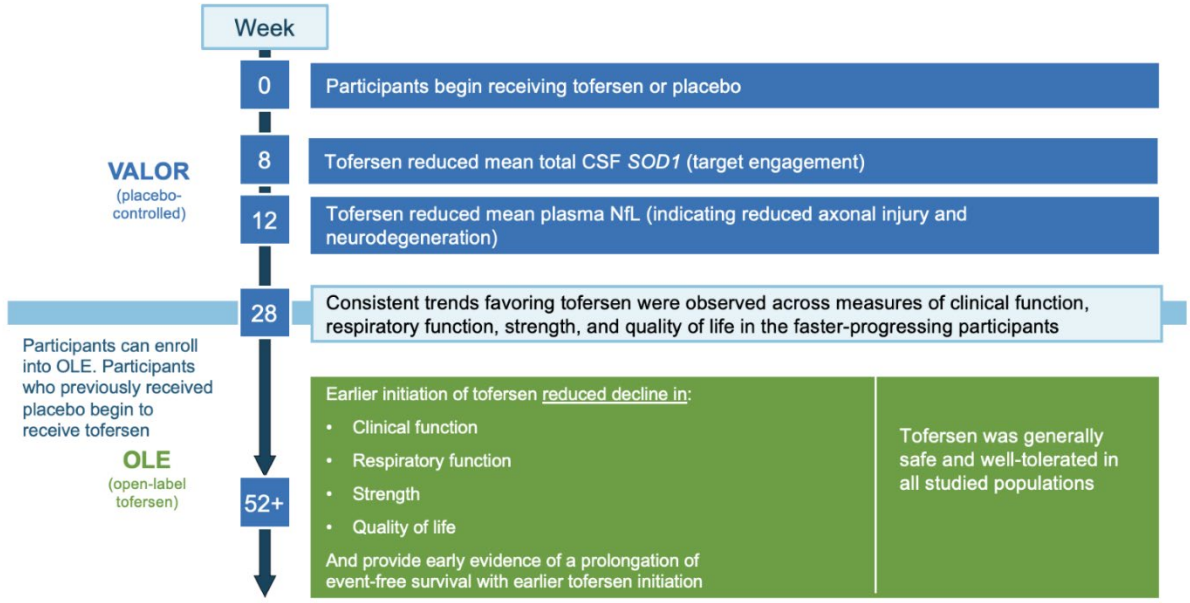
In VALOR+OLE, most AEs were mild to moderate in severity and many were consistent with ALS disease progression or lumbar puncture-related events. Serious neurologic events, including myelitis, radiculitis, papilledema, and aseptic meningitis were seen in tofersen-treated participants. All serious AEs were manageable with SoC.

For tofersen, results have shown: Overall COMP conclusion tofersen-driven reductions in SOD1 protein in CSF over 104 weeks led to a sustained slowing of the neurodegenerative process, as evidenced by robust reductions in NfL over the same period. Although a statistically significant difference was not observed on the primary analysis at Week 28 in Study 101 Part C, by Week 52, clear and meaningful differences favouring early-start tofersen (as compared with delayed- start tofersen) were observed across clinical outcome measures of clinical function (ALSFRS-R), respiratory strength (SVC), muscle strength (HHD megascore). With longer follow-up to 104, there is some apparent convergence of effect between treatment arms, as the placebo/delayed-start group had the opportunity to cross-over to active tofersen at Week 28; however, the differences between arms remain clinically meaningful [138].

Further, the magnitudes of slowing in progression on each of these endpoints when compared with the natural history of ALS/SOD1-ALS, coupled with the nearly 1 in 5 participants experiencing improvement on each of these endpoints over 104 weeks of tofersen treatment, are so at odds with disease natural history, that they are considered to meet the significant benefit criterion for orphan maintenance of a clinically relevant advantage due to improved efficacy, more so, given that riluzole has no effect on clinical function or strength [138].

It is noteworthy that, as tofersen was part of EMA's raw data project, the analyses performed by both Biogen and EMA showed consistently favourable trends for early versus delayed initiation of tofersen across clinical outcome measures [164].

Figure 20. VALOR and OLE summary of key results



Abbreviations: CSF = cerebrospinal fluid; NfL = neurofilament; OLE = open=label extension; SOD1 = Superoxide dismutase 1

Source: Miller et al. ENCALS 2022 [155]. Miller et al. NEJM 2022;387:1099-110 [18].

The key efficacy results from VALOR and OLE are summarised in the tables below.

Table 15. Primary and secondary endpoints in VALOR in the faster-progressing subgroup at the end of the placebo-controlled period (week 28)

Endpoint	Placebo (N=21)	tofersen (N=39)
Primary endpoint		
ALSFRS-R total score *		
Adjusted mean change from VALOR baseline	-8.14	-6.98
Adjusted mean difference: tofersen minus placebo (95% CI)	-	1.2 (-3.1 to 5.5)
P value according to joint rank test and multiple imputation	-	0.97
Secondary endpoints		
Total *SOD1* concentration in CSF		
Adjusted geometric mean ratio to VALOR baseline	1.16	0.71
Geometric mean ratio: tofersen vs. placebo (95% CI)	-	0.62 (0.49 to 0.78)
Concentration of neurofilament light chains in plasma		
Adjusted geometric mean ratio to VALOR baseline	1.20	0.40

Geometric mean ratio: tofersen vs. placebo (95% CI)	-	0.33 (0.25 to 0.45)
Percentage of predicted slow vital capacity – percentage points		
Adjusted mean change from VALOR baseline	-22.20	-14.31
Adjusted mean difference: tofersen minus placebo (95% CI)	-	7.9 (-3.5 to 19.3)
Handheld dynamometry megascore		
Adjusted mean change from VALOR baseline	-0.37	-0.34
Adjusted mean difference: tofersen minus placebo (95% CI)	-	0.02 (-0.21 to 0.26)
Death or permanent ventilation		
No. of events/total no. of participants (%)	2/21 (10)	4/39 (10)
Hazard ratio (95% CI) †	-	1.39 (0.22 to 8.80)
Death		
No. of events/total no. of participants (%)	0/21	1/39 (3)
Hazard ratio (95% CI) †	-	NE (NE to NE)

Abbreviations: CSF, cerebrospinal fluid; NE, not estimated; SOD1, superoxide dismutase 1.

** Sequential analysis failed at this point, and all subsequent secondary endpoints are considered to be not significantly different between trial groups.*
† The hazard ratio is based on a Cox proportional-hazards model adjusted for baseline disease duration since symptom onset, baseline ALSFRS-R score, and use of riluzole or edaravone.

Table 16. Primary and secondary endpoints in the ITT population in VALOR + OLE (week 52)

Endpoint	Early-start participants (N=71)	Delayed-start participants (N=36)
Primary endpoint		
ALSFRS-R total score *		
Adjusted mean change from VALOR baseline	-6.0	-9.5
Adjusted mean difference: tofersen minus placebo (95% CI)	-	3.5 (0.4 to 6.7)
Secondary endpoints		
Percentage of predicted slow vital capacity – percentage points		
Adjusted mean change from VALOR baseline	-9.4	-18.6
Adjusted mean difference: tofersen minus placebo (95% CI)	-	9.2 (1.7 to 16.6)
Handheld dynamometry megascore		
Adjusted mean change from VALOR baseline	-0.17	-0.45
Adjusted mean difference: tofersen minus placebo (95% CI)	-	0.28 (0.05 to 0.52)
Death or permanent ventilation †		
Hazard ratio (95% CI)	-	0.36 (0.14 to 0.94)

Death †		
Hazard ratio (95% CI)	-	0.27 (0.08 to 0.89)

† The median time to death or permanent ventilation and the median time to death could not be estimated owing to the limited number of events.

2.3.2. Comparator studies: SoC

As stated in Section 2.2.2, none of the studies identified to evaluate efficacy and safety of SoC (riluzole and edaravone) in the cSLR were directly used in the cost-effectiveness model and are therefore not reported here. Please refer to Appendix E. Clinical Systematic Literature Review for full efficacy results for SoC identified in the cSLR.

Section 3.8.1 details the clinical inputs for the comparator arm of the cost-effectiveness model.

2.4. Evidence synthesis methods

Not relevant to the current submission.

2.5. Clinical safety

2.5.1. Intervention: tofersen

Most AEs across VALOR + OLE were mild to moderate in severity and did not cause withdrawal or discontinuation of the trial agent.

In the 52-week analysis (Jan 2022 data cut), the most common AEs in >30% participants receiving tofersen in VALOR and the OLE study were headache, procedural pain, fall, back pain and pain in extremities. Four participants who received tofersen in VALOR (6%) and three participants in the OLE (constituting 7% of all participants who received tofersen) had a total of eight neurologic serious (S)AEs, including myelitis, radiculitis, aseptic meningitis, and papilledema (Table 17). All SAEs were manageable with SoC.

Table 17. Safety profile of tofersen and placebo in VALOR and OLE (week 52)

	VALOR		VALOR and OLE Integrated[d]
No. of participants with treatment-emergent event[a]	**Placebo (N = 36) n (%)**	**tofersen 100 mg (N = 72) n (%)**	**tofersen 100 mg (N = 104) n (%)**
Any event	34 (94)	69 (96)	102 (98)
Any event related to study drug[b]	2 (6)	28 (39)	63 (61)
Events related to lumbar puncture[b]	29 (81)	58 (81)	84 (81)
Serious event	5 (14)	13 (18)	38 (37)
Serious event related to study drug	0	4 (6)	7 (7)
Events with fatal outcome	0	1 (1)	14 (13)
Events leading to drug discontinuation	0	4 (6)	18 (17)
SAEs occurring in ≥2% of participants in combined analysis[c]	0	4 (5.6)	7 (6.7)
Respiratory failure	0	1 (1)	10 (10)

Pneumonia aspiration	0	2 (3)	9 (9)
Pulmonary embolism	1 (3)	3 (4)	4 (4)
Acute respiratory failure	0	1 (1)	4 (4)
Dysphagia	0	0	3 (3)

Abbreviations: AE = adverse event; OLE = open-label extension; SAE = serious adverse event.

[a]Participant can appear in more than one category;
[b]Related as assessed by the investigator;
[c]A participant is counted only once in each preferred term (MedDRA version 24.0);

[d]An event in a placebo participant during VALOR is only counted once; an event in a tofersen participant during VALOR is counted in both the "VALOR/tofersen 100 mg" column, and again in the "VALOR and OLE Integrated" column.

Source: Miller TM et al. NEJM 2022;387:1099-110 [18].

Updated safety analyses of tofersen at 104 weeks show that tofersen 100 mg and its administration via lumbar puncture continue to be generally well-tolerated with an acceptable safety profile for the treatment of *SOD1*-ALS [155]. The integrated safety analysis of Study 101 (Part A, B, and C) and the OLE (n=147) shows that most AEs reported during treatment with tofersen were consistent with the types and severities of events seen in *SOD1*-ALS. As of the February 2023 data cut-off:

- The most common AEs in participants receiving tofersen were pain (66%), arthralgia (34%), fatigue (28.6%), CSF white blood cell count increased (26.5%), CSF protein increased (26.5%9, myalgia (19%) and pyrexia (18.4%) [126].
- A total of 25 deaths (at any dose) were reported in patients treated with tofersen, although none were considered to be related to tofersen.
- AEs leading to tofersen treatment discontinuation occurred in 28 (19%) participants.
- The SAEs in tofersen-treated patients were myelitis (2.7%), increase intracranial pressure and/or papilloedema (2.7%), radiculitis (1-4%) and aseptic meningitis (1.4%). All were managable with SoC [126].

The safety profile of tofersen in the global extended access program is comparable with the profile reported in the integrated safety analysis of Study 101 and OLE, and no new safety concerns have been identified. The most common AEs in participants treated with tofersen 100 mg were post lumbar puncture syndrome, back pain, procedural pain, and headache. Twenty-one fatal event in 14 cases were reported, and all were assessed as unrelated to tofersen. Serious neurologica events reported were myelitis, aseptic meningitis (2 participants each), readiculopathy, and papilloedema (1 participant each). Other SAEs reported were consistent with disease progression of ALS.

2.5.2. Comparator: SoC

AE incidences for SoC in the cost-effectiveness model were derived from the placebo arm of the VALOR trial (Table 17). These were assumed to be reflective of AEs of SoC (riluzole, edaravone).

AEs identified in the clinical studies for SoC (riluzole, edaravone) are detailed in the cSLR (Appendix E. Clinical Systematic Literature Review).

2.5.3. Safety discussion

As can be seen from the above clinical trial data, a high proportion of patients experienced AEs in VALOR + OLE, in both the tofersen and placebo arms.

The most common AEs (occurring in ≥ 10% of tofersen-treated patients) were pain, myalgia, arthralgia, fatigue, and CSF white blood cell increased [167]. Table 18 shows all nonserious AEs that have ≥ 5 percentage points difference between the tofersen arm and placebo. These nonserious AEs

are thought to have a plausible causal association with tofersen and were therefore considered for inclusion into the model.

Table 18. Incidence of Nonserious Adverse Events

Adverse Event	tofersen (N = 72)		Placebo (N = 36)		Difference
	n	(%)	N	(%)	
CSF white blood cell increased	10	13.9%	0	0.0%	13.9%
CSF protein increased	6	8.3%	1	2.8%	5.6%
Neuralgia	4	5.6%	0	0.0%	5.6%
Arthralgia	10	13.9%	2	5.6%	8.3%
Myalgia	10	13.9%	2	5.6%	8.3%
Musculoskeletal stiffness	4	5.6%	0	0.0%	5.6%
Limb pain and back pain	30	41.7%	8	22.2%	19.4%
Fatigue	12	16.7%	2	5.6%	11.1%

CSF = cerebrospinal fluid.

Note: CSF white blood cell increased includes preferred terms of CSF white blood cell increased and pleocytosis. Pain includes preferred terms of pain, back pain, and pain in extremity.

Source: [167], Biogen data on file [168].

All nonserious AEs were characterized by mild-to-moderate severity; all were transient and easily treated at negligible cost with paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and aspirin for pain relief. They were mostly managed without additional clinical practice visits (via phone/email) or stronger prescription pain medications. Increased CSF white blood cell and increased CSF protein represent symptomless laboratory results.

The proportion of subjects experiencing SAEs was 18% in the tofersen group and 14% in the placebo group [18]. Most of these SAEs were related to underlying disease progression rather than drug related and there were no fatal AEs [169].

There were serious neurologic events in the VALOR trial that occurred in patients treated with tofersen that did not occur in patients receiving placebo. Myelitis occurred in 2 subjects (2.8%) and radiculitis occurred in 1 subject (1.4%). When these events did not lead patients to permanently discontinue treatment, these patients were asymptomatic or had complete resolution of symptoms.

3. Health economic analysis

The decision problem in the health economic analysis is whether tofersen is cost-effective for the treatment of adult patients with *SOD1*-ALS, positioned as add-on therapy to SoC, when compared with SoC.

The reference country used in this submission is Sweden. The Excel model also includes the option to run the analyses from the other JNHB countries' perspectives[1].

3.1. Model requirements

The JNHB version of the model is a local Nordic adaptation of the Biogen global core model, originally populated with UK data. Amendments have been made to the core model to comply with the JNHB model requirements and to provide relevant local costs for the analysis. The model is built in MS Excel and is enclosed in the submission.

3.2. Model structure and applicability

The model perspective and formalities in the base case analysis are summarised in Table 19 and discussed thereunder.

Table 19. Perspective and formalities applied in the health economic analysis.

Topic	Description
Model type	Markov model
Cycle length	28 days (4 weeks)
Half cycle correction	Yes
Time horizon	Lifetime (50 years)
Perspective	Payer perspective

The model uses a **Markov model structure**, capturing the expected *SOD1*-ALS patient experience from treatment initiation to death. The model structure reflects the treatment pathway and captures the expected clinically important differences in costs and outcomes between patients receiving alternative comparators.

Most model-based economic evaluations in ALS conceptualize the disease course by use of health states defined by levels of disease severity. The model is flexible to consider the most widely accepted staging systems (MiToS and King's staging systems), using the MiToS classification in the base case for the reasons set out in Section 3.3.2.

An alternative approach to a Markov cohort state transition model could be a patient-level simulation, as used in NICE clinical guidance for MND [170]; this approach may be better suited to capturing patient heterogeneity. Such a model could be formulated by grouping ALSFRS-R scores to (1) define health state groups that may be closely related to HRQoL impairment levels; (2) define key milestones for speech, feeding, mobility, and vital capacity that could each be tracked; or (3) distinguish according to disease severity (i.e., "mild," "moderate," "severe," "critical"). A drawback of these approaches, however, would be their departure from the accepted clinical and functional staging systems. A patient-level simulation model would only be justified if resource-use and utility data were available to populate each of the permutations and combinations of impairments.

Therefore, a Markov modeling approach was selected to model the cost-effectiveness of tofersen, consistent with most recent economic evaluations identified in the literature (Section 3.8) and previous HTA submissions in ALS [171, 172]. The Markov model structure and health states are described in section 3.3 below.

[1] In the CEM model's excel file: select country in Sheet "Active Local Inputs"

The **cycle length** of the model is 4-weekly. A 4-weekly cycle length was considered to be a sufficiently short timeframe to account for any changes in the clinical outcomes; it is also aligned with the maintenance dose frequency of tofersen.

The **model time horizon** (50 years) captures the patient lifetime, allowing the extrapolation of the treatment effects and uncertainty associated with them adequately.

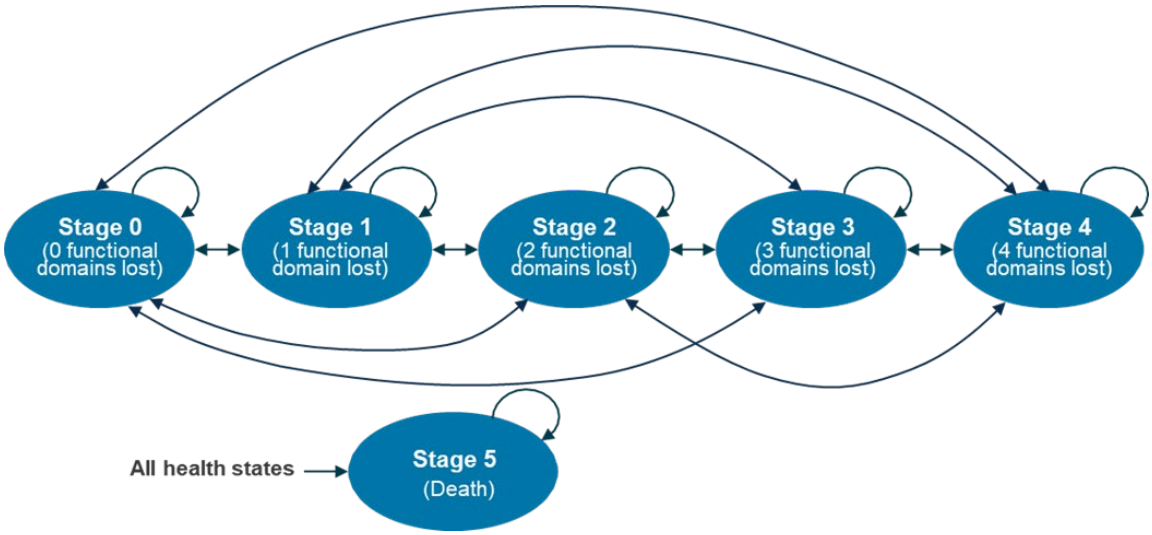
The model allows exploring both the payer and the societal perspective. The base case explores the **payer perspective** which accounts for the direct costs only, whereas the societal perspective accounted for both direct costs and indirect costs. Direct costs considered are drug acquisition, administration, monitoring, disease management, and AE costs.

3.3. Markov model structure and health states

3.3.1. Markov health states

Figure 21 illustrates the Markov model structure, with health states based on the MiToS disease staging system applied in the base case. Patients enter the model on commencement of their treatment, receiving either tofersen or SoC treatment. Once on treatment, patients are distributed into the health states informed by the baseline distribution. Patients may experience disease progression or regression (via forward or backward transitions between health states) as indicated by the arrows in Figure 21. A detailed breakdown of data inputs used in the model is provided in Section 3.8.

Figure 21. Cost-effectiveness Model Structure



MiToS = Milano-Torino functional staging system.

Note: Model structure above depicts MiToS staging.

** Patients in any of the health states may move to Stage 5 (dead).*

3.3.2. Disease Staging Systems

A variety of methods have been used to classify the progression of ALS into stages [173, 174]. The most widely used staging systems are MiToS functional staging [175] and the King's clinical staging [176] (Table 20).

The MiToS system uses 6 stages (0 = normal function; 5 = death) and assesses complete loss of independence in 4 functional domains (swallowing, walking/self-care, communicating, and breathing) [175, 177]. MiToS is directly based on the ALSFRS-R, and inherently consistent with

sequential disease progression [178]. Tracheostomy events are evenly spread across stages [179]. Even though the ALSFRS-R has been shown to have a floor effect and lack sensitivity in later stages of ALS disease course [64], these limitations are removed when using MiToS because it combines different parts of the ALSFRS-R to assess functional burden [173].

The King's system uses 5 stages (1 = symptom onset; 5 = death) and assesses the clinical or anatomical spread of the disease [176]. The first 3 stages of King's are defined by functional involvement of central nervous system regions used in the El Escorial diagnostic criteria for ALS, with King's Stages 2 and 3 approximately correlating with El Escorial [180]. Stages 4a (need for gastrostomy/feeding tube) and 4b (need for noninvasive ventilation) are not regarded as sequential stages.

Table 20. MiToS and King's Staging Systems for ALS

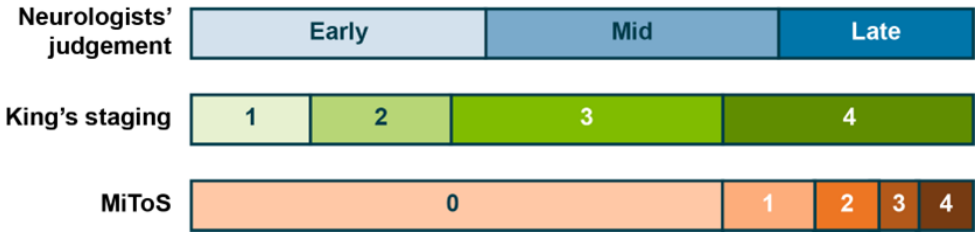
Health state = Stage	MiToS	King's
0 (MiToS)/1 (King's)	0 functional domains[a] lost	Involvement of 1 region[b]
1 (MiToS)/2 (King's)	1 functional domain[a] lost	Involvement of 2 regions[b]
2 (MiToS)/3 (King's)	2 functional domains[a] lost	Involvement of 3 regions[b]
3 (MiToS)/4a (King's)	3 functional domains[a] lost	Need for gastrostomy
4 (MiToS)/4b (King's)	4 functional domains[a] lost	Need for NIV
5 Death	Death	Death

ALS = amyotrophic lateral sclerosis; MiToS = Milano-Torino functional staging system; NIV = noninvasive ventilation.
[a] Functional domains defined as swallowing, walking/self-care, communicating, and/or breathing.
[b] Functional involvement of the central nervous system regions bulbar, lower limb (leg), and/or upper limb (arm).

The MiToS and King's staging systems assess different aspects of disease progression and are therefore complementary and largely not duplicative in terms of the information they provide [173, 181]. King's has a higher resolution in early-mid disease stages, whereas MiToS differentiates better in more advanced disease stages [173, 179, 182].

MiToS Stage 0 largely corresponds to King's Stages 1 to 3, and MiToS Stages 2 to 4 mostly correspond to King's Stage 4 [173]. Figure 22 attempts to visualize how staging systems correspond to each other, although the boundaries between the stages are not, in fact, set in stone. Thus, the illustration is not necessarily representative of true overlap between staging systems.

Figure 22. Illustration of How Staging Systems Correspond to Each Another



MiToS = Milano-Torino functional staging system.
Source: [57]

Both staging systems have limitations. The limitations of MiToS, compared with King's, include more heterogeneity in survival among patients of the same stage and consequently, smaller differences in survival among patients across different stages [179].

MiToS is directly based on ALSFRS-R, whereas King's can be estimated from ALSFRS-R scores using a published mapping algorithm [183]. It has been shown, however, that the ALSFRS-R lacks reliability regarding the retrospective allocation of patients to King's Stages. In a study of 52 patients with ALS, Balendra, Jones [180] reported that, of 103 clinic visits, 20 visits (19.4%) had a discrepancy between

clinical and algorithmically derived stages. Of those 20 visits, 10 were misclassified to be more severe and 10 were misclassified to be less severe, with most of the misclassifications being associated with King's Stage 2.

Further limitations of King's, compared with MiToS, include (1) the increased frequency of nonsequential transitions between states, especially with bulbar onset (i.e., the possibility of moving directly to Stage 4 in the event that gastrostomy is required, when only 1 or 2 regions are involved); (2) the possibility for normally functioning patients not to be assigned a stage (as the lowest King's Stage requires functional impairment of 1 region); (3) the inability to capture early transitions among clinical trial populations that require an ALS diagnosis by El Escorial (i.e., patients would already be in King's Stages 2 or 3 at enrolment); and (4) the fact that stages 4a and 4b may have heterogeneous costs and utilities [184] but are often combined.

3.3.3. Choice of Staging System

MiToS and King's staging systems both correlate well with a decline in functional and QoL measures [185-187]. The choice of staging system used in a cost-effectiveness analysis (CEA) depends on its ability to provide an accurate representation of the clinical pathway, the characteristics of the patient population being modeled, and the time horizon being considered for the evaluation.

If a patient population with early disease is being analyzed over a short-time horizon, King's staging may be more suitable because it differentiates well through early to mid-disease. Conversely, MiToS may be preferable for a mixed population (at any disease stage) that is being modeled over a lifetime horizon, because it includes a stage for patients with normal function and has more stages left for individuals to transition into. MiToS is inherently consistent with sequential disease progression (e.g., no stages can be skipped), whereas King's cannot capture the heterogeneity of natural history, costs, or QoL in patients who require gastrostomy or noninvasive ventilation because they are classified into Stages 4a or 4b, respectively. Because MiToS is based on the complete loss of function in different domains, it may also be more useful for estimating costs and QoL impacts [175, 179].

Therefore, given the need for a lifetime model of a prevalent and incident population across the whole spectrum of disease, MiToS staging was chosen to classify health states in the base-case analyses. King's staging is considered in a scenario analysis.

3.4. Discounting

Annual discount rates for costs and outcomes are applied in the model according to the Nordic countries' specifications.

Table 21). The discount rates change automatically when a given country is selected in the drop-down menu in the model.

Table 21. Country-specific input for discounting

Country	Description
Denmark	3.5 % annually
Finland	3 % annually
Iceland	No preference (Swedish setting applied in the current submission)
Norway	4 % up to 30 years, then 3 % annually beyond 30 years
Sweden	3 % annually, 0% and 5 % in sensitivity analysis

3.5. Population

The submission focuses on the total population of adults with *SOD1*-ALS, in line with the marketing authorisation for tofersen. Therefore, subgroups were not analysed for cost-effectiveness.

The modelled patient population was based on the VALOR trial population, which included patients of at least 18 years of age with a diagnosis of ALS and confirmed *SOD1* mutation. This corresponds to the therapeutic indication. As such, the model population corresponds to the relevant Nordic patient population (see Section 1.3).

The population inputs define the baseline characteristics for the selected model population (Table 22). Population data are calculated as the weighted average across all patients from the baseline characteristics of the VALOR trial [188].

Table 22. Population Inputs

Input	Mean	SD
Percentage female	42.6% (46/108)	—
Age (years)	49.1	12.33

SD = standard deviation.

Source: Biogen data on file [188].

These patient characteristics are reflective of the patient population in the Nordic countries. Data on the mean age of onset for *SOD1*-ALS has only been identified for Norway, where it is reported to be 48.9 (SD 12.8) years [8]. This is in-line with international data which indicate that patients with *SOD1*-ALS have on average an earlier onset of disease as compared with ALS in general, in the range of 40-50 years old [8, 24]. Hence, the model population is similar to the patient population anticipated in Nordic clinical practice. Furthermore, as disease-specific mortality is used in the model, population inputs do not impact mortality and any deviations between the model and clinical practice would be of minor importance. According to the JNHB guidelines, general mortality can be based on life tables of one of the Nordic countries. The model makes use of Swedish life tables for general mortality.

Regarding the baseline distribution of patients across health states defined by MiToS (Table 23), the base case distribution was based on the baseline distribution in the VALOR clinical trial, which includes patients with *SOD1*-ALS only.

Table 23. Baseline Distribution of Patients – MiToS

MiToS Stage	All patients, % (n/N)
	VALOR (Part C) [188]
Stage 0	75.0% (81/108)
Stage 1	21.3% (23/108)
Stage 2	2.8% (3/108)
Stage 3	0.9% (1/108)
Stage 4	0.0% (0/108)

Source: Biogen data on file [188]

3.5.1. *Alternative baseline health state distributions*

An alternative option in the model available as a scenario analysis is based on Thakore, Lapin [189], which reports the baseline distribution of patients with ALS from Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) [189].

Baseline distributions using King's staging are also available in the model.

Scenario analyses were performed assessing these alternative baseline distributions. The baseline distribution input data are available in the cost-effectiveness model (CEM) file.

3.6. Intervention

The intervention in the CE base case analysis is tofersen. In the model base case, tofersen is evaluated as a treatment of SOD-1 ALS to be prescribed in combination with SoC (where riluzole is a constituent part of SoC for this submission, in line with description in section 3.7). The posology applied for tofersen in the CEM is presented in Table 26. It reflects the recommended posology in the SmPC [126] which is also the posology applied in the VALOR clinical trial and the anticipated use in the clinical setting.

Table 24. Posology for tofersen applied in the CEM

Treatment	Dose form	Dosing regimen	Strength per unit (mg)	Source
Tofersen	Intrathecal bolus injection	100 mg once daily on days 1, 15, 29 then every subsequent 28 days	100 mg (15 mL × 6.7 mg/1 mL)	Tofersen SmPC [126]

In the VALOR trial, patients in the intervention arm were administered tofersen by intrathecal bolus over 1-3 minutes, following a dosing regimen of 100 mg tofersen administered on days 1, 15, and 29 initially and every 4 weeks thereafter by intrathecal injection (Biogen data on file [158]). The use of concomitant riluzole (as well as edaravone which is not approved in EU and thus not relevant to this submission) treatment was permitted in both arms during the trial, details of which are outlined below in Table 25. The use of riluzole was balanced between the trial arms. In the comparator arm, 45 out of 72 patients (62%) used riluzole, and 6 out of 72 (8%) used edavarone [18].

Concomitant treatment with riluzole is anticipated in clinical practice in the Nordic countries for *SOD1*-ALS patients also upon introduction of tofersen [145]. Accordingly, riluzole treatment was included as a component of SoC applied in the tofersen arm (as well as in the comparator arm) in the model base case.

A life-lasting treatment duration is anticipated for tofersen, and there are no subsequent treatments of relevance either in the model, clinical trial or clinical practice.

Table 25. Allowed Concomitant Therapy – VALOR

Concomitant therapy	Requirements
Riluzole	Subjects taking concomitant riluzole at study entry must be receiving a stable dose for ≥ 30 days prior to the first dose of study treatment (Day 1). These subjects should remain on this stable dose of riluzole until the completion of the Week 12 Visit, unless riluzole use must be discontinued in the judgment of the Investigator, in which case it should not be restarted until the completion of the Week 12 Visit. If subjects are not receiving riluzole at

	Day 1, they should not initiate it until the completion of the Week 12 Visit.

Source: Biogen data on file [158] [VALOR (Part C) trial protocol].

3.7. Comparator(s)

The comparator in the CE base case analysis is SoC. In the model base case, SoC is composed of riluzole treatment. The posology applied for riluzole in the CEM is presented in Table 26.

Table 26. Posology for riluzole applied in the CEM

Treatment	Dose form	Dosing regimen	Source
Riluzole	Tablet	50 mg twice daily	SmPC [126]

In the clinical setting, the current standard of care in Finland, Norway, Sweden, and Denmark for adult ALS patients is treatment with riluzole. In the Nordic countries, there is not a standardized routine for genetic testing and screening and ALS is diagnosed by clinical assessment of signs and symptoms. Therefore, riluzole is offered to all patients diagnosed with ALS irrespective of the underlying disease mechanism. According to data from Folkhelseinstittutet, approximately 88% of patients with ALS are currently treated with riluzole (Folkehelseinstituttet,2023) [190]. The CEM comparator being SoC including riluzole was therefore considered to be a relevant reflection of the current clinical practice in the Nordic countries. The posology used in the CEM for riluzole was in line with the SmPC [126] and thus considered reflective of the clinical practice.

In the VALOR trial, patients in the comparator arm were administered placebo by intrathecal bolus over 1-3 minutes, following the same dosing regimen as tofersen in the intervention arm (Biogen data on file [158]). The use of concomitant riluzole (as well as edaravone which is not approved in EU) treatment was permitted in both arms during the trial, details of which are outlined in Section 2.3.1 above. The use of riluzole was balanced between the trial arms. In the comparator arm, 22 out of 36 patients (61%) used riluzole, and 3 out of 36 (8%) used edavarone [18].

3.8. Modelling of treatment effectiveness

The CEM was structured as an ALS disease model informed by natural history data, on which the impact of tofersen treatment was implemented by applying a relative treatment effect estimated from the direct treatment comparison of tofersen (early start) and placebo/tofersen (delayed start by six months) in the VALOR trial and its OLE study. A natural history disease model was preferred over informing the disease model by VALOR data since, due to sample size issues inherent to clinical trials in rare diseases such as ALS, it was not possible to derive transition probability matrices for MiToS and King's staging using VALOR trial data.

3.8.1. Natural history

Natural history means the expected disease trajectory of patients receiving the current SoC. Together with survival, the natural history of ALS is characterized by the progression of disease through clinical stages and milestone events such as tracheostomy. Because there is heterogeneity of disease progression and survival in patients with ALS, the prediction of individual disease progression is difficult.

ALS is a rare disease, so clinical trials may not have sufficiently large sample sizes to surmount uncertainty from patient heterogeneity [191, 192], particularly trials in subpopulations with a

specific genetic mutation. To address these limitations, the PRO-ACT database, a multinational registry of prospective clinical trials, was developed. It includes merged, deidentified data from over 10,700 patients with ALS who participated in 23 phase 2/3 clinical trials [151], where the database consists of 40% female participants with an overall mean age of 56.2 years [191]. More than 3,500 of those patients have longitudinal records of ALSFRS-R, a subjective functional assessment commonly used as a primary endpoint in ALS clinical trials [63]. PRO-ACT generalizability is limited by selection bias, heterogeneity, and limited duration of follow-up. Time-invariant stage transition probabilities have been estimated under Markov assumptions from PRO-ACT data [189].

Median survival in the PRO-ACT database was reported to be 479 days (1.31 years/15.75 months) from trial entry in 2014 [191]. At this time, the PRO-ACT database comprised data points from over 8,600 patients with ALS from 16 completed phase 2/3 clinical trials. More recently, Bhattacharya, Harvey [193] reported a median survival of 388 days (12.76 months) from the first ALS-related medical claim in a US Medicare population.

The generalizability of mortality data from global disease-specific natural history sources to specific local populations may be questioned. Application of methods such as standardized mortality ratios could be explored to adjust mortality data derived from natural history sources to different local settings and populations. However, differences between geographical populations have not been found to affect the performance of survival predictions in European patients [194].

Clinical trial inclusion criteria can distort the distribution of rate of disease progression, raising questions about the generalizability of trial results. Several studies have reported differences between ALS clinical trial populations and the general ALS population, including Chiò, Canosa [195], Bedlack, Vaughan [196], and van Eijk, Nikolakopoulos [197]. These studies reported that ALS clinical trial populations demonstrated a significantly longer tracheostomy-free survival than the general ALS population, ALSFRS-R scores plateaued more frequently in clinical trials included in the PRO-ACT database than in the general ALS population, and patients with ALS enrolled in clinical trials consistently had a better prognosis than the overall ALS population [195-197]. Conversely, recent retrospective studies [198, 199] have found the mean rate of ALSFRS-R decline in ALS clinics (0.65-0.77 points per month) to be lower than in PRO-ACT's clinical trial populations (1.02 points per month). However, it is important to note the limitations of clinic-based natural history studies, which can include referral bias and lack the ability to capture data from patients with ALS who are homebound, who tend to be in later stages of disease.

An international retrospective observational study [8] examined a database reporting 1,122 people with *SOD1*-ALS with a comparative ALS population of 10,214 for age of disease onset, and 883 people with *SOD1*-ALS with 9,010 people with ALS for disease duration. This study reports that *SOD1*-ALS gene variants are associated with a distinct phenotype. On average, patients with *SOD1*-ALS have a younger age of onset (49 years vs. 61 years), shorter diagnostic delay (10 months vs. 12 months), and shorter survival (27.7 months vs. 35.1 months) than those with sporadic ALS. Among the over 200 *SOD1* variants found to be associated with ALS, rapidity of disease progression varies substantially with disease durations ranging from less than a year to more than 20 years [8, 161, 200]. For example, the relatively prevalent p.Ala5Val (A5V; A4V) mutation is associated with a median survival at or below 1.2 years based on Kaplan-Meier estimates [8, 161], far shorter than the average survival observed in the broad ALS population. These differences in disease duration and survival resulted in a hazard ratio (HR) of 1.3 (95% CI, 1.2-1.4) for *SOD1*-ALS compared with the broad ALS population, with HRs for variants within *SOD1* reported to be as low as 0.2 (95% CI, 0.1-0.5) for *H47R* and as high as 8.7 (95% CI, 7.5-10.1) for.*A5V*. Hazard ratios were estimated using Cox proportional hazards regression models that were adjusted for gender, age of symptom onset, and site of symptom onset.

SOD1-ALS is clinically distinct from the broad ALS population in that it is predominantly a lower motor neuron disease, more often presenting with limb onset, and with little to no cognitive involvement compared with the broad ALS population [8, 201-203].

A summary of the results of a systematic literature review exploring studies that report natural history and /or prognostic outcomes is provided in Appendix D.

3.8.2. Natural History Applied in the Model

Thakore et al (Thakore, Lapin [189]) analyzed the PRO-ACT database to derive 3-monthly transition probabilities for patients with ALS for health states defined by King's and MiToS staging systems. The reported transition probabilities for MiToS are presented in Table 27.

However, although the transition probabilities reported (Thakore, Lapin [189]) provide a good fit for the patient numbers observed at each disease stage and death at 12 months, progression and mortality are underestimated in extrapolations covering post 12-month period when compared with the PRO-ACT database.

Using the information provided in the study by Thakore, Lapin [189], a **calibration** exercise was therefore undertaken to derive transition probabilities that provided a better fit with the reported patient numbers at each stage and death for the post 12-month period. After calibration, the model-predicted median survival in the SoC arm (15.69 months) (in the overall population [i.e., without applying the HR for *SOD1*-ALS vs. ALS]) matches the reported median survival time in the PRO-ACT database of 479 days (15.75 months) from trial entry [191]. Further details of the calibration exercise are provided in Appendix A.

In the model base case, the SoC transition probabilities are informed by the reported values from Thakore et al converted to 4-week probabilities (Table 28) applied up to month 12, with the calibrated transition probabilities being used thereafter (Table 29).

Given the differences in disease progression and survival between patients with *SOD1*-ALS and the overall ALS population (please see Sections 1.2 and 3.8.1), it was felt appropriate to adjust disease progression and mortality reported for the overall ALS population from PRO-ACT [189] to better reflect the *SOD1*-ALS population. Therefore, the **HR for *SOD1*-ALS** versus ALS reported by [8] was used in the model (Table 30).

Table 27. Three-monthly Transition Probabilities, SoC – Thakore et al. (2018) [PRO-ACT] [MiToS]

From/to	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	Death
Reported by Thakore, Lapin [189]						
Stage 0	0.714	0.232	0.040	0.006	0.001	0.007
Stage 1	0.094	0.605	0.199	0.042	0.010	0.050
Stage 2	0.013	0.164	0.435	0.177	0.066	0.145
Stage 3	0.001	0.025	0.126	0.330	0.269	0.249
Stage 4	0.000	0.002	0.018	0.101	0.574	0.305

MiToS = Milano-Torino functional staging system; PRO-ACT = Pooled Resource Open-Access ALS Clinical Trials; SoC = standard of care; TP = transition probability.

Notes: In some instances, the transition probabilities between health states reported by Thakore, Lapin [189] did not sum to 1 due to rounding. In these cases, the transition probabilities in each row were divided by the sum of the row to ensure the probabilities summed to 1.

Source: Thakore, Lapin [189].

Table 28. 4-Weekly Transition Probabilities, Baseline to Month 12, SoC – Thakore et al. (2018) [PRO-ACT] [MiToS]

From/to	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	Death
Thakore, Lapin [189], converted to 4-weekly transitions						
Stage 0	0.905	0.078	0.012	0.002	0.000	0.002
Stage 1	0.030	0.872	0.066	0.013	0.003	0.016
Stage 2	0.004	0.054	0.816	0.058	0.021	0.047
Stage 3	0.000	0.008	0.041	0.775	0.092	0.084
Stage 4	0.000	0.001	0.006	0.032	0.856	0.106

MiToS = Milano-Torino functional staging system; PRO-ACT = Pooled Resource Open-Access ALS Clinical Trials; SoC = standard of care; TP = transition probability.

Note: Transitions between stages in the above table may sum to greater than 1 due to rounding.

Source: Derived based on data reported by Thakore, Lapin [189].

Table 29. 4-Weekly Transition Probabilities, 12 months+, SoC – Calibrated Thakore, Lapin [189] [PRO-ACT] [MiToS]

From/to	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	Death
Thakore, Lapin [189], 4-weekly calibrated						
Stage 0	0.884	0.076	0.012	0.002	0.000	0.026
Stage 1	0.027	0.788	0.059	0.012	0.003	0.111
Stage 2	0.004	0.047	0.730	0.051	0.018	0.149
Stage 3	0.000	0.007	0.036	0.694	0.081	0.181
Stage 4	0.000	0.001	0.005	0.028	0.754	0.213

MiToS = Milano-Torino functional staging system; PRO-ACT = Pooled Resource Open-Access ALS Clinical Trials; SoC = standard of care; TP = transition probability.

Note: Transitions between stages in the above table may sum to greater than 1 due to rounding.

Source: Derived based on data reported by Thakore, Lapin [189].

Due to sample size issues, inherent to clinical trials in rare diseases such as ALS, it was not possible to derive transition probability matrices for MiToS and King's staging using VALOR trial data. The SoC transition probabilities estimated from PRO-ACT data [189] are the only natural history source available in the model.

3.8.3. Tofersen treatment effect

In the health economic model, tofersen treatment effect is implemented as a reduction in transition rates between discrete health states. The treatment effect is based on combined analyses of VALOR and OLE, which provide a direct treatment comparison between tofersen (early start) and placebo/tofersen (delayed start by 6 months).

The reduction in transition rates is estimated using hazard ratios for tofersen versus SoC that were estimated from time-to-event data, defined as the time from baseline to the first time that a patient progresses by at least 1 MiToS stage, and the time from baseline to death, respectively (the corresponding analyses were also undertaken based on the King's staging). Time to progression was compared using Kaplan-Meier time-to-event analyses and a Cox proportional hazards model. A detailed description of the time-to-event analysis is provided in Appendix B and section 3.8.4.

Briefly, the Cox proportional hazards model was adjusted for baseline plasma NFL, and riluzole or edaravone use. Time to event was defined as the time from baseline to the first time that a patient goes up at least 1 stage. If a patient transitions from an earlier stage (0, 1, 2, 3, 4) to death, the patient is classed as having an event and time to event is defined as the time from baseline to death date. Patients who withdraw due to reasons other than death and who have not got to a later stage are censored at time of withdrawal. Ongoing patients who have not transitioned to a later stage are censored at the last known alive date.

Following the completion of the placebo-controlled VALOR trial, all participants had the opportunity to enroll in an OLE study, where they received open-label tofersen treatment but remained blinded to the treatment received in the double-blind study. This crossover design is expected to underestimate the effect of treatment on ALSFRS-R and survival, compared with a true placebo. The RPSFTM, a common statistical method to correct for crossover, was used to estimate (for each trial participant) the counterfactual time to progression in the absence of tofersen treatment (i.e., to reconstruct data for the placebo arm as if crossover had not occurred). RPSFTM-adjusted time to progression from baseline stage to later stages or death is considered the most appropriate approach. The limitations of these analyses include that they are post hoc exploratory OLE analyses based on a small sample size and low number of transition events observed in VALOR and OLE. High switching proportion combined with the small sample size and low event numbers mean that the results are uncertain. However, a wide range of sensitivity analyses (see Appendix B) demonstrate the reliability of the primary results.

All HRs used in the model are detailed in Table 30.

Table 30. Estimated Hazard Ratios applied in the CEM

HR	Mean	95% CI	Source
SOD1-ALS vs. ALS	1.3	1.2-1.4[a]	[8]
MiToS			
tofersen vs. SoC (Progression)	0.61	0.29-1.27	Appendix B
tofersen vs. SoC (Mortality)	0.10	0.01-0.81	Appendix B
King's			
tofersen vs. SoC (Progression)	0.98	0.51-1.87	Appendix B
tofersen vs. SoC (Mortality)	0.10	0.01-0.81	Appendix B

ALS = amyotrophic lateral sclerosis; CI = confidence interval; CL = VALOR (Part C) and OLE data; HR = hazard ratio; ITT = intention to treat; RPSFTM = rank-preserving structural failure time model; SoC = standard of care; SOD1 = superoxide dismutase 1.

Note: HRs for tofersen vs. SoC are for time to transition from Week 0 stage to later stages (excluding death), or from Week 0 to death. For pooled group CL using RPSFTM, ITT population.

[a] 95% CI were derived based on an assumed standard error of 10% of the mean value.

In line with the methods used to estimate HRs for tofersen from the VALOR and OLE data, the treatment effect (i.e., HRs) is applied to forward transitions only.

Transition probabilities for the tofersen arm of model were derived by applying an HR for tofersen versus SoC, obtained from the VALOR and OLE data. This HR is applied to the derived transition probability matrices for the *SOD1*-ALS population for tofersen (Table 31, Table 32).

Table 31. SOD-1 Population, 4-Weekly Transition Probabilities, Baseline to Month 12, Tofersen [MiToS]

From/to	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	Death
Stage 0	0.926	0.062	0.010	0.001	0.000	0.000
Stage 1	0.030	0.903	0.053	0.010	0.002	0.002
Stage 2	0.004	0.054	0.873	0.046	0.017	0.006
Stage 3	0.000	0.008	0.041	0.866	0.074	0.011
Stage 4	0.000	0.001	0.006	0.032	0.947	0.014

ALS = amyotrophic lateral sclerosis; HR = hazard ratio; SoC = standard of care; SOD1 = superoxide dismutase 1; TP = transition probability.
Note: tofersen transition probabilities are derived by applying the tofersen vs. SoC HRs for progression and mortality (Table 30) to SOD1-ALS-specific transition probabilities for SoC, derived by applying the SOD1-ALS HR [8] to base-case SoC transition probabilities (Table 28, Table 29).
Source: Thakore, Lapin [189]; Biogen data on file [204].

Table 32. SOD-1 population, 4-Weekly Transition Probabilities, Month 12+, tofersen) [MiToS]

From/to	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	Death
Stage 0	0.925	0.061	0.010	0.001	0.000	0.003
Stage 1	0.027	0.899	0.047	0.009	0.002	0.015
Stage 2	0.004	0.047	0.873	0.041	0.015	0.021
Stage 3	0.000	0.007	0.036	0.866	0.065	0.026
Stage 4	0.000	0.001	0.005	0.028	0.936	0.031

SOD1 = superoxide dismutase 1; TP = transition probability.
Source: Thakore, Lapin [189]; Biogen data on file [204].

When King's is the chosen classification system in the model, SoC transition probabilities reported by and calibrated from Thakore, Lapin [189] are available within the model.

3.8.4. Hazard ratio for time to progression to next MiToS stage and time to death

The statistical analyses performed to explore the relative treatment efficacy of tofersen versus SoC (placebo), expressed as a hazard ratio for time to progression to next disease stage and a hazard ratio for time to death, are described in Appendix B.

A brief summary is provided in this section. The outcome of the analysis is the hazard ratios presented above in Table 30.

Following the completion of the VALOR trial, participants were given the option to enroll in an ongoing OLE, while remaining unaware of their trial group assignment. Participants randomized to tofersen in VALOR had the opportunity to continue on tofersen treatment in the open-label extension ("early-start" participants), and participants randomized to placebo in VALOR had the opportunity to switch to tofersen treatment in the open-label extension ("delayed-start" participants).

In the presence of treatment switching, an ITT analysis, in which the data are analyzed according to the arms to which patients were randomized, may lead to biased results. For example, when participants in the placebo group of a trial are allowed to switch onto the experimental treatment in an open-label extension, an ITT analysis may underestimate the treatment effect because after

switching, the placebo group may benefit from the experimental treatment. Underestimation of the efficacy of a treatment could result in access being denied to a cost-effective treatment.

To address the health technology assessment (HTA) decision problem, adjustments for treatment switching may be conducted to obtain a more robust estimate of the treatment effect. HTA organisations such as NICE and NoMA accept that it is reasonable to present analyses from statistical methods that attempt to adjust for treatment switching, to estimate outcomes that would have been observed if treatment switching had not taken place [205] [206]. Statistical methods for addressing treatment switching have been recommended for use in HTA contexts, including inverse probability of censoring weighting, "two-stage" methods, RPSFTM and iterative parameter estimation (IPE). RPSFTM and IPE have previously been used in various therapeutic areas such as oncology, multiple sclerosis, and ALS. RPSFTM and IPE estimate the counterfactual survival times, which represent the survival times that would have been observed if treatment switching had not occurred. In the current submission, the relative treatment effect was estimated using RPSFTM adjustment in the base case analysis, supported by an IPE adjustment sensitivity analysis.

The combined analyses of VALOR and open-label extension in the current submission used data from the January 16, 2022 data cutoff (the "52-week analysis") and are based on the ITT principle, where all participants who underwent randomization in VALOR were included according to the original trial-group assignment. For the January 2022 data cutoff, the median time on study was 88.6 weeks and the mean time on study was 87.0 weeks.

The outcomes of interest in the current analyses were time to death, time to transition to later MiToS stage (excluding death), and time to transition to later King's stage (excluding death) in the overall ITT population, with time to transition event defined as the time from baseline to the first time that a patient goes up (worsens by) at least 1 stage compared with baseline.

Patients who withdrew and who had not reached a later stage were censored at time of withdrawal and ongoing patients who had not transitioned to a later stage were censored at the date they were last known to be alive. In analyses of transition to later Kings stage, King's stages 4a and 4b were combined and counted as the same stage for this analysis since there was a small number of participants in these stages (e.g., the number of subjects in stage 4a at baseline was 1). This approach is also consistent with recent clinical views (12).

ITT analyses were first conducted, ignoring treatment switching to be able to compare with the effect estimates adjusted for treatment switching after implementing RPSFTM and IPE. The ITT analyses examined the data according to the arms to which patients were randomized, regardless of whether they switched onto tofersen in the open-label extension.

RPSFTM were then conducted to estimate counterfactual survival times. Consistent with the amended statistical analysis plan before analysis of the January 2022 data cutoff, adjustment was done for baseline plasma neurofilament light chain (NfL) and background therapy (riluzole and/or edaravone use) at baseline. Baseline plasma NfL and riluzole or edaravone use were included in the RPSFTM g-estimation process. Cox proportional hazards models adjusted for baseline plasma NfL and riluzole or edaravone use were fitted to estimate the hazard ratios for the outcomes of interest. For all RPSFTM analyses, test-based confidence intervals associated with the hazard ratios were calculated using the p-value and z-statistic from the ITT analysis for each outcome.

Results

In **ITT analyses** ignoring treatment switching, the hazard ratio for time to death from VALOR baseline for participants randomized to tofersen compared with participants randomized to placebo was 0.27 (95% CI: 0.08, 0.89), implying a reduction of 73% in the expected time to death associated with being assigned to tofersen compared to placebo. The HR for time to transition from VALOR baseline to

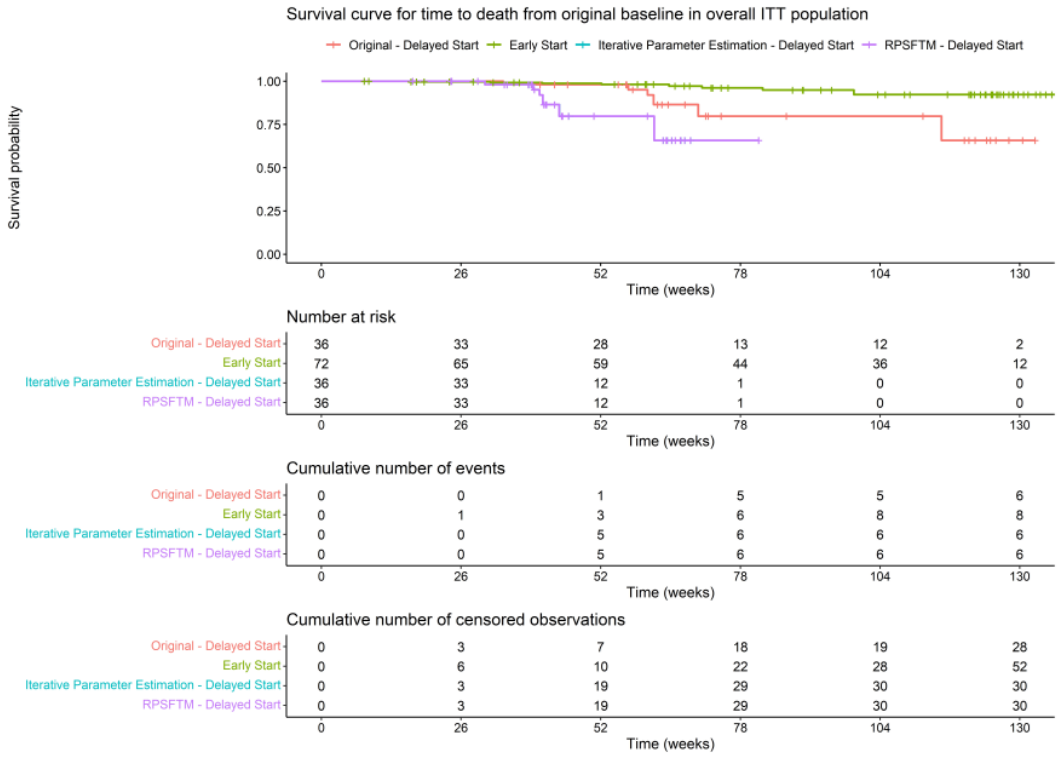
later MiToS stages (excluding death) was 0.69 (95% CI: 0.40, 1.20), and that for time to transition from VALOR baseline to later King's stages (excluding death) was 0.98 (95% CI: 0.56, 1.71).

In the **RPSFTM analyses**, there was a reduction in the hazard of death after adjusting for treatment switching using RPSFTM compared with the result from the ITT analysis. After accounting for treatment switching, the HR for time to death from VALOR baseline for the participants randomized to tofersen compared with participants randomized to placebo was 0.10 (95% CI: 0.01, 0.81), indicating a 90% reduction in the expected time to death associated with tofersen compared to the time expected without tofersen treatment. For the outcomes of time to transition to later stages after adjusting for treatment switching; the HR for time to transition from VALOR baseline to later MiToS stages (excluding death) was 0.61 (95% CI: 0.29, 1.27) and that for time to transition from VALOR baseline to later King's stages (excluding death) was 0.98 (95% CI: 0.51, 1.87).

Figure 23 and Figure 24 show the survival curves for each outcome which were based on Cox proportional hazards models that adjusted for baseline riluzole or edaravone use and plasma NfL using the original ITT data, data adjusted for treatment switching using RPSFTM, and data adjusted for treatment switching using IPE. We found that for all outcomes, survival curves for the delayed-start group were similar after implementing both RPSFTM and IPE. For the outcome of time to death, adjusting for treatment switching decreased the survival probability in the delayed-start group (Figure 23). The curves for the delayed-start group after adjusting for treatment switching using RPSFTM and IPE appear cut off due to the lack of control group non-switchers. Survival curves for the outcomes of time to transition to later MiToS stages are shown in Figure 24.

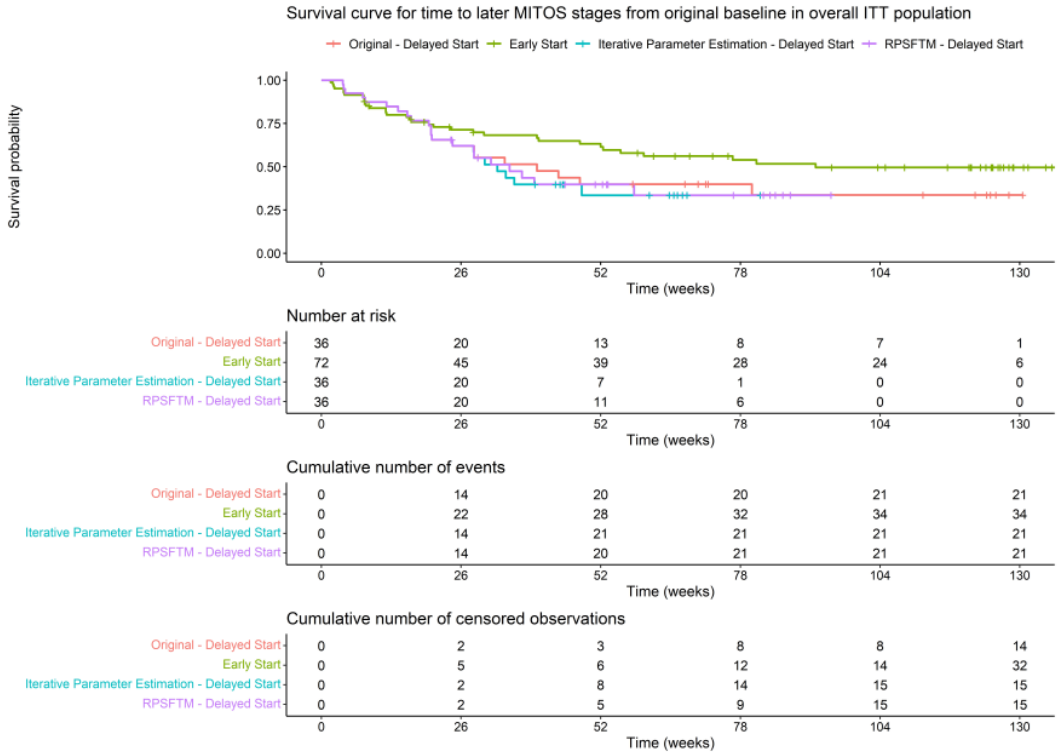
For clarity, in these charts, the curves adjusted for treatment switching (delayed start curves) provide an estimated representation of the counterfactual time-to-event if patients had not switched to tofersen treatment. They are not intended to provide a comparison between different times to initiate treatment with tofersen. In this context, however, the trial results as described above show that early initiation provides the best treatment outcome and that even 2 years later, there is separation in patients who started receiving treatment 6 months earlier.

Figure 23. Survival curve for time to death from VALOR baseline



Note: The curves for the delayed-start group after adjusting for treatment switching using RPSFTM and IPE are overlapping.

Figure 24. Survival curve for time to transition from VALOR baseline stage to later MITOS stages (excluding death)



Modelling of study outcome (intervention and comparator)

See section 3.8.3.

3.8.5. Modelling of time to treatment discontinuation – intervention and comparator

The model allows for exploring treatment discontinuation for tofersen. When patients discontinue treatment, they transition to receive SoC, which patients cannot discontinue in the model.

Discontinuation for tofersen was based on the rate of discontinuation (6.94% over 28 weeks) from the VALOR trial [188], which was converted to a cycle-based (4 weekly) probability (1.02% for 4-weekly cycles) for model use. Estimates for discontinuation were based on the numbers of patients discontinuing treatment during the trial period due to AEs, withdrawn consent, or another reason.

In the model, discontinuation was implemented so that distinct probabilities could be specified per model health state. However, it was not considered appropriate to calculate stage-specific discontinuation rates from the VALOR trial, as patients may transition forward and backward between disease stages throughout the duration of the trial, meaning it is not possible to know if discontinuation in each stage is related to the stage itself or the preceding stage. This could therefore lead to unrealistically high discontinuation rates for lower disease stages in cases where a patients disease stage improves before discontinuation (i.e., the resolution of gastronomy). Therefore, the probability of discontinuation was assumed to be the same across all health states.

3.9. Modelling of safety events

Adverse event incidences were derived from the tofersen and placebo arms of the VALOR (Part C) trial and converted to 4-weekly AE probabilities for use in the model. AE data from the placebo arm of the VALOR trial were assumed to be reflective of AEs of SoC (riluzole, edaravone).

The most common AEs (occurring in ≥ 10% of tofersen-treated patients) were pain, myalgia, arthralgia, fatigue, and CSF white blood cell increased [167]. Table 33 shows all nonserious AEs that have ≥ 5 percentage points difference between the tofersen arm and placebo. These nonserious AEs are thought to have a plausible causal association with tofersen and were therefore considered for inclusion into the model.

Table 33. Incidence of Nonserious Adverse Events

Adverse Event	tofersen (N = 72)		Placebo (N = 36)		Difference
	N	(%)	n	(%)	
CSF white blood cell increased	10	13.9%	0	0.0%	13.9%
CSF protein increased	6	8.3%	1	2.8%	5.6%
Neuralgia	4	5.6%	0	0.0%	5.6%
Arthralgia	10	13.9%	2	5.6%	8.3%
Myalgia	10	13.9%	2	5.6%	8.3%
Musculoskeletal stiffness	4	5.6%	0	0.0%	5.6%
Limb pain and back pain	30	41.7%	8	22.2%	19.4%
Fatigue	12	16.7%	2	5.6%	11.1%

CSF = cerebrospinal fluid.

Note: CSF white blood cell increased includes preferred terms of CSF white blood cell increased and pleocytosis. Pain includes preferred terms of pain, back pain, and pain in extremity.

Source: [167], Biogen data on file [168].

All nonserious AEs were characterized by mild-to-moderate severity; all were transient and easily treated at negligible cost with paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and aspirin for pain relief. They were mostly managed without additional clinical practice visits (via phone/email) or stronger prescription pain medications. Increased CSF white blood cell and increased CSF protein represent symptomless laboratory results. Therefore, none of these nonserious AEs were included in the analyses, except for the most common: **limb pain and back pain.**

The proportion of subjects experiencing SAEs was 18% in the tofersen group and 14% in the placebo group [18]. Most of these SAEs were related to underlying disease progression rather than drug related and there were no fatal AEs [169].

There were serious neurologic events in the VALOR trial that occurred in patients treated with tofersen that did not occur in patients receiving placebo. Myelitis occurred in 2 subjects (2.8%) and radiculitis occurred in 1 subject (1.4%). When these events did not lead patients to permanently discontinue treatment (in which case they are implicitly considered in the modeling via the discontinuation rate), these patients were asymptomatic or had complete resolution of symptoms.

Although the majority of these serious neurologic events may be related to the route of administration rather than specific to the drug itself [169], 2 were selected for inclusion in the analyses because they may require more resources to diagnose/treat in clinical practice: **myelitis** and **radiculitis**. There was also 1 case of chemical meningitis, but it was not included in the model because treatment was not considered to be costly.

The proportions of patients experiencing AEs and SAEs over the 28-week VALOR trial period were converted to inform 4-weekly model cycles and were applied for as long as patients remain on treatment (i.e., they are not one-time events related to treatment initiation).

Table 34. Adverse events included with cycle probabilities applied in the CEM

Adverse event	tofersen		SoC	
	Incidence	**4-weekly probability[2]**	**Incidence**	**4-weekly probability[2]**
Limb pain and back pain	41.7%[1]	0.0741	22.2%[1]	0.0353
Radiculitis	1.39%[1]	0.0020	0%[1]	0
Myelitis	2.78%[1]	0.0040	0%[1]	0

[1] *VALOR (Part C) trial, reported incidence per 28 weeks*

[2] *Calculated as 1 - (1 - Incidence) ^ (4 weeks / Duration in weeks)*

3.10. Health-related quality of life (HRQoL)

Table 35 summarizes the preferred QoL instruments and tariffs in the different JNHB settings. In the current model, utility values based on the UK tariff are applied, as described further below. The base case was informed by utility values obtained from the literature, and values calculated with the Danish or Swedish were unfortunately not available.

Table 35. Country specific preferences for EQ5D instrument and tariffs

Country	Preference for utility calculation
Denmark	EQ-5D-5L with Danish tariffs
Finland	No preference

Iceland	No preference
Norway	EQ-5D-3L with UK tariffs
Sweden	EQ-5D-3L with UK tariffs and EQ-5D-3L Swedish tariff in sensitivity analysis

3.10.1. Health State Utilities Included in the Model

For the MiToS staging system used in the CEM base case, three sources for health-related (HR)QoL utilities were included in the model. Two of these sources were identified in an SLR (Appendix C): Moore et al 2019 and Stenson et al 2022 [207, 208], which were selected for inclusion in the model as they reported utility values that logically decreased with increasing disease severity and included patients from the UK (the core model was done with UK as reference country). Stenson et al. is also available as newer publication from 2024 [209].Utility data from the VALOR trial were also included in the model, which were provided by Biogen [188]. Moore et al reported EQ-5D-5L [207] while the VALOR trial and Stenson et al. reported EQ-5D-5L that were mapped to EQ-5D-3L [188, 208] for use in the model.

The health state utilities reported by Moore et al (Moore, Young [207]) were informed by data from the Trajectories of Outcomes in Neurological Conditions (TONiC) study. TONiC is an ongoing longitudinal cohort study which, at time of data collection, comprised patients from 22 MND clinics in the UK. Data were collected using the EQ-5D-5L questionnaire for 595 patients, of which 39% were female with a mean age of 65 years (SD, 10.89). ALSFRS-R was also collected in the study and was used to assign patients to MiToS Stages. It was found that the usual activities domain of the EQ-5D-5L was most affected by ALS, and patients with bulbar onset tended to have higher utility values (0.68; 95% CI, 0.64-0.72) than those with limb (0.53; 95% CI, 0.49-0.57) or respiratory (0.53; 95% CI, 0.35-0.71) onset. Data were also reported by King's staging, and a utility value was also reported for the full sample.

The health state utilities from the VALOR trial were collected using the EQ-5D-5L questionnaire for 72 patients receiving tofersen 100 mg and 36 patients receiving placebo [188, 210]. Analysis of the EQ-5D-5L utility scores in the mITT population indicated a smaller least square mean change from baseline in the tofersen group (−0.16) compared with the placebo group (−0.35), which were derived from an analysis of covariance (ANCOVA) model with treatment included as a fixed effect and adjusted for covariates including baseline EQ-5D-5L VAS score, baseline disease duration since symptom onset, and use of edaravone or riluzole. Furthermore, a 0.20 point treatment difference (95% CI, 0.062-0.332) in change from baseline was observed at Week 28 (P = 0.0043) [188, 210]. Participant-reported EQ-5D-5L scores by MiToS Stage were mapped to EQ-5D-3L scores for the ITT population (Table 37). Data were also provided by King's staging.

3.10.1.1. Health state utility values applied in the CEM base case

Utility weights reported per MiToS stage by Moore et al (Moore, Young [207]) were used in base-case analyses. The selection was justified given that the utility weights logically decrease for increasing disease severity and that the study is based on the largest sample size for a UK population (Table 36).

Table 36. Patient Utility Estimates – Moore, Young [207] [MiToS]

MiToS Stage	Utility weights [EQ-5D-5L] (n)	95% CI
Stage 0	0.71 (n = 301)	0.69-0.73
Stage 1	0.48 (n = 198)	0.44-0.51

Stage 2	0.36 (n = 73)	0.31-0.42
Stage 3	0.33 (n = 18)	0.23-0.43
Stage 4	0.25 (n = 5)	0.07-0.42

CI = confidence interval; MiToS = Milano-Torino functional staging system.

Source: Moore, Young [207].

It is, however, noted that while Moore et al was considered the best data set to use in the model, these utility weights are not fully consistent with JNHB guidelines, which recommends the use of EQ-5D-3L (with UK tariffs) for the Swedish and Norwegian analyses; therefore, the utility estimates from the VALOR (Part C) trial that were mapped to the EQ-5D-3L (Table 37) were explored in a scenario analysis.

Furthermore, the CEM Excel model includes health state utility data sets reported for ALS health states defined by the King's staging system. These are applied automatically in the model if the King's staging system is selected.

Table 37. Patient Utility Estimates – VALOR (Part C) [MiToS]

MiToS Stage	Utility weights (n)[a]	95% CI
Stage 0	0.60 (n = 810)	0.59-0.61
Stage 1	0.40 (n = 303)	0.37-0.43
Stage 2	0.18 (n = 109)	0.12-0.24
Stage 3	0.28 (n = 22)	0.18-0.38
Stage 4	0.15 (n = 15)	0.02-0.27

CI = confidence interval; MiToS = Milano-Torino functional staging system.

Note: n refers to the number of observations.

[a] EQ-5D-5L mapped to EQ-5D-3L.

Source: Biogen data on file [188].

3.10.2. Carer Utilities

Caregiver HRQoL impacts were incorporated in the model, under the assumption that each patient has an average of 1 caregiver in base-case analyses, with mean age equal to the patient.

Carer utility values were reported by Stenson et al (Stenson, Agnese [208]) using the EQ-5D-5L instrument by MiToS stage, which demonstrated statistically significant differences for all EQ-5D dimensions. The utility estimates from Stenson et al Stenson, Agnese [208] used for carer utilities in the model are outlined in Table 38. Limitations of this study are outlined above in Section 3.9.

Table 38. Carer Utility Estimates – Stenson, Agnese [208], Biogen data on file [211] [MiToS]

MiToS Stage	Utility weights (n)[a]	95% CI
Stage 0	0.85 (n = 43)	0.780-0.910
Stage 1	0.79 (n = 12)	0.637-0.943
Stage 2	0.72 (n = 8)	0.581-0.851
Stage 3	0.75 (n = 5)	0.574-0.926
Stage 4	0.72 (n = 11)	0.474-0.960

CI = confidence interval; MiToS = Milano-Torino functional staging system.

[a] EQ-5D-5L mapped to EQ-5D-3L. EQ-5D-5L values also available [208].

Source: Stenson, Agnese [208], Biogen data on file [211].

Carer utility estimates per King's disease staging system were also reported by Stenson et al. and are included in the Excel model and automatically applied if the King's staging system is selected.

3.10.3. Age-adjustment to Utility Values

The impact of aging on QoL was modeled by applying an age-adjustment index to utility values. The age-adjustment index was calculated based on the Swedish general population utilities reported by Bjurström et al. [212] and a mean baseline age of 49.1 years [188]. Adjustment indices were calculated by dividing the general population utility value for each age group by the mean age of 49 years old used in the model for the baseline population, based on the VALOR trial population [188].

3.10.4. Adverse Event Utility Decrements

Utility decrements associated with AEs were included in the model. The utility decrements for each AE are reported in Table 39. Each AE considered was assumed to last for 7 days.

Table 39. Adverse Event Utility Decrements

Adverse event	Utility decrement	SE	Source
Limb pain and back pain	−0.0072	0.0007	NICE [213], TA767 [Table 50]
Radiculitis	−0.0072	0.0007	Assumption (equal to limb and back pain disutility)
Myelitis	−0.0072	0.0007	Assumption (equal to limb and back pain disutility)

SE = standard error.

3.11. Resource use and costs

The CE analysis was performed using Sweden as the reference country, hence applying Swedish unit costs in the base case analysis. Cost inputs for the other countries are included in the CE model. The country setting can be changed in the Excel model using a drop-down switch, whereby the cost inputs applied in the CE analyses are changed automatically.

Currency exchange rates applied in the model are presented in Table 40. The conversion from SEK to local currency was used for health care resource unit costs. The conversion from GBP to local currency was used for in scenario analyses including societal costs per disease stage, which were converted from literature reported values to current GBP value in the core model. Since these costs were only applied in scenario analyses, this pragmatically simplified approach was considered to be justified.

Table 40. Currency exchange rates applied in the model

Country	Value of 1 SEK	Value of 1 GBP	Source
Sweden	-	13.57634	Riksbanken, mean exchange rate SEK/GBP in May 2024
Norway	0.99815 -	- 13.54940	Riksbanken, mean exchange rate NOK/SEK May 2024 Norges Bank, mean exchange rate NOK/GBP May 2024
Finland	0.08610 -	- 1.16870	ECB, mean exchange rate EUR/SEK May 2024 Bank Norge, mean exchange rate EUR/GBP May 2024
Denmark	0.64240 -	- 8.72432	Riksbanken, mean exchange rate DKK/SEK May 2024 Danmarks Nationalbank, mean exchange rate DKK/GBP May 2024
Iceland	12.91470 -	- 175.31	Riksbanken, mean exchange rate ISK/SEK May 2024 Sedlabanki Islands, mean exchange rate ISK/GBP May 2024

3.11.1. Medicine acquisition costs

Pharmaceutical costs applied in the model per each country are provided in Table 41, together with the calculated cost per 28-day cycle in the model.

Wastage is not relevant in the model since there is no excess content that is discarded; all solution in a tofersen pack is administered, and there is no wastage associated with riluzole tablets.

Lifelong treatment is assumed, hence there are no relevant subsequent treatments. Patients who discontinue tofersen treatment in the model are assumed to maintain on riluzole over the lifetime horizon.

No treatment stopping rules are applied in the model.

Table 41. Medicine acquisition costs per country and pharmaceutical

Drug, generic name	Country	Package number	Pack Price	Cost, first cycle[6]	Cost per cycle[6]
Tofersen, 1 x 100 mg, intrathecal bolus injection	Sweden, SEK	060720	AIP: 237,873.23 AUP: 239,173.23	- 478,346.46	- 239,173.23
	Norway, NOK	035770	AIP: 237,918.05 AUP excl VAT: 243,895.04	- 487,790.08	- 243,895.04
	Finland, EUR	060720	Wholesale price: 20,108.00	40,216.00	20,108.00
	Denmark, DKK	035770	AIP: 150,095.52	300,191.04	150,095.52
	Iceland, ISK	035770	Wholesale price: 2,957,727.06	5,915,454.12	2,957,727.06
Riluzole, 56 x 50 mg, Tablet	Sweden, SEK	Periodens vara 112036	729.85[1]	729.85	729.85
	Norway, NOK	123992	1,688.16[2]	1,688.16	1,688.16
	Finland, EUR	123992	155.30[3]	155.30	155.30
	Denmark, DKK	384889	320.00[4]	320.00	320.00
	Iceland, ISK	123992	32,395.00[5]	32,395.00	32,395.00

[1] SEK; Riluzole 56 x 50 mg; 3-month average June-August 2024 Periodens Vara substitution group 112036; (TLV)

[2] NOK; Rilutek 56 x 50 mg; Max AUP incl VAT = 2110.20 NOK; (NoMA) (AUP excl. VAT)

[3] EUR; Rilutek Sanofi 56 x 50 mg; Reference price; (KELA medicinal products database) (wholesale price)

[4] DKK; Glentek 56 x 50 mg; (medicinpriser.dk) (AIP)

[5] ISK; Rilutek 56 x 50 mg; Reimbursement price with VAT = 32,395 (Icelandic Medicines Agency Drug Price List 1 August 2024)

[6] Based on dosing regimens of 100mg tofersen once daily on day 1, 15, 29 then every subsequent 28 days (SmPC) = 2 doses in first cycle, then 1 dose per 28 days cycle; and 50 mg riliuzole twice daily (SmPC) = 56 tablets per 28 days cycle

3.11.2. Medicine administration and monitoring costs

The administration costs were calculated using the unit administration costs reported in Table 42. For tofersen, patients were assumed to require an intrathecal bolus injection per administration. Riluzole is administered orally, hence no administration resources were assumed.

The unit cost for intrathecal injection was applied based on Swedish price lists. For the other countries, the corresponding cost was derived using currency exchange rates from SEK to respective currency as specified in Table 40 above.

Table 42. Administration unit costs

Items	Unit costs SEK	NOK	EUR	DKK	ISK	Source[1]
Intrathecal bolus injection	6,709	6,697	577.64	4,310	86,645	Prislista södra sjukvårdsregionen - DT012 Läkemedelstillförsel intratekal – Hematologi
Oral administration	0	0	0	0	0	Assumption

[1] Source refer to the unit cost for Sweden. The costs in other currencies were derived by currency conversion using the mean exchange rates in May 2024 presented in Table 40.

The monitoring costs were calculated using the unit monitoring costs detailed in Table 43.

Regarding monitoring resources used: for tofersen, it was assumed patients would require urinalysis, platelet count, and coagulation tests every 3 months. For riluzole, it was assumed that the treatment did not require monitoring. In the analyses, the costs of monitoring and administration are included as a per cycle cost.

Table 43. Monitoring Unit Costs

Items	Unit costs SEK	NOK	EUR	DKK	ISK	Source[1]
Urinalysis	910	908	78.35	585	11,752	Prislista södra sjukvårdsregionen - Klinisk Kemi och farmakologi - Njurmedicin Laboratoriediagnostik 310 Urinsediment
Platelet count	19	19	1.64	12	245	Prislista södra sjukvårdsregionen - Klinisk Kemi och farmakologi - NPU03568 B-Trombocyter
Coagulation tests	118	118	10.16	76	1,524	Prislista södra sjukvårdsregionen - Klinisk Kemi och farmakologi - SKA02366 Provtagning vid Klinisk kemis provtagningsenhet

[1] Source refer to the unit cost for Sweden. The costs in other currencies were derived by currency conversion using the mean exchange rates in May 2024 presented in Table 40.

3.11.3. Health state and event costs

For disease management cost calculation, the resource use reported by Moore et al. (2019) [207] and unit costs from Swedish price lists were used [214].

Moore et al. (2019) [207] estimated the health utilities and costs of ALS within the UK setting by recruiting patients from 22 regional clinics. Estimates were reported for a 3-month period. The resource use included primary and secondary care such as nurse and doctor visits, inpatients stay, and ambulance use. Further resources such as tests (blood, urine, imaging tests) and community care visits (health visitor, social worker, counsellor, physiotherapist, and psychologist) were also included in the analysis. Details on the resource use are reported in Table 44. In the model, resource use and costs were adjusted to reflect 4-weekly cycles.

Moore et al also reported health care resource use by King's stage. If King's staging is applied in the CEM analyses, the corresponding resource use by King's stage is applied. For consistency, these input data are available in the Excel model.

Table 44. Health Care Resource Use per 3 months by MiToS stage from Moore et al 2019

Resource category	MiToS stage				
	0	1	2	3	4
Primary care					
Nurse GP surgery visits	0.48	0.54	0.30	0.50	2.20
Doctor GP surgery visits	1.05	0.83	0.58	0.50	1.60
Nurse at home visits	0.61	1.78	6.25	5.38	15.20
Doctor at home visits	0.04	0.43	0.63	1.17	2.20
Secondary care					
Emergency department visits	0.18	0.31	0.40	0.17	0.00
Nurse outpatient visits	0.71	1.29	1.10	1.61	0.40
Doctor outpatient visits	2.17	2.19	1.31	3.00	1.80
Ambulance use	0.10	0.27	0.60	0.11	0.00
Inpatient stays, number of admissions	0.10	0.40	0.34	0.11	0.20
Tests					
Blood tests	1.10	1.04	1.54	1.00	0.40
Urine tests	0.06	0.14	0.21	0.33	1.20
Ultrasound scans	0.04	0.09	0.10	0.11	0.00
X-ray scans	0.14	0.21	0.30	0.11	0.00
CT scan	0.12	0.16	0.05	0.00	0.00
MRI scans	0.23	0.20	0.15	0.00	0.00
EMG scans	0.25	0.25	0.16	0.06	0.00
Community care					
Health visitor visits	0.44	1.25	1.36	1.00	1.00
Social worker visits	0.22	0.52	0.67	1.28	1.20
Physiotherapist visits	1.72	2.31	2.60	4.95	2.40
Psychologist visits	0.07	0.18	0.15	0.33	0.00
Counsellor visits	0.04	0.10	0.27	0.22	0.00

Source: [207]

Unit costs for the healthcare services were sourced from Swedish price lists as shown in Table 45.

Table 45. Health care resource unit costs

Health care resource	Unit cost					Source[1]
	SEK	NOK	EUR	DKK	ISK	
Primary care						
Nurse GP surgery	930	928	80	597	12,011	Utomregional prislista 2023 Region Stockholm / Gotland. Prislista övrig öppen vård. Besök hos övrigt hälso+och sjukvårdpersonal, vårdgivare med avtal
Doctor GP surgery	2,093	2,089	180	1,345	27,030	Utomregional prislista 2023 Region Stockholm / Gotland. Prislista övrig öppen vårdÖ Privatpraktiserande specialist med avtal
Nurse home	2,323	2,319	200	1,492	30,001	Södra sjukvårdsregionen prislista 2024 HEMBSVB Hembesök, kompl till besökstjänst BSVB01
Doctor home	4,558	4,550	392	2,928	58,865	Södra sjukvårdsregionen prislista 2024, ZV025 Hembesök, kmpl till besökstjänst
Secondary care						
Casualty dpt.	5,997	5,986	516	3,852	77,449	Södra sjukvårdsregionen prislista 2024, BLÄK10 Läkarbesök, akutmottagning
Nurse outpatient	4,991	4,982	430	3,206	64,457	Södra sjukvårdsregionen prislista 2024, BSVB01 Besök annan HS personal (neurologi)
Doc outpatient	5,295	5,285	456	3,402	68,383	Södra sjukvårdsregionen prislista 2024, BLÄK01Å Läkarbesök, återbesök (outpatient)
Ambulance use	2,000	1,996	172	1,285	25,829	Lägsta ersättning för ambulanstransporter uppgår till kilometerersättning 100 kr x 20 km = 2000 kr
Inpatient stay	12,891	12,867	1,110	8,281	166,483	Södra sjukvårdsregionen prislista 2024, Omvårdnadsdag + Intagning (Neurologi)
Tests						
Blood	45	45	3.87	29	581	Södra sjukvårdsregionen prislista 2024, Klinisk Kemi och farmakologi - Laboratoriemedicin Bas (Baskemi)
Urine	45	45	3.87	29	581	Södra sjukvårdsregionen prislista 2024, Klinisk Kemi och farmakologi - Laboratoriemedicin Bas (Baskemi)
Ultrasound	1,384	1,381	119	889	17,874	Södra sjukvårdsregionen prislista 2024, Användande av ultrljud (Neurologi) SKA00000 Urintestremsa (7 parametrar) 45
X Ray	1,067	1,065	92	685	13,780	Södra sjukvårdsregionen prislista 2024, 62230, Rtg med tomosyntes bröstrygg
CT scan	1,526	1,523	131	980	19,708	Södra sjukvårdsregionen prislista 2024, DT huvud och hals (Onkologi och stråliningsfysik)
MRI	2,469	2,464	213	1,586	31,886	Södra sjukvårdsregionen prislista 2024, MRT Hjärna (Onkologi och stråliningsfysik)
EMG	5,035	5,026	434	3,234	65,026	Södra sjukvårdsregionen prislista 2024, Elektromyo- och neurografier (Högspecialiserad vård och länssjukvård)

Health care resource	Unit cost					Source[1]
	SEK	NOK	EUR	DKK	ISK	
Community care						
Health visitor	1,218	1,216	105	782	15,730	Södra sjukvårdsregionen prislista 2024, Besök annan HS personal (Rehabiliteringsmedicin)
Social worker	1,218	1,216	105	782	15,730	Södra sjukvårdsregionen prislista 2024, Besök annan HS personal (Rehabiliteringsmedicin)
Physiotherapist	2,512	2,507	216	1,614	32,442	Fysioterapeutbesök O (DRG code Y82O), from: https://www.regionstockholm.se/491c61/contentassets/6f0275ce70be462193c2480734710703/bilaga-2-utomregional-prislista-karolinska-universitetssjukhuset-2024.pdf
Psychologist	12,168	12,145	1,048	7,817	157,146	Södra sjukvårdsregionen prislista 2024, Psykologbesök (neurologi)
Counselor	1,895	1,891	163	1,217	24,473	Södra sjukvårdsregionen prislista 2024, Besök annan HS personal, psycholog (Rehabiliteringsmedicin)

[1] *Source refer to the unit cost for Sweden. The costs in other currencies were derived by currency conversion using the mean exchange rates in May 2024 presented in Table 40.*

Total disease management costs were calculated by multiplying the resource use by MiToS stage reported by Moore et al. (2019) [207] (Table 44) by the correspondent unit cost in Table 45. The resulting disease management costs per MiToS stage over three months for tests, primary, secondary- and community care, are detailed in Table 46. The corresponding costs per King's stage are presented in Table 47.

Table 46. Annual disease management costs by MiToS stage

Country	MiToS stage				
	HS 0	HS 1	HS 2	HS 3	HS 4
Sweden, SEK	120,658	186,644	209,686	264,782	294,472
Norway, NOK	120,435	186,298	209,299	264,292	293,927
Finland, EUR	10,389	16,070	18,054	22,798	25,354
Denmark, DKK	77,511	119,900	134,703	170,096	189,169
Iceland, ISK	1,558,261	2,410,448	2,708,037	3,419,578	3,803,018

Calculated based on data in Table 44 and Table 45.

Table 47. Annual disease managements costs by King's stage

Country	MiToS stage				
	HS 1	HS 2	HS 3	HS 4a	HS 4b
Sweden, SEK	115,575	133,804	141,352	229,903	229,903
Norway, NOK	115,361	133,556	141,091	229,478	229,478
Finland, EUR	9,951	11,521	12,170	19,795	19,795
Denmark, DKK	74,246	85,956	90,805	147,690	147,690
Iceland, ISK	1,492,620	1,728,037	1,825,523	2,969,129	2,969,129

3.11.4. Adverse events costs

Adverse event unit costs were based on DRG tariffs from Södra Sjukvårdsregionen's pricelist for 2024 [214]. To focus on AEs most likely to have an important impact on costs, only SAEs were included in the analyses, as outlined in Section 3.9. It was assumed that all non-serious AE are transient and easily treated at negligible cost with paracetamol or NSAIDs such as ibuprofen and aspirin for pain relief (except for limb and back pain which were the most frequent AE in both treatment arms of the VALOR trial and thus, included and accounted for in the model). They were mostly managed without additional clinical practice visits (via phone/email) or stronger prescription pain medications.

The costs associated with AEs were calculated based on AE probabilities from Table 34, and the unit costs from Table 48. The resulting costs were applied per cycle and per treatment in the CEM. For riluzole, the AEs were applied also in the intervention arm in the base case analysis when the model was set to include SoC in the tofersen arm.

Table 48. Adverse event unit costs applied in the CEM

Adverse Event	Unit Cost					Source[1]
	SEK	NOK	EUR	DKK	ISK	
Limb pain and back pain	8,206	8,191	707	5,272	105,978	Södra sjukvårdsregionen 2024 - W98O Läkarbesök smärtproblem O
Radiculitis	7,420	7,406	639	4,767	95,827	Södra sjukvårdsregionen 2024 - A99Q Läkarbes sjd i nervsystemet U O
Myelitis	7,420	7,406	639	4,767	95,827	Södra sjukvårdsregionen 2024 - A99Q Läkarbes sjd i nervsystemet U O

[1] Source refers to the unit cost for Sweden. The costs in other currencies were derived by currency conversion using the mean exchange rates in May 2024 presented in Table 40.

3.11.5. Miscellaneous costs

3.11.5.1. Societal annual costs

Societal or indirect costs were not used in the model base-case analysis but were included in a scenario analysis. Costs by MiToS stage were obtained from Ploug et al. (2022) [215]**.** Costs were reported annually and comprised non-treatment-related out-of-pocket costs and were reported by King's and MiToS staging systems. Costs were initially reported in 2021 Euros but were converted to current value annual GBP costs in the core CE model. In the local adaptation, these costs were converted to local currency using the mean GBP exchange rate in May 2024. Since these costs were only applied in scenario analyses, this pragmatically simplified approach was considered to be justified. The annual societal costs by MiToS stage used in the CEM are presented in Table 49.

Table 49. Annual societal costs by MiToS stage

MiToS stage	Annual Societal costs						Source[1]
	GBP	SEK	NOK	EUR	DKK	ISK	
HS0	1,019	13,838	13,811	1,191	8,893	178,692	Ploug et al. (2022) [215]
HS1	9,077	123,236	122,992	10,609	79,193	1,591,339	
HS2	79	1,078	1,076	93	693	13,917	
HS3	3,629	49,274	49,177	4,242	31,664	636,276	
HS4	247	3,348	3,342	288	2,152	43,235	

[1] *Source refer to the societal cost in GBP. The costs in other currencies were derived by currency conversion using the mean exchange rates in May 2024 presented in Table 40.*

3.11.5.2. *SOD1* genetic test costs

Prior to initiation of tofersen, genetic testing would be required to confirm the presence of *SOD1* mutation.. However, given that it is standard clinical practice in Sweden to perform genetic testing of ALS patients, the *SOD1* genetic test cost was excluded from the CE analysis since the testing is performed independently of the potential introduction of tofersen treatment.

4. Health economic analysis - Results

4.1. Incremental analysis of costs and outcomes

4.1.1. Base case results

Deterministic results of the base case analysis reported here are from a Swedish payer perspective, with annual discounting applied. Results for the other countries in the submission can be generated within the Excel model but are not presented in the dossier.

The results of the CE base case analysis comparing tofersen + SoC with SoC over a lifetime horizon (Table 50) indicated that treatment with tofersen was estimated to generate an additional 2.07 life years (LY; 3.35 vs. 1.28), and 2.47 incremental QALYs (4.16 vs. 1.70), as compared with SoC. The additional total cost with tofersen treatment was 10,619,031 SEK per patient (10,856,362 vs. 237,331) which generated an ICER of **4,306,571 SEK per QALY** gained with tofersen as compared with SoC over a lifetime horizon.

The costs are mainly accrued to tofersen treatment costs which account for 10.2m SEK (around 93%) of the total incremental costs. Disaggregation of the health outcomes indicate that LY are gained in all health states, and that the QALY gain is distributed over all health states as well, with the largest gain resulting in MiToS HS0. The results indicate that in addition to the patient benefit, QoL improvement for caregivers is an important benefit of tofersen treatment, easing the burden of disease carried by carers of ALS *SOD1* patients.

Undiscounted results showed that patients treated with tofersen as compared with SoC are expected to gain 2.28 LY (3.58 vs. 1.30) and 2.01 additional QALYs (4.42 vs. 2.72) at an added cost of 11,322,271 SEK per patient (11,562,602 vs. 240,331) corresponding to an undiscounted ICER of 5,643,196 SEK per QALY gained.

Table 50. Summary of results of the incremental cost-effectiveness analysis

Per patient	Intervention: tofersen + SoC	Comparator: SoC	Difference
Life years gained			
Total life years gained	**3.35**	**1.28**	**2.07**
Life years gained, MiToS HS0	1.07	0.55	0.53
Life years gained, MiToS HS1	1.01	0.42	0.59
Life years gained, MiToS HS2	0.54	0.18	0.36
Life years gained, MiToS HS3	0.32	0.07	0.24
Life years gained, MiToS HS4	0.41	0.06	0.35
QALYs			
Total QALYs	**4.16**	**1.70**	**2.47**
QALYs, MiToS HS0	0.75	0.38	0.36
QALYs, MiToS HS1	0.47	0.20	0.27
QALYs, MiToS HS2	0.19	0.07	0.12
QALYs, MiToS HS3	0.10	0.02	0.08
QALYs, MiToS HS4	0.10	0.01	0.08
QALYs, Caregiver, MiToS HS0	0.89	0.46	0.43
QALYs, Caregiver, MiToS HS1	0.78	0.33	0.45
QALYs, Caregiver, MiToS HS2	0.38	0.13	0.25
QALYs, Caregiver, MiToS HS3	0.23	0.05	0.17
QALYs, Caregiver, MiToS HS4	0.28	0.04	0.24
QALYs, AE disutilitites	-0.01	0.00	-0.01
Costs			
Total costs	**10,856,362**	**237,331**	**10,619,031**
Medicine costs	9,891,599	12,190	9,879,409
Administrative costs	276,575	0	276,575
Monitoring costs	12,958	0	12,958
Disease management (HS) costs	636,357	220,308	416,049
Adverse reactions	38,873	4,833	34,040
Societal costs	0	0	0
Incremental results	**Intervention vs. Comparator**		
ICER (per QALY)	**4,306,571**		
ICER (per life year gained)	**5,132,726**		

4.1.2. Sensitivity and scenario analysis related to the modelling uncertainty

4.1.2.1. Deterministic sensitivity analysis

Univariate (one-way) sensitivity analysis (OWSA) was performed to identify the parameters that had the most influence on the ICER. For the parameters for which individual level trial data were available (i.e., AE rates, utility values), 95% confidence intervals were calculated using these data. For other parameters where input on variation was lacking such as for cost parameters, standard errors of ±10% were applied in the OWSA.

Results for all included parameters are presented in, together with a specification of the low and high input values used in the OWSA and the associated source of variation. The results are also presented graphically in the form of a tornado diagram for the 10 most influential parameters. The OWSA indicates that the parameters where the uncertainty around the point estimate have the largest influence on the cost-effectiveness concern tofersen treatment efficacy: HR for mortality with tofersen vs. SoC, and HR for disease progression with tofersen vs. SoC. It is unsurprising that the extent of prolonged survival that can be achieved with tofersen treatment will be the dominating benefit of treatment in the CE analysis. The large ICER span that is observed in the OWSA for HR for mortality reflects the broad 95% CI for this parameter input, which in turn is a result of the small patient sample that is available for the very rare SOD-1 subpopulation of ALS.

Figure 25. Tornado diagram of the 10 most influential parameters in the OWSA

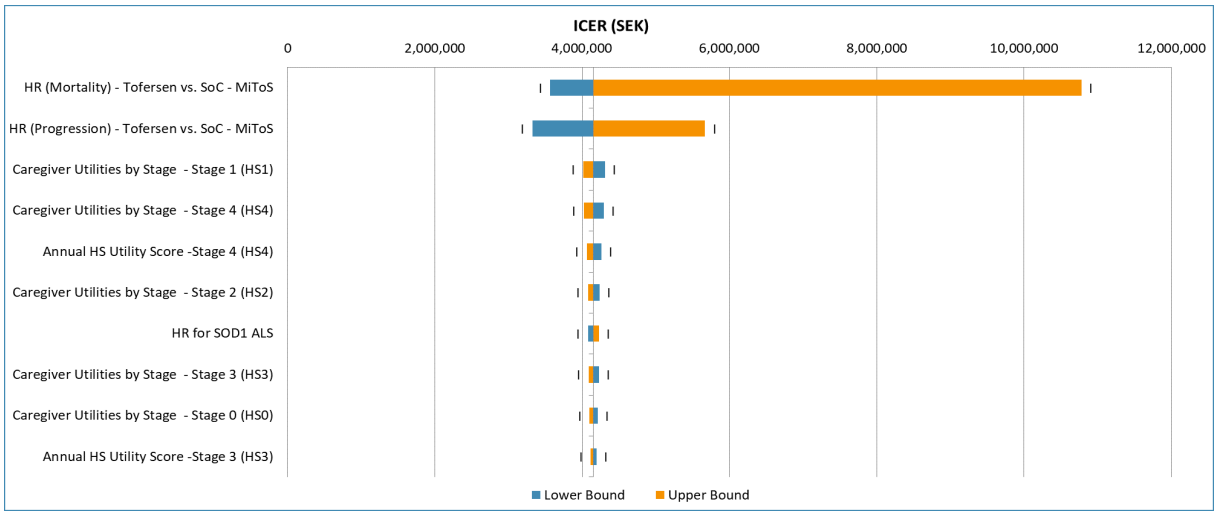


Table 51. One-way sensitivity analyses: Inputs and Resulting ICERs

Parameter	Source of variation	Base case input	Low input	High input	Low ICER	High ICER
Mean age (years)	±10%	49.1	44.2	54.0	4,035,325	4,034,547
Percentage cohort (female)	±10%	0.426	0.383	0.469	4,155,563	4,155,563
Annual HS cost - Stage 0 (HS0)	±10%	120,658	108,592	132,724	4,152,976	4,158,150
Annual HS cost - Stage 1 (HS1)	±10%	186,644	167,979	205,308	4,151,095	4,160,030
Annual HS cost - Stage 2 (HS2)	±10%	209,686	188,718	230,655	4,152,506	4,158,619
Annual HS cost - Stage 3 (HS3)	±10%	264,782	238,304	291,260	4,152,969	4,158,156
Annual HS cost - Stage 4 (HS4)	±10%	294,472	265,025	323,919	4,151,395	4,159,731
Annual HS Utility Score - Stage 0 (HS0)	95% CI	0.71	0.69	0.73	4,172,940	4,138,329
Annual HS Utility Score - Stage 1 (HS1)	95% CI	0.48	0.44	0.51	4,194,318	4,126,963
Annual HS Utility Score - Stage 2 (HS2)	95% CI	0.36	0.31	0.42	4,184,950	4,120,838
Annual HS Utility Score - Stage 3 (HS3)	95% CI	0.33	0.23	0.43	4,195,160	4,116,706
Annual HS Utility Score - Stage 4 (HS4)	95% CI	0.25	0.07	0.42	4,260,136	4,061,406
Caregiver Utilities by Stage - Stage 0 (HS0)	95% CI	0.85	0.78	0.91	4,212,291	4,100,342
Caregiver Utilities by Stage - Stage 1 (HS1)	95% CI	0.79	0.64	0.94	4,307,686	4,013,817
Caregiver Utilities by Stage - Stage 2 (HS2)	95% CI	0.72	0.58	0.85	4,236,019	4,078,106
Caregiver Utilities by Stage - Stage 3 (HS3)	95% CI	0.75	0.57	0.93	4,225,924	4,087,506
Caregiver Utilities by Stage - Stage 4 (HS4)	95% CI	0.72	0.47	0.96	4,298,013	4,022,252
Disutility - Limb pain and back pain	±10%	-0.0072	-0.0065	-0.0079	4,154,755	4,156,371
Disutility - Radiculitis	±10%	-0.0072	-0.0065	-0.0079	4,155,545	4,155,581
Disutility - Myelitis	±10%	-0.0072	-0.0065	-0.0079	4,155,526	4,155,599
HR for *SOD1* ALS	±10%	1.30	1.17	1.43	4,079,602	4,225,809

HR (Progression) - tofersen vs. SoC – MiToS	95% CI	0.61	0.29	1.27	3,323,398	5,670,463
HR (Mortality) - tofersen vs. SoC – MiToS	95% CI	0.10	0.01	0.81	3,564,500	10,785,136
AE probability per cycle - tofersen – Limb pain and back pain	±10%	0.074	0.067	0.082	4,154,891	4,156,234
AE probability per cycle - tofersen – Radiculitis	±10%	0.002	0.002	0.002	4,155,545	4,155,581
AE probability per cycle - tofersen – Myelitis	±10%	0.004	0.004	0.004	4,155,526	4,155,599

4.1.2.2. Scenario analyses

Scenario analyses were conducted to assess the impact of alternative plausible inputs and assumptions on model result. The variables included in the analysis are listed below:

Table 52. Variables included in the scenario analyses

Scenario	Scenario description	Details
Scenario 1	King's staging to classify health states	Respective parameter values for King's staging are applied
Scenario 2	Overall ALS population	Overall ALS population, instead of *SOD1* mutation population, is selected. Therefore, the HR for *SOD1*-ALS [8] is not applied, and the disease progression reflects the overall ALS population.
Scenario 3	PRO-ACT baseline distribution of patients, in conjunction with PRO-ACT age (56.2 years) and female distribution (40%)	Instead of VALOR (Part C) baseline distribution, in conjunction with its age and gender distribution
Scenario 4	Societal perspective	Societal health state costs and one-off societal costs are included
Scenario 5	Calibration excluded	Using SoC transition probabilities in their original form as reported by Thakore et al (Thakore, Lapin [189])
Scenario 6	Alternative source of health state utilities	Instead of the values reported by Moore et al 2019 (Table 36), values derived from the VALOR trial (Table 37) were applied.

ALS = amyotrophic lateral sclerosis; HR = hazard ratio; PRO-ACT = Pooled Resource Open-Access ALS Clinical Trials; QALY = quality-adjusted life-year; SoC = standard of care; SOD1 = superoxide dismutase 1.

Table 53 reports the results of the scenario analyses. The results ranged between 4.0m - 4.7m SEK per QALY, indicating that the analysis is fairly robust to optional modelling choices that can be considered in the model, e.g. concerning the source of different model inputs.

Table 53. Results of scenario analyses

Scen. No	Scenario	Parameter and changed input value(s)	Incremental cost (SEK)	Incremental benefit (QALYs)	ICER (SEK/QALY)
	Base Case		10,619,031	2.47	4,306,571
1	King's staging to classify health states	Staging system = "King's"	10,8335,300	2.53	4,288,588
2	Overall ALS population	Population of interest by genetic mutation = "Overall ALS population"	12,243,561	2.97	4,116,170
3	PRO-ACT baseline distribution and patient characteristics	Source for population characteristics and baseline distribution = "PRO-ACT (Thakore et al., 2018)"	10,677,904	2.53	4,217,236
4	Societal perspective	Societal costs = "Included"	10,712,541	2.47	4,344,494
5	Calibration excluded	Calibration of SoC disease progression = "Excluded"	14,795,106	3.63	4,080,537
6	Alternative source of health state utilities	Health State Utilities Source (MiToS) = "VALOR C Trial"	10,619,031	2.25	4,714,402

4.1.2.3. Probabilistic sensitivity analysis (PSA)

For the probabilistic analysis, the model is run for 1,000 iterations. Because the base-case ICER stabilizes from approximately 500 iterations onward (Figure 29), 1,000 iterations were decided to be sufficiently stable without incurring a significant runtime.

Probabilistic sensitivity analyses included all model parameters with second order uncertainty; estimates of uncertainty were based on the uncertainty in the source data (where data availability permits). Where no such data were available, the model applies a user-defined percentage of the mean value as the standard error.

Parameters were sampled from appropriate statistical distributions [216], such as the following:

- Mean utility weights may be sampled from a beta distribution of the parameter as defined by the mean and standard error.
    - Beta distributions are bounded from 0 to 1 and are thus suitable for sampling health-utility data.
- Mean costs may be sampled from a gamma distribution defined by the mean and standard error.
    - Gamma distributions are restricted to positive values, which are deemed to be appropriate for sampling costs.
- Patient characteristics, including age and weight, may be sampled from a normal distribution of the parameter as defined by the mean and standard error.
- Transition probabilities may be sampled from a gamma distribution using the Dirichlet method in the absence of variance-covariance data.

All distributions are fully documented within the "Parameter Sheet" of the model and provided in Appendix G.

The outcome of the 1,000 PSA iterations is presented below as the cost-effectiveness plane (Figure 30) and a Cost-Effectiveness Acceptability Curve (

Figure 31). The mean QoL gain was 3.74 QALYs, and the mean added cost was 14,071,721 SEK, resulting in a probabilistic ICER of 3,763,860 SEK per QALY. This is lower than the base case deterministic ICER. The cost-effectiveness plane shows a stretched shape, indicating a roughly dependent relation between costs and QALY outcomes.

Figure 26. Model convergence over 1000 PSA iterations

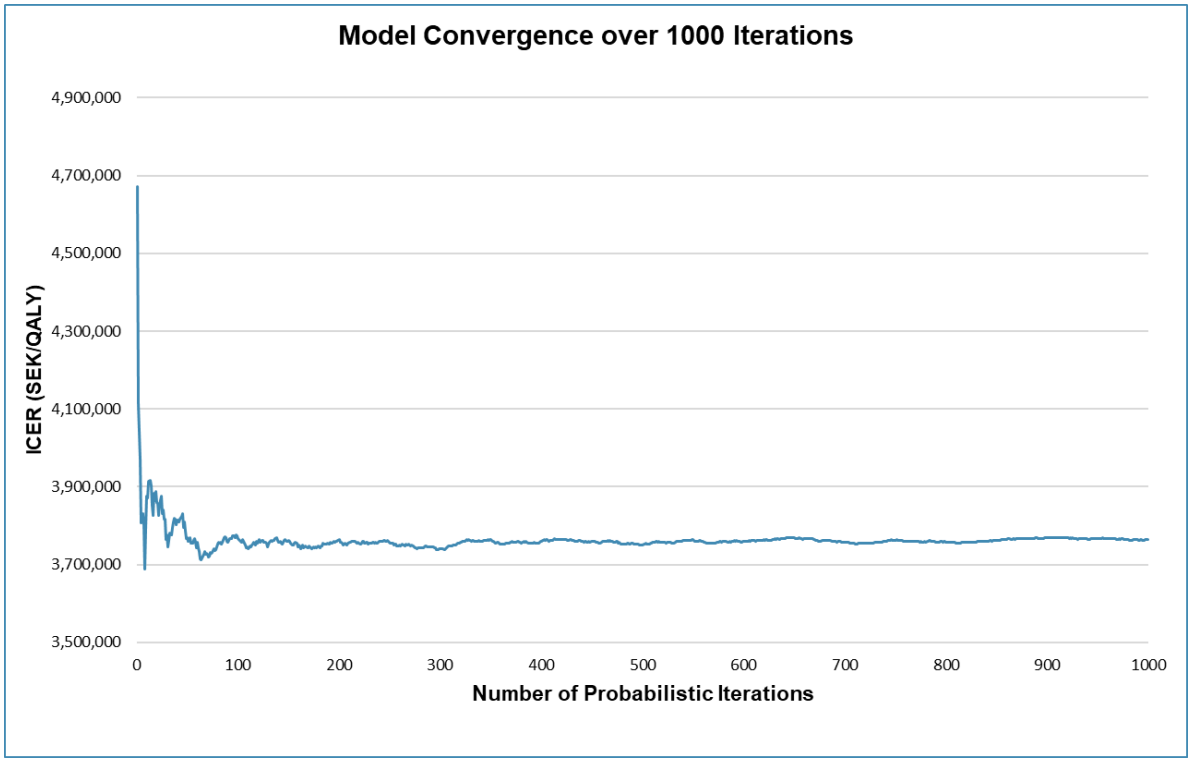
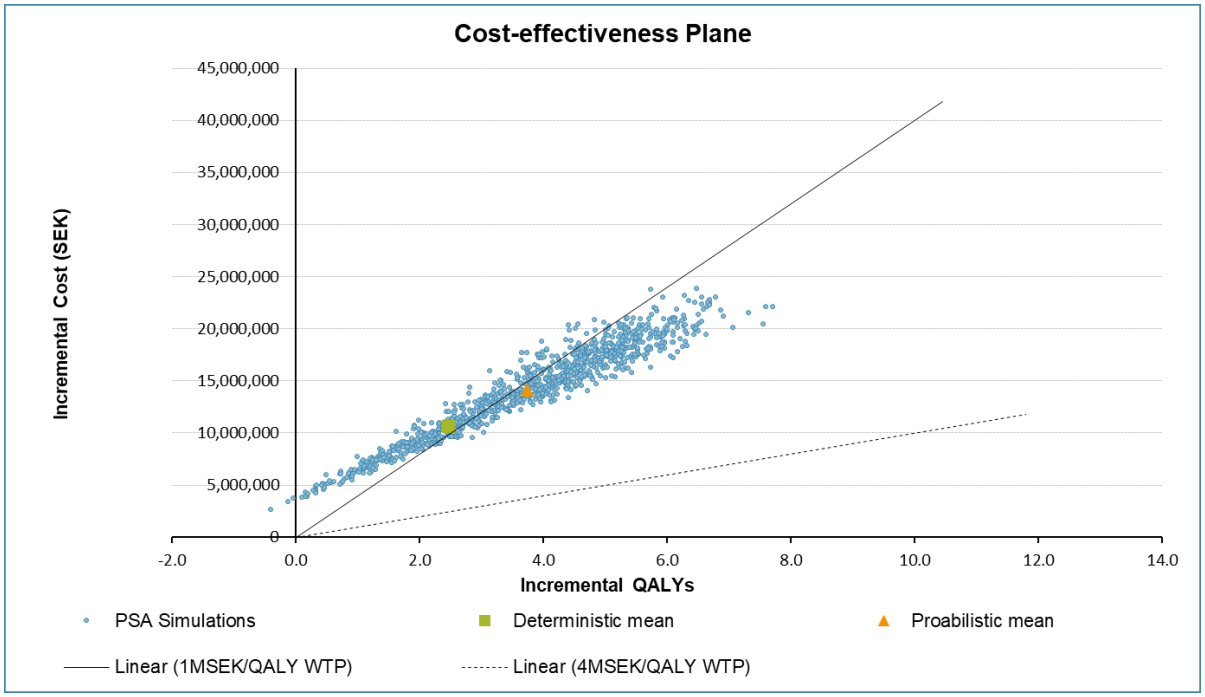
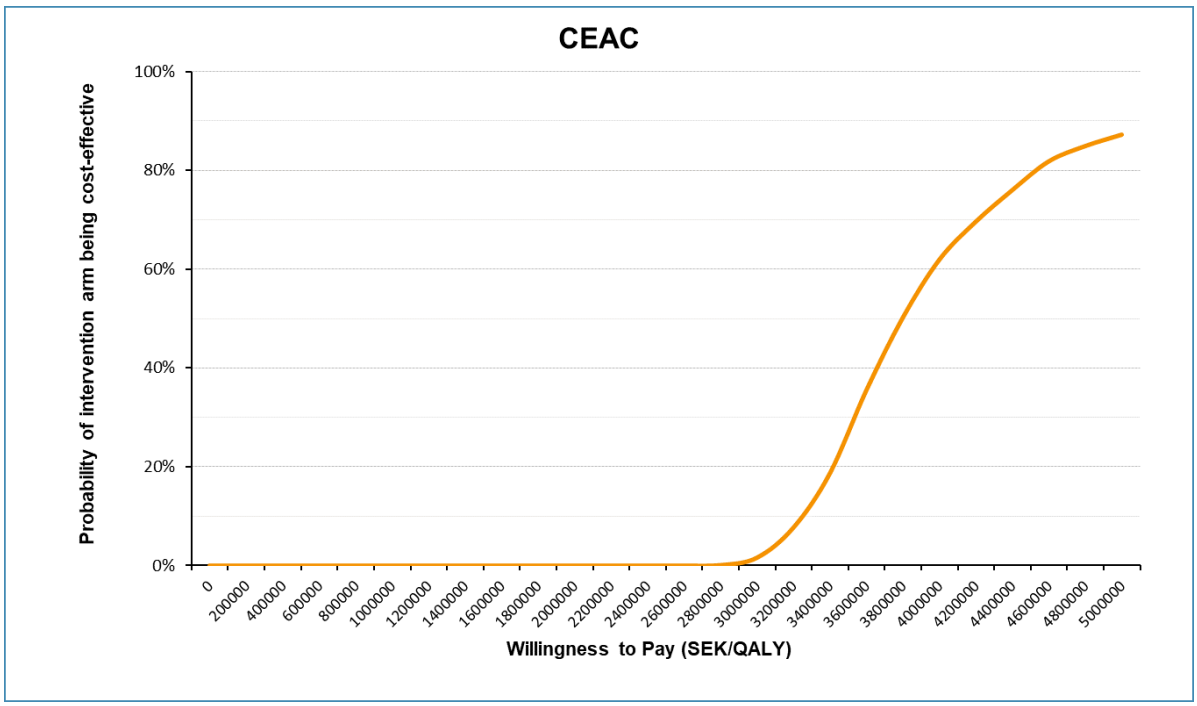


Figure 27. Cost-Effectiveness Plane



PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year; WTP = willingness to pay.

Figure 28. Cost-Effectiveness Acceptability Curve tofersen Plus Riluzole



CEAC = cost-effectiveness acceptability curve; QALY = quality-adjusted life-year.

4.1.3. Discussion of the Cost-Effectiveness Analysis

A cohort-level Markov structure was developed to assess the cost-effectiveness of tofersen and SoC combination therapy compared with SoC in treating patients with *SOD1*-ALS.

The model structure reflects the treatment pathway and captures the expected clinically important differences in costs and outcomes between patients receiving alternative treatments. The base case compared tofersen and SoC (composed of riluzole) combination therapy with SoC based on MiToS staging and a payer cost perspective over patient lifetime. The base-case results suggest that the intervention arm was associated with higher costs and higher QALYs.

The deterministic sensitivity analysis demonstrated that the ICER was most sensitive to changes in HR for mortality (tofersen vs. SoC), and HR for progression (tofersen vs. SoC). Drug acquisition costs were excluded from the deterministic sensitivity analysis, because there would not be any uncertainty around list prices of drugs. Scenario analyses conducted suggested that alternative approaches used in various scenarios lead to ICERs roughly similar to the base case (within 10% deviation).

There are several limitations to this CEA. First, because it was not feasible to obtain relevant outcomes by analyzing phase 3 trial data due to small sample size, the transition probabilities reported by Thakore, Lapin [189] derived from the PRO-ACT database was the only source available to inform the transition probability matrix of the SoC arm. The PRO-ACT database has a considerably larger sample size than that of the VALOR trial and PARALS, a data registry in Italy [217] which helps to reduce the parameter uncertainty. However, the treatments allowed in the trials pooled in the PRO-ACT database would differ from the treatments allowed in the placebo arm of the VALOR (Part C) trial. Relevant literature has been used to adjust the relevant outcomes for an *SOD1*-ALS population, given that the PRO-ACT database is not specific to patients with *SOD1*-ALS [8]. Furthermore, although the transition probabilities reported by Thakore, Lapin [189] provide a good fit for the patient numbers observed at each disease stage and death up to 12 months, progression and mortality were underestimated in extrapolations beyond 12 months when compared with the PRO-ACT database. Therefore, a calibration exercise was undertaken to derive transition probabilities that provided a better fit with the reported patient numbers at each stage and death for the post 12-month period using data from the PRO-ACT database reported by Thakore, Lapin [189]. Although the model-predicted median survival in the SoC arm in the overall ALS population is in line with the reported median survival time in the PRO-ACT database [191], these outcomes are subject to the limitations of the methods used for calibration exercise. Finally, although the utility weights reported by Moore, Young [207] used in the base case logically decrease with increasing disease severity based on a large UK-based sample of patients with ALS, these utility weights are not consistent with reference cases that recommend the use of EQ-5D-3L. Therefore, utility estimates from VALOR trial that were mapped to the EQ-5D-3L were provided as alternative sources in the model.

More broadly, there are several challenges associated with conducting CEAs in ALS. First, due to considerable heterogeneity in disease progression and survival among patients with ALS, generalizability of clinical outcomes and prediction of individual disease progression is difficult. Second, clinical trials in ALS may not have sufficiently large sample sizes to surmount uncertainty from patient heterogeneity [191, 192], particularly trials in subpopulations with a specific genetic mutation. Although the differences between geographical populations have not been found to affect the performance of survival predictions in European patients [194], the generalizability of mortality data from disease-specific natural history sources to specific local populations may be questioned. Third, despite widespread use of the ALSFRS-R endpoint in clinical trials in ALS, it has several limitations, such as the variability by assessor/center and visit [218], and ambiguity in the meaning of questions and responses allowed [219]. Therefore, an aggregate ALSFRS-R score should be

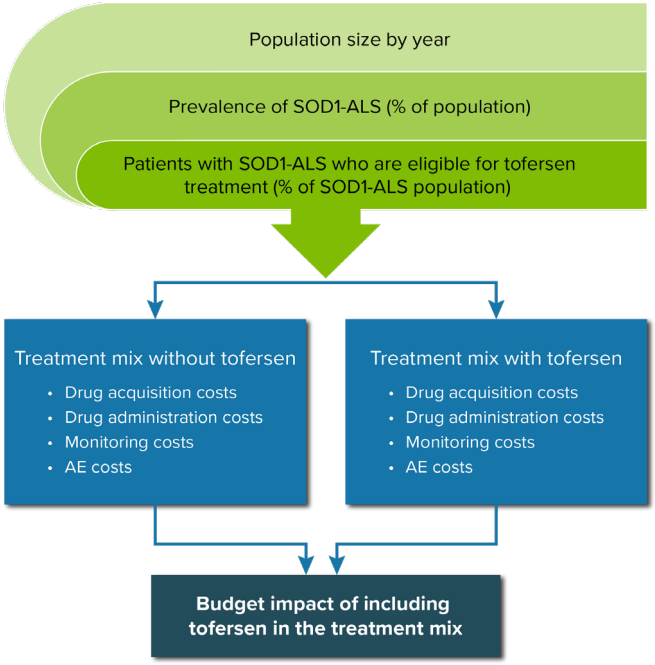
interpreted with caution. Third, although MiToS staging is directly based on the ALSFRS-R and King's staging can also be estimated from ALSFRS-R with high concordance, both King's and MiToS do not use all ALSFRS-R questions in their staging [178], are subject to limitations such as the increased frequency of nonsequential transitions between states (King's is also subject to the possibility for normally functioning patients not to be assigned a stage), and are subject to the limitations of the ALSFRS-R itself (Section 3.3.2). Fourth, in rapidly progressing diseases such as ALS that are associated with short survival, the limited duration of placebo-controlled clinical trials for ethical reasons limits their ability to produce information about long-term outcomes of the treatment options. Linear disease progression assumption used to extrapolate the treatment effect observed in clinical trials may not be realistic in ALS [154]. Finally, as patients with ALS experience a response shift and maintain their QoL by placing less importance on physical well-being and a greater emphasis on mental well-being, social interaction, and spirituality [220], QALY gains estimated by measures such as EQ-5D may underestimate utility gains subjectively experienced by patients.

5. Budget impact analysis

The budget impact analysis (BIA) considered total drug, administration/monitoring, and AE costs associated with the management of *SOD1*-ALS in adult patients with and without the introduction of tofersen. To determine the impact of the introduction of tofersen, the BIA considers the following 2 treatment mix scenarios (Figure 32):

- Scenario 1: A market without the introduction of tofersen
- Scenario 2: A market with an expected uptake of tofersen

Figure 29. Structure of budget impact analysis



AE = adverse event; ALS = amyotrophic lateral sclerosis; SOD1 = superoxide dismutase 1

To estimate the budgetary impact, the BIA estimates total drug costs for each scenario separately, based on the unit costs described in Section 3.11, and the average dose, based on the relevant values reported in clinical trials identified for each treatment. Costs are undiscounted and the VAT was added.

After summarizing the cost element of each regimen, the BIA estimates the annual cost for each scenario by weighting all the regimen costs by market share data and multiplying the result by the size of the modeled population. The budget impact is the difference between the costs of the scenarios.

5.1.1. Epidemiology of the disease in the Nordics

The epidemiology of *SOD1*-ALS is described in Section 1.2.2.

The prevalence and incidence of *SOD1*-ALS is not expected to change in the next 5 years, other than following general population trends.

An overview of the epidemiology of ALS and *SOD1*-ALS in the Nordic countries is presented in Table 54.

Table 54. Epidemiology of ALS and SOD1-ALS in the Nordic countries

Input parameter	Value	Source
FINLAND		
Prevalence of ALS	0.0119% (11.9/100,000)	Hanhisuanto et al. (2023) [28]
Prevalence of FALS*	NR	
Prevalence of SALS*	NR	
Prevalence of *SOD1* ALS*	7%	Laaksovirta, H. (2023) [30]
NORWAY		
Prevalence of ALS	0.008% (7.6/100,000)	Olsen et al. (2022) [24]
Prevalence of FALS*	12%	Olsen et al. (2022) [24]
Prevalence of SALS*	88%	Olsen et al. (2022) [24]
Prevalence of *SOD1* ALS*	4%	Olsen et al. (2022) [24]
SWEDEN		
Prevalence of ALS	0.006% (6.23/100,00)	Brown et al. (2021) [31]
Prevalence of FALS*	NR	
Prevalence of SALS*	NR	
Prevalence of *SOD1* ALS*	4-5%	Socialstyrelsen (2022) [134]
DENMARK		
Prevalence of ALS	0.007% (6.8/100,000)	RehabiliteringsCenter for Muskelsvind (n.d.) [33]
Prevalence of FALS*	15-20%	Lindquist et al. (2014) [35]
Prevalence of SALS*	90-95%	Lindquist et al. (2014) [35]
Prevalence of *SOD1* ALS*	2%	Lindquist et al. (2014) [35]
ICELAND		
Prevalence of ALS	0.009% (27/270,000)	Icelandic MND association [221]
Prevalence of FALS*	NR	
Prevalence of SALS*	NR	
Prevalence of *SOD1* ALS*	20%	Based on assumed ALS prevalence and actual number of ALS SOD1 patients

*ALS = amyotrophic lateral sclerosis; FALS = familial amyotrophic lateral sclerosis; NR = not reported; SOD1 = superoxide dismutase 1; *= % of ALS population. The distinction between fALS and sALS is not relevant for population sizing for BIA purposes.*

5.1.2. Eligible patient population

The number of patients with *SOD1*-ALS in the Nordic countries eligible for treatment with tofersen was estimated. The annual projected population growth was considered each year.

Table 55 presents the base case population inputs, estimated based on population projections from each country.

Table 55. Population inputs

Population	2025	2026	2027	2028	2029	Source
Finland	5,576,186	5,582,076	5,587,372	5,591,887	5,595,724	Statistics Finland [222]
Adults	4,575,005	4,591,891	4,609,307	4,626,797	4,642,790	
Norway	5,600,121	5,638,838	5,666,689	5,694,657	5,722,427	SSB [223]
Adults	4,490,908	4,535,170	4,572,027	4,608,854	4,644,034	
Sweden	10,602,310	10,626,026	10,648,490	10,671,560	10,695,134	SCB [224]
Adults	8,472,752	8,521,852	8,570,873	8,622,207	8,667,561	
Denmark	5,984,461	5,966,968	5,981,620	5,996,169	6,010,444	Statistics Denmark [225]
Adults	4,842,203	4,838,733	4,859,247	4,876,659	4,893,512	
Iceland	400,558	407,148	413,845	420,600	427,403	Statistics Iceland [226]
Adults	267,044	271,157	275,222	279,199	282,921	

Based on the population projections from each Nordic country and the epidemiology described in Table 54 above, the expected number of patients with *SOD1*-ALS are presented in Table 56.

Although tofersen is indicated for treatment of adult amyotrophic lateral sclerosis caused by *SOD1* mutation, the estimated number of patients who will be expected to receive treatment are based on several factors that may reduce the percentage of total *SOD1* ALS patients eligible for treatment with tofersen in individual countries, including:

- Large heterogeneity in the rate of disease progression among *SOD1* ALS patients – *SOD1* mutation type, as well as levels of neurofilaments, are some of the key predictive factors for disease progression rate.
- Guidelines and defined start criteria developed by national authorities / clinical expert groups

This is Biogen's understanding on the patient numbers based on insights from treating physicians.

Therefore, the number of patients expected to be eligible for treatment with tofersen in the years 2025-2029 are presented separately in Table 56.

Table 56. Estimated number of patients with SOD1-ALS who are expected to be eligible for treatment and also treated with tofersen

Country	2025	2026	2027	2028	2029
Finland: total eligible	38	38	38	39	39
Treated with tofersen, n (11%)	**4.19**	**4.21**	**4.22**	**4.24**	**4.25**
Norway: total eligible	14	15	15	15	15
Treated with tofersen, n (35%)	**5.03**	**5.08**	**5.12**	**5.16**	**5.20**
Sweden: total eligible	25	26	26	26	26
Treated with tofersen, n (48%)	**12.20**	**12.27**	**12.34**	**12.42**	**12.48**
Denmark: total eligible	7	7	7	7	7
Treated with tofersen, n (61%)	**4.02**	**4.01**	**4.03**	**4.05**	**4.06**
Iceland: total eligible	**5**	**5**	**5**	**5**	**5**
Treated with tofersen, n (100%)	**5**	**5**	**5**	**5**	**5**

The proportion of patients expected to be eligible for treatment with tofersen in each country

5.1.3. Budgetary consequences and expected sales

5.1.3.1. Resource use and costs

The costs included in this section of the model are direct medical costs and are broken into drug acquisition costs, monitoring and administration costs, and AE costs.

5.1.3.1.1. Medicine acquisition costs

Pharmaceutical applied in the budget impact analysis (per patient per year) are presented in Table 57.

Table 57. Annual per patient medicine acquisition costs in each country

Treatment	Annual medicine acquisition costs per patient	
FINLAND		
tofersen+riluzole	• Year 1: • Year 2 onwards:	284,255 EUR 262,122 EUR
Riluzole	• Year 1 onwards:	2,024 EUR
NORWAY		
tofersen+riluzole	• Year 1: • Year 2 onwards:	3,445,247 NOK 3,201,352 NOK
Riluzole	• Year 1 onwards:	22,006 NOK
SWEDEN		
tofersen+riluzole	• Year 1: • Year 2 onwards:	3,366,481 SEK 3,127,308 SEK
Riluzole	• Year 1 onwards:	9,514 SEK
DENMARK		
tofersen+riluzole	• Year 1: • Year 2 onwards:	2,110,374 DKK 1,960,278 DKK
Riluzole	• Year 1 onwards:	3,676 DKK
ICELAND		
tofersen+riluzole	• Year 1: • Year 2 onwards:	80,069,897 ISK 77,112,170 ISK
Riluzole	• Year 1 onwards:	38,556,085 ISK

Note: In the VALOR (Part C) trial, patients in the intervention arm followed a dosing regimen of 100 mg tofersen administered on days 1, 15, and 29 initially and every 4 weeks thereafter by intrathecal injection (Biogen data on file [158]). This corresponds to 2 doses in the first cycle and 1 dose in every subsequent cycles; in the budget impact analysis, medicine acquisition costs for year 1 include 14 doses of tofersen, and for subsequent years include 13 doses of tofersen. The number of doses of riluzole are assumed to be the same in year 1 and subsequent years.

5.1.3.1.2. Medicine administration and monitoring costs

Medicine administration and monitoring costs applied in the budget impact analysis (per patient per year) are presented in Table 58.

Table 58. Annual administration and monitoring costs per patient

Treatment	Annual administration costs		Annual monitoring costs	
FINLAND				
tofersen	• Year 1: • Year 2 onwards:	8,108 EUR 7,530 EUR	• Year 1 onwards:	361 EUR
Riluzole	• Year 1 onwards:	0 EUR	• Year 1 onwards:	0 EUR
NORWAY				
tofersen	• Year 1: • Year 2 onwards:	93,991 NOK 87,295 NOK	• Year 1 onwards:	4,180 NOK
Riluzole	• Year 1 onwards:	0 NOK	• Year 1 onwards:	0 NOK
SWEDEN				
tofersen	• Year 1: • Year 2 onwards:	94,166 SEK 87,457 SEK	• Year 1 onwards:	4,188 SEK
Riluzole	• Year 1 onwards:	0 SEK	• Year 1 onwards:	0 SEK
DENMARK				
tofersen	• Year 1: • Year 2 onwards:	60,492 DKK 56,182 DKK	• Year 1 onwards:	2,690 DKK
Riluzole	• Year 1 onwards:	0 DKK	• Year 1 onwards:	0 DKK
ICELAND				
tofersen	• Year 1 onwards: • Year 2 onwards:	1,216,121 ISK 1,126,476 ISK	• Year 1 onwards:	54,087 ISK
Riluzole	• Year 1:	0 ISK	• Year 1 onwards:	0 ISK

Note: In the VALOR (Part C) trial, patients in the intervention arm followed a dosing regimen of 100 mg tofersen administered on days 1, 15, and 29 initially and every 4 weeks thereafter by intrathecal injection (Biogen data on file [158]). This corresponds to 2 doses in the first cycle and 1 dose in every subsequent cycles; in the budget impact analysis, administration costs for year 1 include 14 doses of tofersen, and for subsequent years include 13 doses of tofersen. Due to its oral administration, there were no administration costs associated with riluzole.

For tofersen, it was assumed patients would require urinalysis, platelet count, and coagulation tests every 3 months i.e., 4 times per year, and that this would be the same for all years. For riluzole, it was assumed that the treatment did not require monitoring.

5.1.3.1.3. Adverse events

AE costs applied in the budget impact analysis (per patient per year) are presented in Table 59.

For the BIA, the AE probabilities in Table 34 (from the CEM) were converted to yearly probabilities (52 weeks).

The annual treatment costs of AEs for riluzole + tofersen were obtained from the sum of treatment costs of AEs of riluzole and tofersen individually.

Table 59. Annual adverse event costs per patient

Treatment	Annual AE costs per patient
FINLAND	
tofersen+riluzole	759 EUR
Riluzole	263 EUR
NORWAY	
tofersen+riluzole	8,804 NOK
Riluzole	3,052 NOK
SWEDEN	
tofersen+riluzole	8,820 SEK
Riluzole	3,058 SEK
DENMARK	
tofersen+riluzole	5,666 DKK
Riluzole	1,964 DKK
ICELAND	
tofersen+riluzole	113,907 ISK
Riluzole	39,489 ISK

5.1.4. Market shares

To estimate the overall budget in each of the proposed scenarios, the market share of each treatment/treatment combination for each year between 2025 and 2027 was estimated. Market share data were estimated by Biogen based on company expectations [227]. It is expected that patients who start treatment with tofersen will also continue stable riluzole therapy (see Section 1.5.4). The market shares for each treatment with and without the introduction of tofersen are shown in Table 60 and Table 61, respectively.

Table 60. Market shares of SOD1-ALS treatments without the introduction of tofersen

Treatment	2025	2026	2027	2028	2029
Riluzole	100%	100%	100%	100%	100%

ALS = amyotrophic lateral sclerosis. Source: Biogen data on file [227].

Table 61. Market shares of SOD1-ALS treatments with the introduction of tofersen

Treatment	2025	2026	2027	2028	2029
FINLAND					
tofersen+riluzole	11.0%	11.0%	11.0%	11.0%	11.0%
Riluzole monotherapy	89.0%	89.0%	89.0%	89.0%	89.0%

NORWAY					
tofersen+riluzole	35.0%	35.0%	35.0%	35.0%	35.0%
Riluzole monotherapy	65.0%	65.0%	65.0%	65.0%	65.0%
SWEDEN					
tofersen+riluzole	48.0%	48.0%	48.0%	48.0%	48.0%
Riluzole monotherapy	52.0%	52.0%	52.0%	52.0%	52.0%
DENMARK					
tofersen+riluzole	61.0%	61.0%	61.0%	61.0%	61.0%
Riluzole monotherapy	39.0%	39.0%	39.0%	39.0%	39.0%
ICELAND					
tofersen+riluzole	100.0%	100.0%	100.0%	100.0%	100.0%
Riluzole monotherapy	0.0%	0.0%	0.0%	0.0%	0.0%

ALS = amyotrophic lateral sclerosis. Source: Biogen data on file [227].

5.1.5. Expected patients treated per treatment option

The number of patients included in the BIA was calculated by multiplying the number of patients to be treated per year (Table 56) by the corresponding estimated market share for the given treatment option (Table 60, Table 61). Given the nature of the disease, it is assumed that all patients will be followed up and monitored in the specialist healthcare services. The tables below show the number of patients expected to be treated over the next 5-year period for both scenarios.

Table 62. Number of patients expected to be treated over the next five-year period - if tofersen is introduced.

Treatment	2025	2026	2027	2028	2029
FINLAND					
tofersen + Riluzole	4.19	4.21	4.22	4.24	4.25
Riluzole	33.92	34.04	34.17	34.30	34.42
Total	38.11	38.25	38.40	38.54	38.67
NORWAY					
tofersen + Riluzole	5.03	5.08	5.12	5.16	5.20
Riluzole	9.34	9.43	9.51	9.59	9.66
Total	14.37	14.51	14.63	14.75	14.86
SWEDEN					
tofersen + Riluzole	12.20	12.27	12.34	12.42	12.48
Riluzole	13.22	13.29	13.37	13.45	13.52
Total	25.42	25.57	25.71	25.87	26.00
DENMARK					

tofersen + Riluzole	4.02	4.01	4.03	4.05	4.06
Riluzole	2.57	2.57	2.58	2.59	2.60
Total	6.59	6.58	6.61	6.63	6.66
ICELAND					
tofersen + Riluzole	5	5	5	5	5
Riluzole	0	0	0	0	0
Total	5	5	5	5	5

Table 63. Number of patients expected to be treated in the next five-year period - if tofersen is NOT introduced.

Treatment	2024	2025	2026	2027	2028	2029
FINLAND						
Riluzole	38.11	38.25	38.40	38.54	38.67	38.11
NORWAY						
Riluzole	14.37	14.51	14.63	14.75	14.86	14.37
SWEDEN						
Riluzole	25.42	25.57	25.71	25.87	26.00	25.42
DENMARK						
Riluzole	6.59	6.58	6.61	6.63	6.66	6.59
ICELAND						
Riluzole	5	5	5	5	5	5

5.1.6. Results

Table 64 shows the expected budget impact of introducing tofersen for the total patient population eligible for treatment per year.

More detailed results can be found in the accompanying file “Biogen tofersen_BIM”.

Table 64. Expected budget impact of introducing tofersen

Country	2025	2026	2027	2028	2029
FINLAND					
tofersen is introduced (EUR)	1,315,336	1,233,155	1,237,832	1,242,529	1,246,824
tofersen is NOT introduced (EUR)	96,871	97,228	97,597	97,967	98,306
Budget impact (EUR)	1,218,465	1,135,927	1,140,235	1,144,562	1,148,518
NORWAY					

tofersen is introduced (NOK)	18,112,226	17,017,886	17,156,189	17,294,379	17,426,390
tofersen is NOT introduced (NOK)	402,457	406,424	409,727	413,027	416,180
Budget impact (NOK)	17,709,769	16,611,462	16,746,462	16,881,352	17,010,210
SWEDEN					
tofersen is introduced (SEK)	42,546,566	39,775,790	40,004,596	40,244,197	40,455,887
tofersen is NOT introduced (SEK)	394,589	396,876	399,159	401,549	403,662
Budget impact (SEK)	42,151,977	39,378,914	39,605,437	39,842,648	40,052,226
DENMARK					
tofersen is introduced (DKK)	8,765,061	8,138,964	8,173,470	8,202,757	8,231,105
tofersen is NOT introduced (DKK)	49,632	49,597	49,807	49,985	50,158
Budget impact (DKK)	8,715,429	8,089,367	8,123,663	8,152,772	8,180,947
ICELAND					
tofersen is introduced (DKK)	216,390,136	215,956,912	215,956,912	215,956,912	215,956,912
tofersen is NOT introduced (DKK)	2,499,529	2,499,529	2,499,529	2,499,529	2,499,529
Budget impact (DKK)	**213,890,607**	**213,457,383**	**213,457,383**	**213,457,383**	**213,457,383**

5.1.7. Conclusions

The BIA compared the budgetary impact of *SOD1*-ALS treatments with and without the introduction of tofersen over a 5-year time horizon from a healthcare perspective in the Nordic countries.

Difference in drug price was observed to be the main driver of the BIA. An increase in administration costs over time was associated with the increased uptake of tofersen, based on estimated market shares. The results of the BIA and overall costs would be expected to vary depending on the number of patients that are expected to be eligible for treatment with tofersen, resulting in a higher or lower overall budget impact.

AE costs were similar between the 2 scenarios and slightly higher in the tofersen + riluzole treatment arm. This is likely due to the way the costs were estimated i.e., as a sum of the AE-related costs for tofersen and riluzole as individual treatments. The frequency of AEs was derived from a 28-week observation period (see Section 3.9) and extrapolated to a yearly (i.e., 52-week) probability. The true yearly incidence of AEs may vary from the estimated results. However, AE treatment costs were observed to have only a modest impact on the budget impact results.

The budgetary consequences were calculated based on Swedish unit costs for which the respective exchange rates were applied. Using national unit costs may lead to different results, although it is assumed that these differences would be minimal.

6. Quantification of severity (Norway only)

The severity of disease was quantified using the Excel tool provided by the Norwegian Medical Products Agency [228]. The baseline age in the CEM base case analysis was applied as average age at treatment initiation. The expected remaining QALYs were sourced from the CEM base case

undiscounted analysis by summing the total patient health state QALYs resulting from the SoC comparator arm.

The estimated absolute shortfall associated with SOD-1 ALS was a loss of 27.5 QALYs (Table 65).

Given the very few remaining QALYs for a newly diagnosed ALS SOD-1 patient, the age at diagnosis is the most influential factor on the absolute shortfall (Table 66).

Table 65. Severity calculations

Average age at treatment initiation	**A**	**49.1**
Expected remaining QALYs (undiscounted) for the general population without the disease	$QALYs_A$	28.2
Expected remaining QALYs (undiscounted) for those with the disease and without the new treatment (that is, prognosis of patients treated with current standard treatment)	P_A	0.7
Number of QALYs lost due to disease (absolute shortfall)	AS	27.5

Table 66. Sensitivity analysis for absolute shortfall calculation

Undiscounted QALYs resulting from comparator arm	**Age at treatment initiation**				
	45	**47**	**49**	**51**	**53**
0.3	31.1	29.5	27.9	26.3	24.8
0.5	30.9	29.3	27.7	26.1	24.6
0.7	30.7	29.1	27.5	25.9	24.4
0.9	30.5	28.9	27.3	25.7	24.2
1.1	30.3	28.7	27.1	25.5	24

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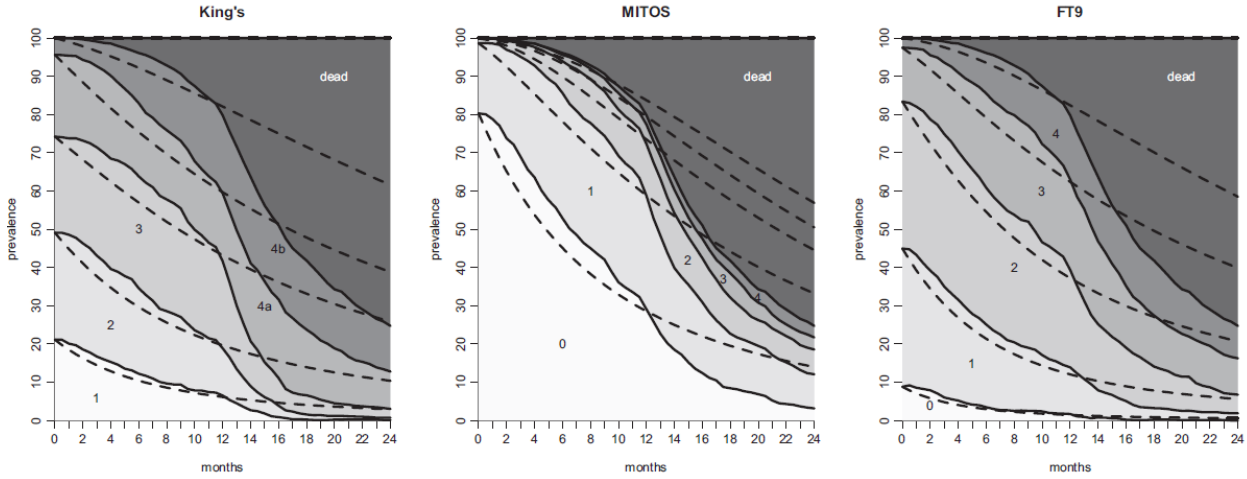
Appendices

7. Appendix A. Calibration of Thakore, Lapin [189] Transition Probabilities

Thakore, Lapin [189] undertook an analysis where transition probabilities between King's, MiToS, and FT9 health states were estimated using a Markov multi-state modeling approach and data from the PRO-ACT database.

The long-term outcomes of their analyses were notably underestimated when compared with data from PRO-ACT. Figure 33, sourced from Thakore, Lapin [189] shows the modeled prevalences derived from analyses as dashed lines and the actual prevalences from the PRO-ACT database as shaded areas in a stacked prevalences plot.

Figure 30. Stacked Prevalence Plots of Stages and Death for Each System Over the First 24 Months of Observation [189]



Source: Thakore, Lapin [189]

"The shaded areas depict observed prevalences, whereas areas separated by dotted lines depict modeled prevalences employing time-homogeneous Markov models. Note that modeled prevalences approximate observed prevalences up to about 12 months of observation, beyond which timepoint models underestimate progression and mortality."

Figure 33 demonstrates that the modeled prevalences do not fit the observed prevalences from PRO-ACT well beyond 12 months, with the modeled prevalence of death for all CSSs being most significantly underestimated. Therefore, it was felt that the use of Thakore, Lapin [189] as the SoC transition probability matrix source in the CEM may lead to an underestimation of progression and mortality outcomes.

Therefore, a calibration exercise was undertaken to adjust the SoC transition probabilities reported by Thakore, Lapin [189] from month 12 onward to better align with outcomes from the PRO-ACT database. To do this, Excel solver was used to adjust the transition probability of death from each health state. It was decided to vary the transition probability of death in the calibration exercise because this was the outcome most significantly underestimated by the modeled prevalences in Thakore, Lapin [189]. The calibration exercise was initiated as follows:

1. The prevalences of each stage and death reported in Table 67 from the PRO-ACT database were digitized from month 12 onward (12 month+) at 2-monthly intervals to derive numerical values for stacked prevalences at several timepoints. These stacked prevalences were then converted to absolute prevalences, which informed the proportion of patients we expect to be in each health state per 2-monthly time interval from the PRO-ACT database.
2. The baseline distribution of patients across MiToS health states from Thakore et al. (2018) was used as the baseline distribution in a Markov trace that was constructed to be used in the calibration exercise.
3. Up to month 12, the transition probabilities reported by Thakore et al. (2018) were applied in the Markov trace to transition patients between MiToS health states using a 1-monthly cycle length. The transition probabilities reported by Thakore et al. (2018) were used up to month 12 as it was felt the modeled prevalences and observed prevalences fit well up to year 1.

Table 67. One-monthly Transition Probabilities, SoC – Thakore et al. (2018) [PRO-ACT] [MiToS]

From/to	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	Death
Stage 0	0.898	0.084	0.014	0.002	0.000	0.002 (pd_{HS0})
Stage 1	0.032	0.862	0.071	0.014	0.003	0.017 (pd_{HS1})
Stage 2	0.004	0.058	0.801	0.063	0.023	0.051 (pd_{HS2})
Stage 3	0.000	0.008	0.044	0.757	0.099	0.091 (pd_{HS3})
Stage 4	0.000	0.001	0.006	0.035	0.844	0.114 (pd_{HS4})

MiToS = Milano-Torino functional staging system; PRO-ACT = Pooled Resource Open-Access ALS Clinical Trials; SoC = standard of care; TP = transition probability.

Note: Probabilities of death are henceforth labelled as pd_{HS0}, pd_{HS1}, pd_{HS2}, pd_{HS3}, and pd_{HS4}, corresponding to the probability of death for Stage 0, Stage 1, Stage 2, Stage 3, and Stage 4, respectively.

Source: Derived based on data reported by Thakore, Lapin [189]

4. A separate transition probability matrix was applied from month 12+, which was to be used in the calibration exercise.

Prior to adjusting the probabilities of death in the month 12+ matrix, a formula was introduced in Excel to link the probabilities of death to the transition probabilities between other health states. This step was undertaken to ensure that when the probability of death was changed in the calibration exercise, other probabilities would vary proportionately. To do this, death was factored out of the transition probability matrix by dividing the transition probabilities in each 'from' row in Table 67 by 1–the probability of death for each health state. It is noted that this step implicitly implies that the probability of death is uniform across health states. The resultant transition probability matrix with death factored out is outlined in Table 68, with each calculation shown in brackets.

Table 68. One-monthly Transition Probabilities With Death Removed, SoC – Thakore et al. (2018) [PRO-ACT] [MiToS]

From/to	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
Stage 0	0.8997 (= 0.898/[1−pd_{HS0}])	0.0844 (= 0.084/[1−pd_{HS0}])	0.0135 (= 0.014/[1−pd_{HS0}])	0.0020 (= 0.002/[1−pd_{HS0}])	0.0003 (= 0.000/[1−pd_{HS0}])
Stage 1	0.0329 (= 0.032/[1−pd_{HS1}])	0.8768 (= 0.862/[1−pd_{HS1}])	0.0724 (= 0.071/[1−pd_{HS1}])	0.0144 (= 0.014/[1−pd_{HS1}])	0.0034 (= 0.003/[1−pd_{HS1}])
Stage 2	0.0046 (= 0.004/[1−pd_{HS2}])	0.0611 (= 0.058/[1−pd_{HS2}])	0.8444 (= 0.801/[1−pd_{HS2}])	0.0662 (= 0.063/[1−pd_{HS2}])	0.0237 (= 0.023/[1−pd_{HS2}])
Stage 3	0.0004 (= 0.000/[1−pd_{HS3}])	0.0092 (= 0.008/[1−pd_{HS3}])	0.0483 (= 0.044/[1−pd_{HS3}])	0.8330 (= 0.757/[1−pd_{HS3}])	0.1091 (= 0.099/[1−pd_{HS3}])
Stage 4	0.0000 (= 0.000/[1−pd_{HS4}])	0.0008 (= 0.001/[1−pd_{HS4}])	0.0068 (= 0.006/[1−pd_{HS4}])	0.0393 (= 0.035/[1−pd_{HS4}])	0.9531 (= 0.844/[1−pd_{HS4}])

MiToS = Milano-Torino functional staging system; PRO-ACT = Pooled Resource Open-Access ALS Clinical Trials; SoC = standard of care; TP = transition probability.

Source: Derived based on data reported by Thakore, Lapin [189].

Then, death was reintroduced by multiplying the resultant transition probabilities in Table 69 by 1-the probability of death for each health state, which numerically returned the original SoC transition probability matrix except each transition probability was linked to the probability of death by use of an Excel formula.

Table 69. One-monthly Transition Probabilities Linked to Death, SoC – Thakore et al. (2018) [PRO-ACT] [MiToS]

From/to	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	Death
Stage 0	0.8997 × (1−pd_{HS0}) = 0.8976	0.0844 × (1−pd_{HS0}) = 0.0842	0.0135 × (1−pd_{HS0}) = 0.0135	0.0020 × (1−pd_{HS0}) = 0.0020	0.0003 × (1−pd_{HS0}) = 0.0003	pd_{HS0} = 0.0023
Stage 1	0.0329 × (1−pd_{HS1}) = 0.0323	0.8768 × (1−pd_{HS1}) = 0.8620	0.0724 × (1−pd_{HS1}) = 0.0712	0.0144 × (1−pd_{HS1}) = 0.0142	0.0034 × (1−pd_{HS1}) = 0.0033	Pd_{HS1} = 0.0169
Stage 2	0.0046 × (1−pd_{HS2}) = 0.0044	0.0611 × (1−pd_{HS2}) = 0.0580	0.8444 × (1−pd_{HS2}) = 0.8014	0.0662 × (1−pd_{HS2}) = 0.0629	0.0237 × (1−pd_{HS2}) = 0.0225	Pd_{HS2} = 0.0509
Stage 3	0.0004 × (1−pd_{HS3}) = 0.0003	0.0092 × (1−pd_{HS3}) = 0.0084	0.0483 × (1−pd_{HS3}) = 0.0439	0.8330 × (1−pd_{HS3}) = 0.7572	0.1091 × (1−pd_{HS3}) = 0.0992	Pd_{HS3} = 0.0910
Stage 4	0.0000 × (1−pd_{HS4}) = 0.0000	0.0008 × (1−pd_{HS4}) = 0.0007	0.0068 × (1−pd_{HS4}) = 0.0060	0.0393 × (1−pd_{HS4}) = 0.0348	0.9531 × (1−pd_{HS4}) = 0.8444	Pd_{HS4} = 0.1141

MiToS = Milano-Torino functional staging system; PRO-ACT = Pooled Resource Open-Access ALS Clinical Trials; SoC = standard of care; TP = transition probability.

Source: Derived based on data reported by Thakore, Lapin [189]

Next, constraints were added into Excel's solver function to ensure the calibration exercise returned outcomes that were logical and were aligned with data from the PRO-ACT database. Transition probabilities of death were set as the 'changing variable' cells (i.e., pd_{HS0} pd_{HS1}, pd_{HS2}, pd_{HS3}, and pd_{HS4} were varied), which were varied so that outcomes from the Markov trace at month 14, 16, 18, 20, 22, and 24 matched the corresponding absolute prevalences from the digitized PRO-ACT data. The sum of transitions from each health state to other health states being equal to 1 and the probability of death increasing for increasing disease severity were additional constraints that were included in Excel solver. The object solved was the sum of transition probabilities from Stage 4 to other stages,

which was set to equal 1; it is noted that this could have been replaced with any of the other constraints. Unconstrained variables were also set to be non-negative, and the Generalized Reduced Gradient (GRG) nonlinear solving method was used.

The resultant transition probability matrix is shown below in

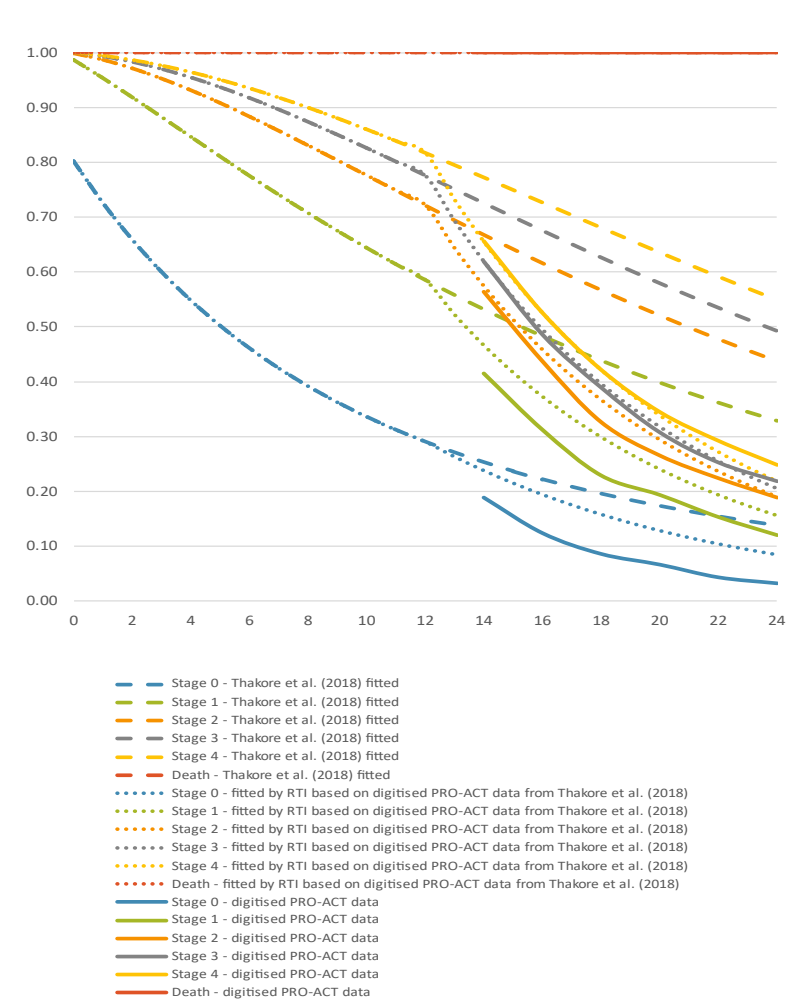
Table 70, with a stacked prevalence plot shown in Figure 34.

Table 70. One-monthly Transition Probabilities Linked to Death, SoC – Thakore et al. (2018) [PRO-ACT] [MiToS]

From/to	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	Death
Stage 0	0.8741	0.0820	0.0132	0.0020	0.0003	0.0284
Stage 1	0.0289	0.7715	0.0637	0.0127	0.0030	0.1202
Stage 2	0.0039	0.0513	0.7092	0.0556	0.0199	0.1601
Stage 3	0.0003	0.0074	0.0389	0.6707	0.0879	0.1948
Stage 4	0.0000	0.0006	0.0053	0.0303	0.7353	0.2285

MiToS = Milano-Torino functional staging system; PRO-ACT = Pooled Resource Open-Access ALS Clinical Trials; SoC = standard of care; TP = transition probability.
Source: Derived based on data reported by Thakore, Lapin [189]

Figure 31. Stacked Prevalence Plots of Stages and Death Estimated from the Calibration Exercise [MiToS]



MiToS = Milano-Torino functional staging system.

When compared with the stacked prevalence plot from Thakore, Lapin [189] for modeled prevalences, the transition probabilities derived from the calibration exercise, (which are applied from month 12+) better fit the observed prevalences PRO-ACT up to month 24. The same calibration exercise was undertaken for the King's staging, which yielded the following results:

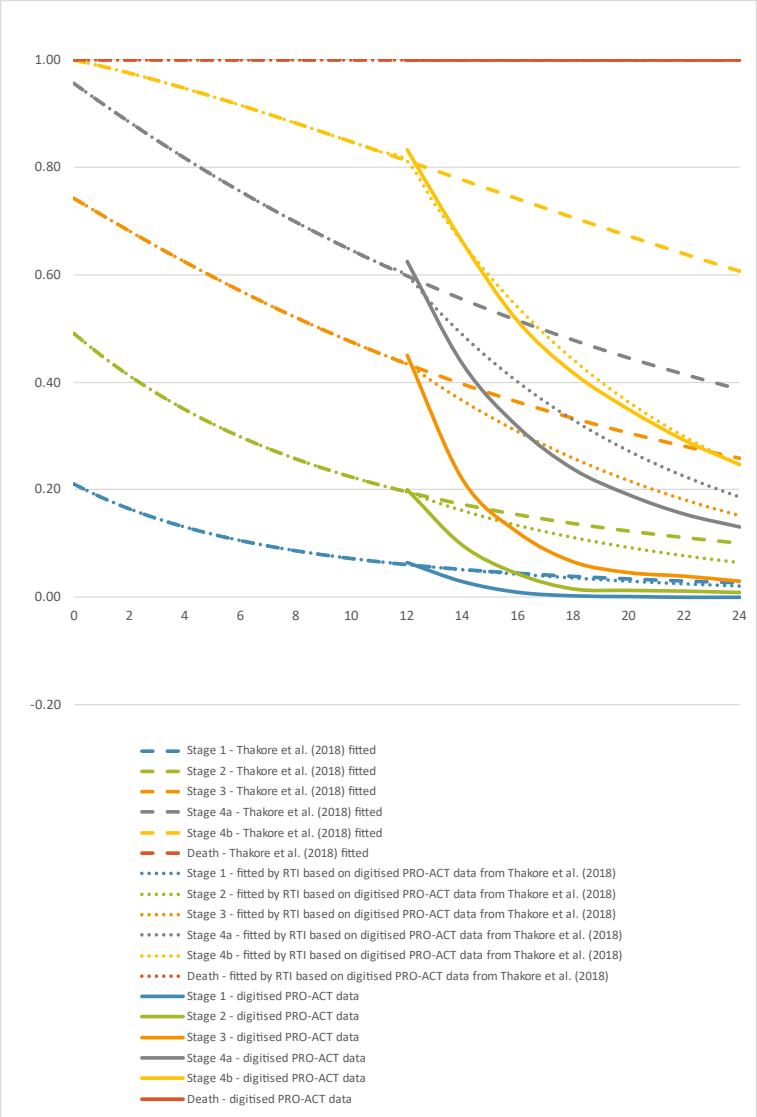
Table 71. One-monthly Transition Probabilities Linked to Death, SoC – Thakore et al. (2018) [PRO-ACT] [King's]

From/to	Stage 1	Stage 2	Stage 3	Stage 4a	Stage 4b	Death
Stage 1	0.8311	0.1151	0.0324	0.0084	0.0108	0.0022
Stage 2	0.0327	0.7732	0.1071	0.0086	0.0217	0.0567
Stage 3	0.0039	0.0408	0.8406	0.0176	0.0404	0.0567
Stage 4a	0.0000	0.0012	0.0127	0.8119	0.0368	0.1374
Stage 4b	0.0000	0.0012	0.0124	0.0100	0.8075	0.1689

PRO-ACT = Pooled Resource Open-Access ALS Clinical Trials; SoC = standard of care; TP = transition probability.

Source: Derived based on data reported by Thakore, Lapin [189].

Figure 32. Stacked Prevalence Plots of Stages and Death Estimated from the Calibration Exercise [King's]



8. Appendix B. Adjusting the Treatment Effect of Tofersen to Account for Treatment Switching in VALOR Open-Label Extension

8.1. Introduction

Health technology assessment (HTA) bodies may require economic evaluations that compare a state of the world in which the new therapy is available to a state of the world in which it is not [229]. In the presence of treatment switching, an "intention to treat" (ITT) analysis, an analysis in which the data are analyzed according to the arms to which patients were randomized, may lead to biased results [229]. For example, when participants in the placebo group of a trial are allowed to switch onto the experimental treatment in an open-label extension, an ITT analysis may underestimate the treatment effect because after switching, the placebo group may benefit from the experimental treatment [229]. Underestimation of the efficacy of a treatment could result in access being denied to a cost-effective treatment [230].

To address the HTA decision problem, adjustments for treatment switching may be conducted to obtain a more robust estimate of the treatment effect [229]. Statistical methods for addressing treatment switching have been recommended for use in HTA contexts, including inverse probability of censoring weighting, "two-stage" methods, rank preserving structural failure time models (RPSFTM) and iterative parameter estimation (IPE) [229, 231, 232]. Notably, inverse probability of censoring weighting and "two-stage" methods [229] are not appropriate in a context in which all (or nearly all) control group participants switch onto treatment in an open-label extension of a trial. However, RPSFTM and IPE can be applied in a situation where most control group participants switch onto treatment [229]. RPSFTM and IPE have previously been used in various therapeutic areas such as oncology, multiple sclerosis, and amyotrophic lateral sclerosis (ALS) [233-236]. RPSFTM and IPE estimate the counterfactual survival times, which represent the survival times that would have been observed if treatment switching had not occurred.

Our aim was to adjust treatment effect estimates of tofersen using RPSFTM and IPE to account for treatment switching in the placebo group after entering the open-label extension of VALOR. RPSFTM and IPE allow us to estimate the treatment effect of tofersen by comparing the disease experience of participants randomized to tofersen with the disease experience of participants randomized to placebo if they had not switched onto tofersen treatment in the open-label extension (i.e., if participants randomized to placebo stayed on placebo during the open-label extension). This report describes the rationale for the approaches chosen to address this research question, details of the statistical methods, results, and discussion of the findings and limitations of this work.

8.2. Methods

8.2.1. Data Source

VALOR (Part C) was a 28-week, phase 3, double blind, randomized, placebo-controlled trial that evaluated the clinical efficacy of tofersen administered to adults with amyotrophic lateral sclerosis (ALS) and a confirmed *SOD1* mutation[18]. Following the completion of the VALOR trial, participants were given the option to enroll in an ongoing open-label extension, while remaining unaware of their trial group assignment. Participants randomized to tofersen in VALOR had the opportunity to

continue on tofersen treatment in the open-label extension ("early-start" participants), and participants randomized to placebo in VALOR had the opportunity to switch to tofersen treatment in the open-label extension ("delayed-start" participants). Sixty-three of 72 participants initially randomized to tofersen entered the open-label extension and 32 of 36 participants initially randomized to placebo entered the open-label extension and switched onto tofersen. The combined analyses of VALOR and open-label extension in the current report used data from the January 16, 2022 data cutoff and are based on the ITT principle, where all participants who underwent randomization in VALOR were included according to the original trial-group assignment. For the January 2022 data cutoff, the median time on study was 88.6 weeks and the mean time on study was 87.0 weeks.

The outcomes of interest in the current analyses were time to death, time to transition to later MiToS stage (excluding death), and time to transition to later King's stage (excluding death) in the overall ITT population, with time to transition event defined as the time from baseline to the first time that a patient goes up (worsens by) at least 1 stage compared with baseline. The ALS Milano-Torinos staging (MiToS) system was developed to capture the observed progressive loss of independence and function in ALS in 4 key domains including swallowing, walking/self-care, communicating, and breathing [175]. King's staging is based on clinical milestones that consider involvement of 1-3 anatomical regions (Stages 1, 2, 3) and the need for gastrostomy (Stage 4a), and non-invasive ventilation (Stage 4b) [180]. The definitions and details of MiTOS and King's stages are described in the Supplemental Information below. Patients who withdrew and who had not reached a later stage were censored at time of withdrawal and ongoing patients who had not transitioned to a later stage were censored at the date they were last known to be alive. In analyses of transition to later Kings stage, King's stages 4a and 4b were combined and counted as the same stage for this analysis since there was a small number of participants in these stages (e.g., the number of subjects in stage 4a at baseline was 1). This approach is also consistent with recent clinical views [237].

We first conducted ITT analyses ignoring treatment switching to be able to compare with the effect estimates adjusted for treatment switching after implementing RPSFTM and IPE. The ITT analyses examined the data according to the arms to which patients were randomized, regardless of whether they switched onto tofersen in the open-label extension.

8.2.2. RPSFTM

RPSFTM uses a causal model to produce counterfactual survival times in order to estimate a causal treatment effect if treatment had not occurred: counterfactual event times = $T_i^{off} + T_i^{on}\exp(\psi)$, where T_i^{off} and T_i^{on} represent the time spent off and on treatment, and ψ represents the treatment effect [231, 238]. The treatment effect, ψ, is estimated by balancing average counterfactual event times between treatment groups. A g-estimation procedure (grid search) is used to find ψ. Once ψ has been identified, survival times under no treatment can be calculated for the control group. We can then obtain an estimate of the treatment effect adjusted for treatment switching by comparing the observed experimental treatment group survival times with the counterfactual survival times for the control group.

We used RPSFTM to estimate counterfactual survival times. Consistent with the amended statistical analysis plan before analysis of the January 2022 data cutoff, we adjusted for baseline plasma neurofilament light chain (NfL) and riluzole or edaravone use. NfL is a prognostic marker of disease progression; participants with higher baseline NfL levels are expected to lose more function over the study period than those with lower baseline NfL levels. In VALOR, baseline plasma NfL

concentrations were 15 to 25% higher in participants randomized to tofersen than in those who were randomized to placebo [18]. Thus, incorporating baseline plasma NfL as a covariate can help reduce imbalances in baseline disease heterogeneity between treatment groups. We also adjusted for background therapy (riluzole and/or edaravone use) at baseline given this was a factor used for stratified randomization in VALOR. We included baseline plasma NfL and riluzole or edaravone use in the RPSFTM g-estimation process and used the Wald test for the RPSFTM g-test. We fit Cox proportional hazards models adjusted for baseline plasma NfL and riluzole or edaravone use to estimate the hazard ratios for the outcomes of interest. For all RPSFTM analyses, test-based confidence intervals associated with the hazard ratios were calculated using the p-value and z-statistic from the ITT analysis for each outcome.

8.2.3. IPE

We used IPE to check if the results were similar to those of RPSFTM. IPE builds on the RPSFTM method by replacing the test-based estimation of ψ with a likelihood-based analysis [232]. An initial estimate of ψ is obtained by comparing the groups as randomized using a parametric accelerated failure time model. For a given initial point estimate of ψ, the survival times of patients who switch treatment in the control arm are transformed using the formula to obtain counterfactual event times, $T_i^{off} + T_i^{on} \exp(\psi)$. Using these transformed times and the original observed survival times for all other patients, the two groups are compared again using the parametric survival analysis, which provides another estimate of ψ. This new estimate of ψ is used in a subsequent transformation of the survival times of control group participants who switch onto the experimental treatment. This entire process is repeated until the value of ψ used in the transformation is close (within 10^{-5}) to the value used in the previous iteration. At that point, the procedure is considered to have converged [232].

Similar to the ITT and RPSFTM analyses, we included baseline plasma NfL and riluzole or edaravone use as adjustment covariates in the IPE process. A key step in IPE is to identify a parametric survival time distribution for event times. We considered various distributions including Weibull, log-normal, log-logistic, and gamma. To identify the most appropriate parametric distribution, we examined the Cox-Snell residuals obtained from fitting the aforementioned survival models to the data of patients originally randomized to tofersen and compared the models with respect to Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). After assessing each parametric accelerated failure time model with respect to the closeness of the Cox-Snell residuals to the line through the origin and the lowest AIC and BIC values, we chose the most appropriate distribution for each endpoint. A Cox proportional hazards model adjusting for baseline plasma NfL and riluzole or edaravone use was used to calculate the hazard ratio. Bootstrapping of the entire adjustment process (based on 200 resampled datasets) was used to generate 95% confidence intervals (CIs) for the hazard ratios for time to transition to later King's stage and time to transition to later MiToS stage. However, given the rarity of death and non-convergence issues, a test-based confidence interval for the hazard ratio for time to death was calculated using the p-value and z-statistic from the ITT analysis. We used an ever-treated analytic approach for both RPSFTM and IPE analyses.

We conducted RPSTFM and IPE analyses without re-censoring counterfactual event times. Re-censoring is usually performed to address informative censoring due to the existence of control group non-switchers [239]. Adjusting survival times for control group switchers but not control group non-switchers can induce informative censoring. Given the lack of placebo participants who did not switch onto tofersen in the open-label extension, adjusting survival times for switchers will not induce informative censoring. Re-censoring may actually induce a loss of longer-term survival

information which can be problematic when long-term survival effects are required for HTA decision making [239].

8.2.4. Sensitivity Analyses

The first sensitivity analysis we performed was to assess the impact of adjustment for baseline plasma NfL and riluzole/edaravone use by comparing the results of analyses that did not adjust for these two variables with the results of analyses that did adjust for them.

The second sensitivity analysis sought to examine the impact of violations of the common treatment effect assumption on study results. RPSFTM and IPE both make an important assumption of the common treatment effect which states that the treatment effect is the same for all participants (with respect to time spent on treatment) regardless of when treatment is received. This assumption may not hold when the average treatment effect received by participants who switch is different from the effect in participants initially randomized to the experimental treatment at baseline. We introduced deviations from the common treatment effect assumption by varying the treatment effect across individuals. This can be done by multiplying ψ with some factor k_i such that counterfactual event times = $T_i^{off} + T_i^{on} \exp(k_i \psi)$ [231, 238]. We introduced violations of the common treatment effect assumption by setting the treatment effect to be 10%, 20%, 30%, 40%, and 50% lower in the delayed-start group compared with the early-start group, which corresponds with setting $k_i = 1$ for participants randomized to tofersen and $k_i = 0.9, 0.8, 0.7, 0.6, and\ 0.5$, respectively for participants randomized to placebo at baseline in VALOR. We then examined the impact on the overall hazard ratio comparing participants randomized to tofersen with participants randomized to placebo if they had stayed on placebo during the open-label extension.

A third sensitivity analysis was conducted to re-baseline analyses to Week 12. The results from the VALOR trial and its OLE showed a temporal relationship between biological and clinical effects. Consistent with its mechanism, which targets the underlying and upstream cause of *SOD1*-ALS, Tofersen administration led to reductions in neurofilament that were sustained over time. It took approximately 8 weeks to achieve maximum reductions in *SOD1* protein, consistent with the pharmacokinetics of tofersen and estimated half-life of *SOD1* protein. Around 12 to 16 weeks after tofersen was initiated, neurofilament levels reach their new nadir. Although early signs of clinical benefit with tofersen treatment started to emerge at around 12 weeks, it was only at 28 weeks and beyond that this benefit started to become more clear. At 28 weeks (duration of VALOR trial), trends suggested Tofersen was slowing decline on clinical outcomes, but these effects were not statistically significant. By 52 weeks and beyond, there is consistent evidence that earlier initiation of Tofersen is reducing decline in strength, function, and quality of life. Due to an imbalance in baseline NfL levels between treatment groups, tofersen-treated participants were more highly progressed than placebo participants at baseline in the VALOR trial and had greater disease progression before tofersen had the opportunity to provide a clinical benefit. Based on the temporal relationship between biological and clinical effects and the imbalance in baseline disease progression, re-baselining analyses to a timepoint before Week 16 may help better capture changes.

As the last clinical visit before Week 16 occurred at Week 12, re-baselining analyses to Week 12 may help better elucidate the treatment effect of tofersen. However, re-baselining to Week 12 may also introduce violations to the randomization assumption and requires that the initial 12 weeks of treatment in the group randomized to tofersen had no impact on outcomes. Given that NfL was substantially reduced at 12 weeks in participants treated with tofersen and that NfL levels increased slightly in the placebo group, it may not be reasonable to assume that the prognosis of the

randomized groups at Week 12 was the same. In this report, we provide the results of analyses using the original baseline (VALOR baseline) alongside those re-baselined to Week 12. For the analyses re-baselined to Week 12, we repeated all the analyses that were performed for the original VALOR baseline but using Week 12 as the baseline instead. Subjects who withdrew from the study prior to Week 12 were excluded from the re-baselined analysis.

8.3. Results

8.3.1. ITT

The baseline characteristics of the study sample have been previously published [18]. In ITT analyses ignoring treatment switching, the hazard ratio for time to death from VALOR baseline for participants randomized to tofersen compared with participants randomized to placebo was 0.27 (95% CI: 0.08, 0.89), implying a reduction of 73% in the expected time to death associated with being assigned to tofersen compared to placebo (Table 1). The hazard ratio for time to transition from VALOR baseline to later MiToS stages (excluding death) was 0.69 (95% CI: 0.40, 1.2), and that for time to transition from VALOR baseline to later King's stages (excluding death) was 0.98 (95% CI: 0.56, 1.71). Table 2 shows the number of overall subjects, subjects with an event, and subjects who were censored for each outcome of interest.

8.3.2. RPSFTM

There was a reduction in the hazard of death after adjusting for treatment switching using RPSFTM compared with the result from the ITT analysis. After accounting for treatment switching, the hazard ratio for time to death from VALOR baseline for the participants randomized to tofersen compared with participants randomized to placebo was 0.10 (95% CI: 0.01, 0.81), indicating a 90% reduction in the expected time to death associated with tofersen compared to the time expected without tofersen treatment (Table 1). For the outcomes of time to transition to later stages after adjusting for treatment switching; the hazard ratio for time to transition from VALOR baseline to later MiToS stages (excluding death) was 0.61 (95% CI: 0.29, 1.27) and that for time to transition from VALOR baseline to later King's stages (excluding death) was 0.98 (95% CI: 0.51, 1.87). i

8.3.3. IPE

We also used IPE, another method for addressing treatment switching, to check if the results were similar to those obtained from RPSFTM. After assessing each parametric accelerated failure time model fit to the data of patients randomized to tofersen with respect to the closeness of the Cox-Snell residuals to the line through the origin and the lowest AIC and BIC values, we chose the most appropriate distribution for each outcome. The Weibull distribution was chosen for time to death. The log-normal distribution was chosen for time to MiToS and King's stage transitions.

After IPE, the hazard ratio for time to death from VALOR baseline was 0.10 (95% CI: 0.01, 0.81) (Table 1). The hazard ratio for time to transition from VALOR baseline to later MiToS stages (excluding death) was 0.65 (95% CI: 0.32, 1.47). Finally, the hazard ratio for time to transition from VALOR baseline to later King's stages (excluding death) was 0.97 (95% CI: 0.52, 2.15). Overall, the effect estimates adjusting for treatment switching obtained from RPSFTM and IPE were similar.

Figures 1 - 3 show the survival curves for each outcome which were based on Cox proportional hazards models that adjusted for baseline riluzole or edaravone use and plasma NfL using the original intention-to-treat data, data adjusted for treatment switching using RPSFTM, and data adjusted for treatment switching using IPE. We found that for all outcomes, survival curves for the

delayed-start group were similar after implementing both RPSFTM and IPE. For the outcome of time to death, adjusting for treatment switching decreased the survival probability in the delayed-start group (Figure 1). The curves for the delayed-start group after adjusting for treatment switching using RPSFTM and IPE appear cut off due to the lack of control group non-switchers. Survival curves for the outcomes of time to transition to later MiToS and King's stages are shown in Figures 2 - 3.

8.3.4. Sensitivity Analyses

We assessed the impact of adjustment for baseline plasma NfL and riluzole or edaravone use by comparing the results of models not adjusting for these baseline variables (not adjusting for baseline variables in the g-estimation/IPE process nor in the Cox regression model) with models that adjusted for these two baseline variables (in the g-estimation/IPE process and in the Cox regression model). Analyses not accounting for these baseline variables underestimated the effect of tofersen for time to death from VALOR baseline (Table 3). Not adjusting for baseline plasma NfL and riluzole or edaravone use in the analyses for time to later MiToS stages and time to later King's stages yielded results generally similar in magnitude and direction to results that were adjusted for these baseline covariates (Table 3).

We evaluated the assumption of the common treatment effect in the RPSFTM analyses by setting the treatment effect to be lower in the delayed-start group compared with the early-start group. We examined what happened when the treatment effect was 10%, 20%, 30%, 40%, and 50% lower in the delayed-start group than the early-start group. Despite varying the degree of the reduction of the treatment effect in the delayed-start group compared to the early-start group, the results comparing the hazard of death and transition to later MITOS/King's stages in the early-start group to the hazard of these outcomes in the delayed-start group if the delayed-start group had not received any tofersen treatment remained consistent (Table 4).

We also conducted sensitivity analyses that re-baselined to Week 12 (i.e., using data from week 12 as the baseline) and found that the re-baselined results were similar to those using the original VALOR baseline. For example, the hazard ratio for time to death adjusting for treatment switching using RPSFTM was 0.10 (95% CI: 0.01, 0.81) using the original VALOR baseline and 0.09 (95% CI: 0.01, 0.80) using Week 12 baseline (Table 5). The Z graphs and Kaplan-Meier plots of transformed treatment-free time were also similar to those of analyses using the original VALOR baseline. The same distributions were identified for IPE analyses using Week 12 baseline (Weibull for time to death and log-normal for time to MiToS and King's stage transitions). Figures 4 -6 suggest that the survival curves for the delayed-start group were similar after implementing both RPSFTM and IPE in analyses re-baselined to Week 12. After adjusting for treatment switching using RPSFTM and IPE for the outcome of time to death, the survival probability for the delayed-start group was decreased. Sensitivity analyses for baseline covariate adjustment and the common treatment effect assumption yielded similar results as those seen using the original VALOR baseline. Overall, the general results and conclusions were similar using the original VALOR baseline and Week 12 baseline.

8.4. Conclusions

Treatment switching poses a challenge in HTAs. Standard ITT analyses may be inappropriate in the presence of treatment switching because they may lead to underestimation of the treatment effect. In this report, we adjust for treatment switching in the estimation of the effect of tofersen on time to death and time to transition to later MiToS and King's stages using RPSFTM and IPE and data from VALOR and open-label extension. After adjusting for treatment switching, the impact of tofersen on reducing the rate of death became greater than that observed in the ITT analysis ignoring treatment

switching. However, the results did not change meaningfully after adjusting for treatment switching for time to transition to later MiToS and King's stages. These findings were robust in a range of sensitivity analyses that assessed the impact of covariate adjustment, the common treatment effect assumption, and re-baselining analyses to Week 12.

The findings in this report should be interpreted in the context of several important limitations. First, RPSFTM relies on the rank preservation assumption, which states that the ranking of participants' potential outcomes under treatment is the same as the ranking of their potential outcomes under no treatment [231]. Rank preservation may be regarded as implausible [240] since the effect of treatment often depends on participants' behaviors and characteristics, and the reasonableness of analyses based on the rank preservation assumption remains to be determined [241]. Moreover, another fundamental assumption in RPSFTM is correct specification of the model used to derive counterfactual survival times [231]. The model assumes that the treatment effect is multiplicative on time (extends survival time by a fixed factor), every day on treatment leads to an immediate extension of survival (mortality decreases constantly during the study period), and that the benefit of treatment is the same for all patients at all times [242]. Violations of these assumptions may lead to biased counterfactual survival times. We considered other methods for addressing treatment switching such as inverse probability of censoring weighting and "two-stage" methods [229], but these methods are unsuitable when most participants switch, as was the case in the VALOR trial where 32 of 36 participants initially randomized to placebo entered the open-label extension and switched onto tofersen. Inverse probability of censoring weighting involves censoring patients who switched, identifying patients who had similar prognostic characteristics to switchers but who themselves did not switch, and upweighting them to account for the censored switchers [229]. This approach is only possible if some non-switchers remain in the dataset, which is not the case when combining VALOR and the OLE study. "Two-stage" methods assume that treatment switching only happens after some disease-related time-point, such as disease progression, and then estimates the effect of switching by comparing post-disease progression outcomes in switchers and non-switchers [229]. The estimated effect of switching is then used to derive estimates of outcomes would have been observed in switchers, had they not switched. "Two-stage" stage methods cannot be applied in the case of VALOR combined with the OLE study, firstly because the switching time-point was not a disease-related time-point, and secondly because in the OLE phase there were no non-switchers against whom switchers can be compared.

A second limitation of this work is that there was some non-overlap in the counterfactual event curves under no treatment for the early-start and delayed-start participants for time to death. This suggests that there may be residual confounding of the association between tofersen and death in the RPSFTM and IPE analyses. Although we adjusted for the baseline covariates of plasma NfL and edaravone or riluzole use, there may be remaining imbalances between the treatment groups that were not controlled for. Another potential explanation for the non-overlap in the counterfactual event curves is that the simple model for estimating counterfactual event times that is relied upon by RPSFTM and IPE was not plausible due to assumption violations. Despite there being overlap in the counterfactual event curves for the earlier time points for time to death, there appears to be a divergence in the curves at approximately week 40, though there is lack of information on the treatment-free time for time to death in the early-start group for the later timepoints. This suggests that there remains uncertainty in the effect estimate of tofersen on time to death after adjusting for treatment switching.

Another limitation is potential violation of the common treatment effect assumption. This assumption may not hold when the treatment effect in participants who switch is different from the

effect in participants originally randomized to the experimental treatment. Early initiation of tofersen is associated with improved outcomes compared with delayed-initiation of tofersen [18]. When we varied the magnitude of the ratio of the treatment effect in the early-start group vs delayed-start group in a sensitivity analysis, we found that the overall hazard ratios comparing the early-start group to the delayed-start group if the delayed-start group had remained on placebo in open-label extension for all outcomes remained similar. However, the counterfactual event curves for the treatment groups were non-overlapping for time to death and time to later MiToS stages when assessing the common treatment effect assumption. Therefore, residual confounding and model specification for the counterfactual survival times are also potential concerns in the sensitivity analyses for the common treatment effect assumption. The analyses were also limited by the small size of the trial and the small number of deaths that were observed which reduced the precision of effect estimates.

These results suggest that tofersen may reduce the expected time to death compared with placebo. By adjusting survival estimates in the presence of treatment switching using RPSFTM and IPE, a stronger effect of tofersen on reducing time to death was observed compared to an ITT analysis. Adjusting for treatment switching had little impact for the other outcomes of time to transition to later MiToS and King's stages.

Table 72. Hazard ratios for the association between tofersen and time to death from VALOR baseline and time to transition to later MITOS and King's stages using ITT analyses, RPSFTM, and IPE to address treatment switching

	ITT	RPSFTM	IPE
Time to death using original baseline, hazard ratio (tofersen vs placebo to tofersen), 95% CI	0.27 (0.08, 0.89)	0.1 (0.01, 0.81)	0.1 (0.01, 0.81)
Time to transition from original baseline to later MITOS stages (excluding death) hazard ratio (tofersen vs placebo to tofersen), 95% CI	0.69 (0.4, 1.2)	0.61 (0.29, 1.27)	0.65 (0.32, 1.47)
Time to transition from original baseline to later King's stages (excluding death) hazard ratio (tofersen vs placebo to tofersen), 95% CI	0.98 (0.56, 1.71)	0.98 (0.51, 1.87)	0.97 (0.52, 2.15)

Table 73. Number of overall subjects, subjects with an event, and subjects who were censored from VALOR + OLE baseline

	Number of subjects in placebo + delayed start tofersen 100mg group	Number of subjects in early-start tofersen 100mg group	Number of subjects with an event in placebo + delayed start tofersen 100mg group (%)	Number of subjects with an event in early-start tofersen 100mg group (%)	Number of subjects who were censored in placebo + delayed start tofersen 100mg group (%)	Number of subjects who were censored in early-start tofersen 100mg group (%)
Time to death	36	72	6 (16.7)	8 (11.1)	30 (83.3)	64 (88.9)
Time to transition from original baseline to later MITOS stages	36	72	21 (58.3)	34 (47.2)	15 (41.7)	38 (52.8)
Time to transition from original baseline to	36	72	19 (52.8)	40 (55.6)	17 (47.2)	32 (44.4)

later King's stages						

Table 74. Assessment of the impact of adjustment for baseline plasma NfL and riluzole or edaravone use

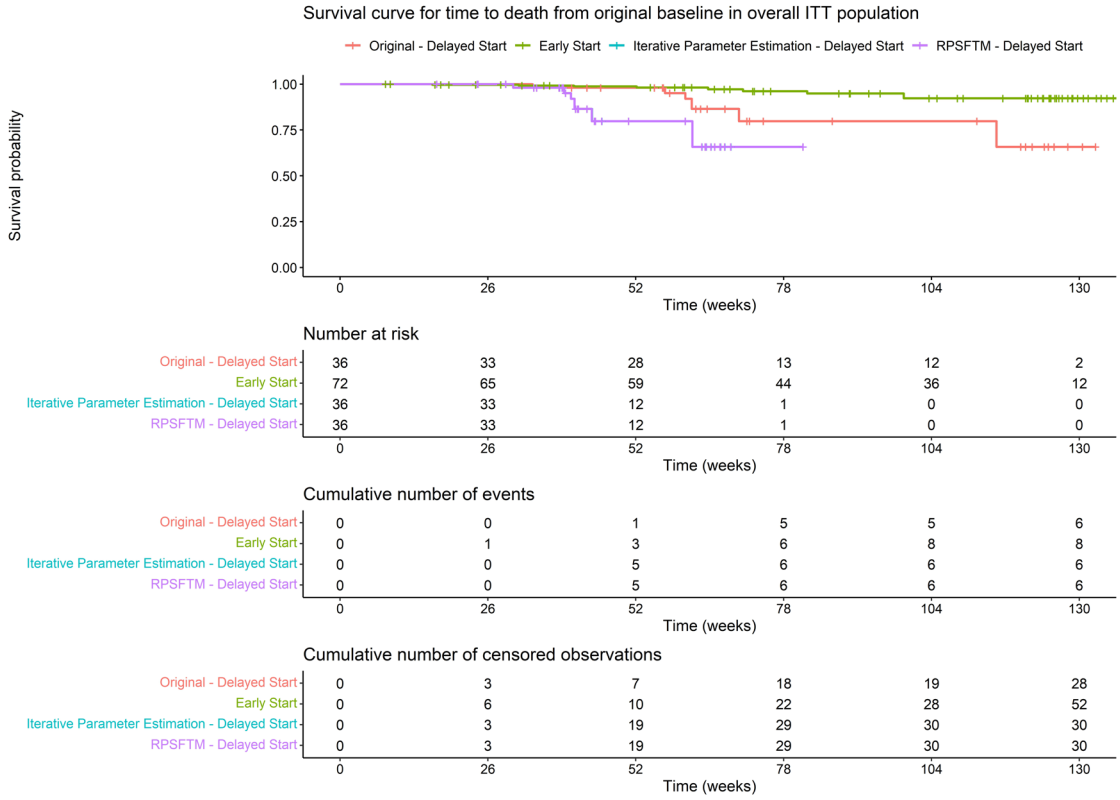
	ITT		RPSFTM		IPE	
	Unadjusted for baseline covariates	**Adjusted for baseline covariates**	**Unadjusted for baseline covariates**	**Adjusted for baseline covariates**	**Unadjusted for baseline covariates**	**Adjusted for baseline covariates**
Time to death using original baseline, hazard ratio (tofersen vs placebo to tofersen), 95% CI	0.54 (0.19, 1.56)	0.27 (0.08, 0.89)	0.28 (0.03, 2.47)	0.1 (0.01, 0.81)	0.29 (0.04, 2.39)	0.1 (0.01, 0.81)
Time to transition from original baseline to later MITOS stages (excluding death) hazard ratio (tofersen vs placebo to tofersen), 95% CI	0.74 (0.43, 1.29)	0.69 (0.4, 1.2)	0.66 (0.31, 1.42)	0.61 (0.29, 1.27)	0.72 (0.39, 1.43)	0.65 (0.32, 1.47)
Time to transition from original baseline to later King's stages (excluding death) hazard ratio (tofersen vs placebo to tofersen), 95% CI	1 (0.58, 1.73)	0.98 (0.56, 1.71)	1 (0.58, 1.73)	0.98 (0.51, 1.87)	1 (0.55, 2.21)	0.97 (0.52, 2.15)

Table 75. Assessment of the RPSFTM common treatment effect assumption

Outcome	Ratio of the treatment effect in the delayed-start group vs the early-start group	Multiplicative factor	RPSFTM hazard ratio (early-start group vs delayed-start group), 95% CI
Time to death			
Time to death	100%	-0.9454	0.0983 (0.0119, 0.8118)
Time to death	90%	-0.9408	0.0983 (0.0119, 0.8118)
Time to death	80%	-0.8996	0.1127 (0.0154, 0.8218)
Time to death	70%	-0.8752	0.1165 (0.0165, 0.8243)
Time to death	60%	-0.8304	0.1235 (0.0184, 0.8286)
Time to death	50%	-0.7891	0.1336 (0.0214, 0.8345)
Time to later MITOS stages			
Time to transition to later MITOS stages	100%	-0.9356	0.6105 (0.2943, 1.2665)

Time to transition to later MITOS stages	90%	-0.9144	0.6097 (0.2954, 1.2584)
Time to transition to later MITOS stages	80%	-0.8828	0.6105 (0.2964, 1.2576)
Time to transition to later MITOS stages	70%	-0.8573	0.6114 (0.2975, 1.2567)
Time to transition to later MITOS stages	60%	-0.8310	0.6114 (0.2975, 1.2567)
Time to transition to later MITOS stages	50%	-0.8072	0.6114 (0.2975, 1.2567)
Time to later King's stages			
Time to transition to later King's stages	100%	-0.0352	0.9779 (0.5107, 1.8722)
Time to transition to later King's stages	90%	-0.0352	0.9777 (0.5109, 1.8710)
Time to transition to later King's stages	80%	-0.0352	0.9777 (0.5109, 1.8710)
Time to transition to later King's stages	70%	-0.0349	0.9777 (0.5109, 1.8710)
Time to transition to later King's stages	60%	-0.0350	0.9777 (0.5109, 1.8710)
Time to transition to later King's stages	50%	-0.0350	0.9777 (0.5109, 1.8710)

Figure 33. Survival curve for time to death from VALOR baseline



Note: The curves for the delayed-start group after adjusting for treatment switching using RPSFTM and IPE are overlapping.

Figure 34. Survival curve for time to transition from VALOR baseline stage to later MITOS stages (excluding death)

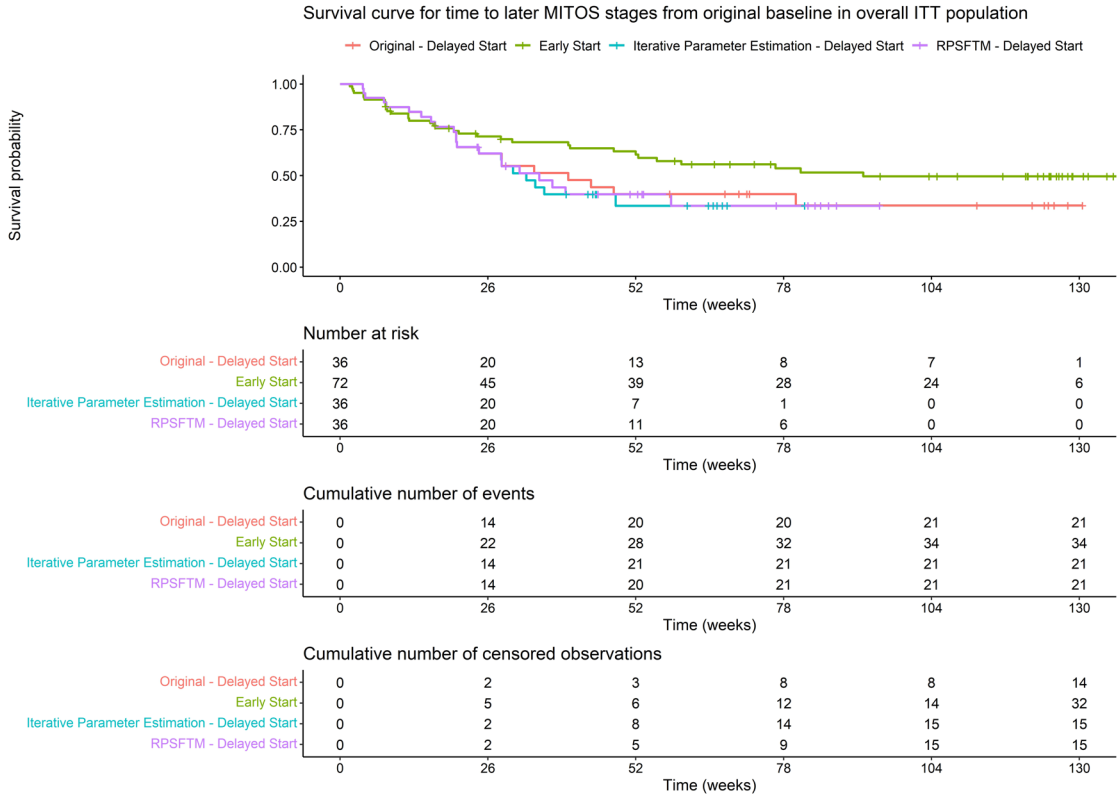


Figure 35. Survival curve for time to transition from VALOR baseline stage to later King's stages (excluding death)

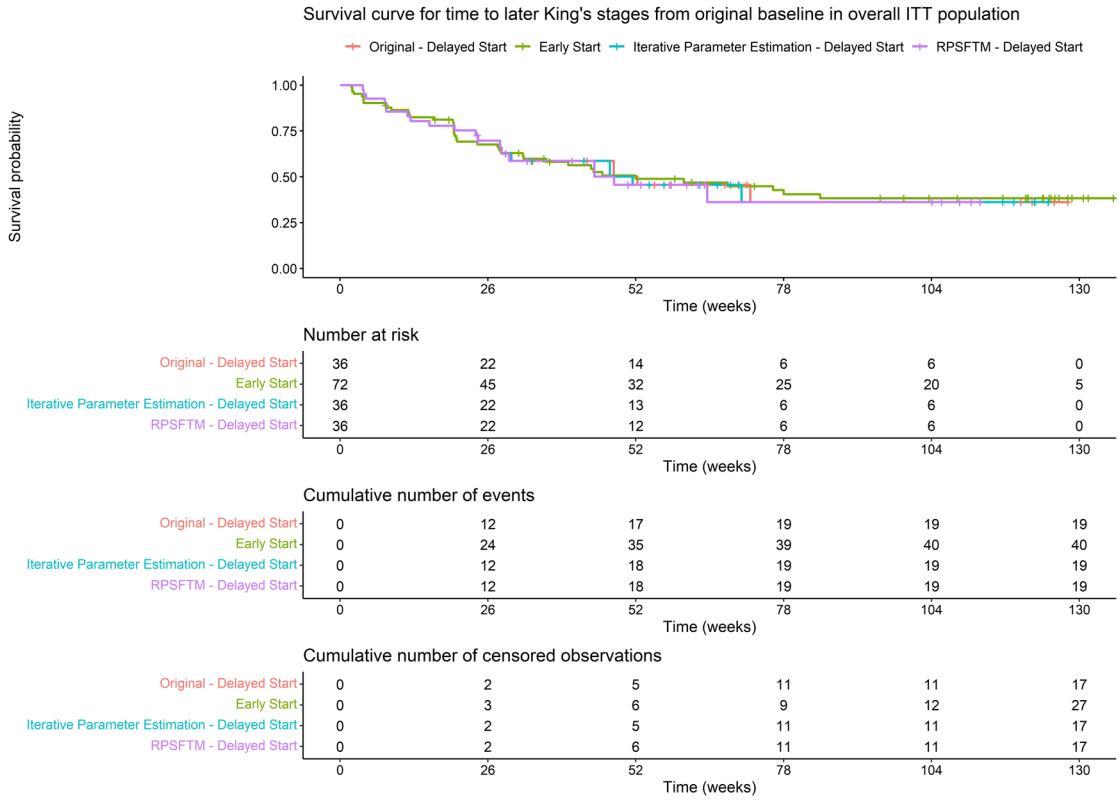


Table 76. Hazard ratios for the association between tofersen and time to death from Week 12 baseline and time to transition to later MITOS and King's stages using ITT analyses, RPSFTM, and IPE to address treatment switching

	ITT	RPSFTM	IPE
Time to death using Week 12 baseline, hazard ratio (tofersen vs placebo to tofersen), 95% CI	0.27 (0.08, 0.89)	0.09 (0.01, 0.8)	0.08 (0.01, 0.79)
Time to transition from Week 12 baseline to later MITOS stages (excluding death) hazard ratio (tofersen vs placebo to tofersen), 95% CI	0.72 (0.39, 1.3)	0.59 (0.23, 1.53)	0.6 (0.25, 1.46)
Time to transition from Week 12 baseline to later King's stages (excluding death) hazard ratio (tofersen vs placebo to tofersen), 95% CI	0.93 (0.52, 1.67)	0.88 (0.3, 2.54)	0.88 (0.49, 2.29)

Table 77. Number of overall subjects, subjects with an event, and subjects who were censored from Week 12 baseline

	Number of subjects in placebo + delayed start tofersen 100mg group	Number of subjects in early-start tofersen 100mg group	Number of subjects with an event in placebo + delayed start tofersen 100mg group (%)	Number of subjects with an event in early-start tofersen 100mg group (%)	Number of subjects who were censored in placebo + delayed start tofersen 100mg group (%)	Number of subjects who were censored in early-start tofersen 100mg group (%)
Time to death	36	70	6 (16.7)	8 (11.4)	30 (83.3)	62 (88.6)
Time to transition from Week 12 baseline to later MITOS stages	36	70	17 (47.2)	31 (44.3)	19 (52.8)	39 (55.7)
Time to transition from Week 12 baseline to later King's stages	36	70	17 (47.2)	36 (51.4)	19 (52.8)	34 (48.6)

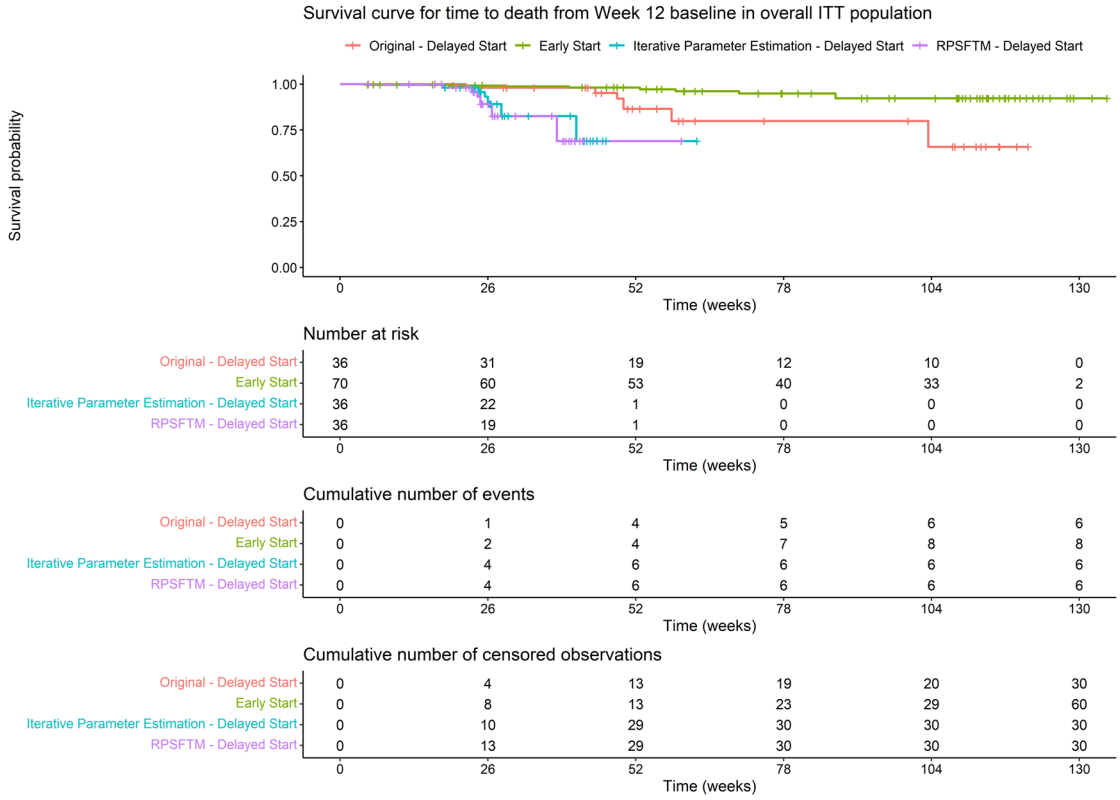
Table 78. Assessment of the impact of adjustment for baseline plasma NfL and riluzole or edaravone use from Week 12 baseline

	ITT		RPSFTM		IPE	
	Unadjusted for baseline covariates	Adjusted for baseline covariates	Unadjusted for baseline covariates	Adjusted for baseline covariates	Unadjusted for baseline covariates	Adjusted for baseline covariates
Time to death using Week 12 baseline, hazard ratio (tofersen vs placebo to tofersen), 95% CI	0.54 (0.19, 1.56)	0.27 (0.08, 0.89)	0.23 (0.02, 2.89)	0.09 (0.01, 0.8)	0.23 (0.02, 2.89)	0.08 (0.01, 0.79)
Time to transition from Week 12 baseline to later MITOS stages (excluding death) hazard ratio (tofersen vs placebo to tofersen), 95% CI	0.8 (0.44, 1.44)	0.72 (0.39, 1.3)	0.66 (0.22, 1.97)	0.59 (0.23, 1.53)	0.73 (0.32, 1.68)	0.6 (0.25, 1.46)
Time to transition from Week 12 baseline to later King's stages (excluding death) hazard ratio (tofersen vs placebo to tofersen), 95% CI	1 (0.56, 1.79)	0.93 (0.52, 1.67)	1 (0.56, 1.79)	0.88 (0.3, 2.54)	0.98 (0.51, 2.91)	0.88 (0.49, 2.29)

Table 79. Assessment of the RPSFTM common treatment effect assumption from Week 12 baseline

Outcome	Ratio of the treatment effect in the delayed-start group vs the early-start group	Multiplicative factor	RPSFTM hazard ratio (early-start group vs delayed-start group), 95% CI
Time to death			
Time to death	100%	-1.2308	0.0929 (0.0107, 0.8048)
Time to death	90%	-1.2757	0.0877 (0.0096, 0.8006)
Time to death	80%	-1.2506	0.0901 (0.0101, 0.8026)
Time to death	70%	-1.1996	0.0889 (0.0099, 0.8015)
Time to death	60%	-1.1418	0.0887 (0.0098, 0.8014)
Time to death	50%	-1.0550	0.0897 (0.0100, 0.8022)
Time to later MITOS stages			
Time to transition to later MITOS stages	100%	-0.8461	0.5871 (0.2259, 1.5258)
Time to transition to later MITOS stages	90%	-0.8405	0.5883 (0.2263, 1.5294)
Time to transition to later MITOS stages	80%	-0.8241	0.5883 (0.2263, 1.5294)
Time to transition to later MITOS stages	70%	-0.8107	0.5896 (0.2278, 1.5266)
Time to transition to later MITOS stages	60%	-0.8069	0.5896 (0.2278, 1.5266)
Time to transition to later MITOS stages	50%	-0.7836	0.5903 (0.2285, 1.5252)
Time to later King's stages			
Time to transition to later King's stages	100%	-0.2651	0.8771 (0.3029, 2.5394)
Time to transition to later King's stages	90%	-0.2389	0.8734 (0.3138, 2.4310)
Time to transition to later King's stages	80%	-0.2295	0.8734 (0.3138, 2.4310)
Time to transition to later King's stages	70%	-0.2214	0.8764 (0.3232, 2.3765)
Time to transition to later King's stages	60%	-0.2212	0.8764 (0.3232, 2.3765)
Time to transition to later King's stages	50%	-0.2110	0.8795 (0.3331, 2.3223)

Figure 36. Survival curve for time to death from Week 12



Note: The curves for the delayed-start group after adjusting for treatment switching using RPSFTM and IPE are overlapping.

Figure 37. Survival curve for time to transition from Week 12 baseline stage to later MITOS stages (excluding death)

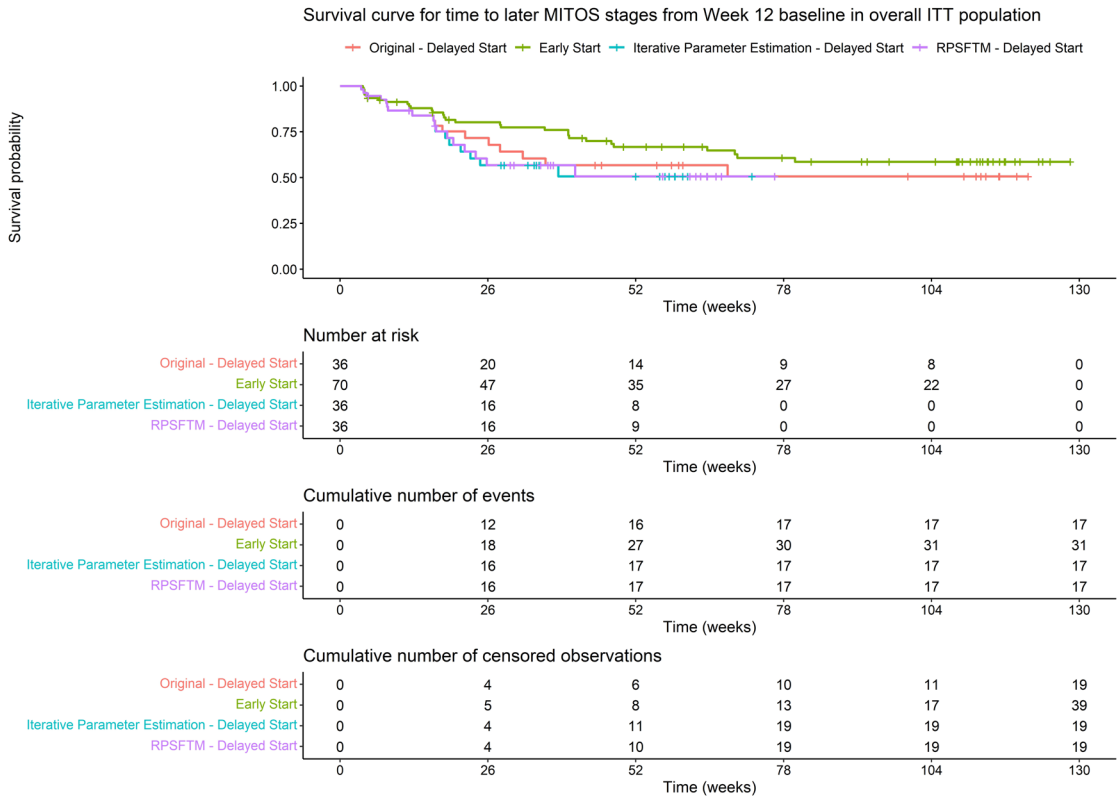
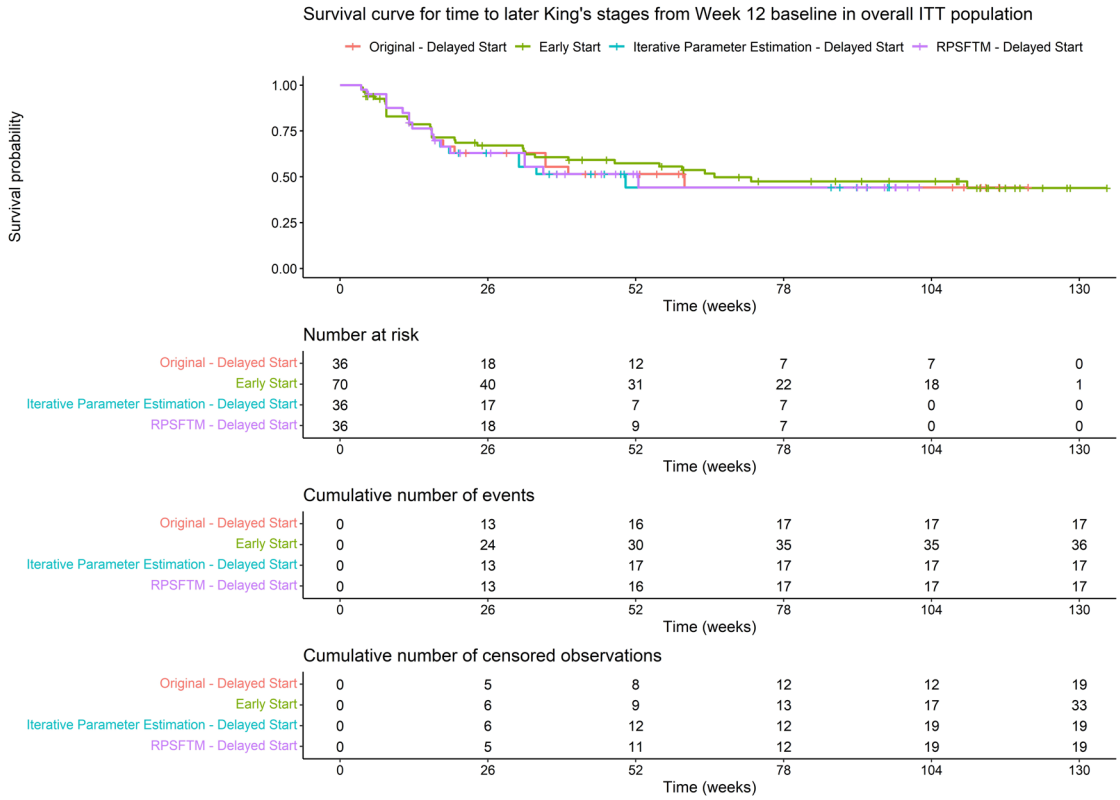


Figure 38. Survival curve for time to transition from Week 12 baseline stage to later King's stages (excluding death)



9. Appendix C. Health State Utilities Identified in a Systematic Literature Review

Twenty-three studies reporting utility values were identified in the economic systematic review. Twenty-one of these 23 studies used the EQ-5D as the instrument to elicit utility weights. Eleven of these 21 studies used EQ-5D-3L, and 10 used EQ-5D-5L. Of these 21 studies, 9 were conducted in the UK [95, 185, 207, 208, 243-247]. Of the remaining studies, 4 were in Germany [88, 248-250]; 2 were in the US [251, 252]; 1 apiece was in Spain [124], Canada [253], China [254], and South Korea [255]; 1 was a multicountry study [256]; and 1 did not report the country (likely to be the US) [257].

Fifteen studies reported health state utility values related to disease severity [88, 124, 185, 207, 208, 243, 246, 248, 250, 252, 254, 255, 257-259]. The definitions of severity used to describe health states varied between studies. Six studies reported utility in accordance with the King's staging [88, 185, 207, 208, 248, 254] and 3 studies reported in accordance with MiToS [207, 208, 246]. Three studies defined the health states in accordance with the ALS Health State Scale, namely mild, moderate, severe, and terminal [243, 255, 259]; 2 were defined by early/late stage of disease [252, 257]; 1 was based on ALS Health State Classification System [258]; 1 was based on low and high severity [124]; and 1 was based on the Amyotrophic Lateral Sclerosis Severity Scale [250].

Overall, higher disease severity was associated with lower utility values. For example, Moore, Young [207] and Stenson, Agnese [208] reported diminishing utility values as health states became more severe using MiToS and King's staging in the UK. Similarly, Peseschkian, Cordts [248] and Schönfelder, Osmanovic [88] show diminishing utility values for health states defined by King's staging in Germany, Jones, Jivraj [185] in the UK, and Wei, Hou [254] in China. Gebrehiwet and Sarocco [246] reported diminishing utility values based on an RCT population using health states defined by MiToS only. For a UK population, Green, Kiebert [243] reported diminishing utility values by ALS HSS and lower utility in patients with ALS at a later stage of their disease based on EQ-5D (as opposed to standard gamble). For the ALS population in Germany, Winter, Schepelmann [250] reported a mean utility of 0.54, where pronounced HRQoL impairment was related to physical health and motor symptoms and the treatment of depression was found to be an independent predictor of HRQoL. Kiebert, Green [259] also reported a consistent pattern of lower HRQoL associated with higher levels of disease severity for an ALS population in the UK using the standard gamble method, with utility values ranging from 0.79 (level 1) to 0.45 (level 4).

10. Appendix D. Results of Review on Studies Reporting Natural History/Prognostic Outcomes

In addition to reviewing the studies reporting outcomes related to economic evaluations, an attempt was made to identify and summarize specific outcomes on natural history and prognostics in ALS in the economic systematic review. Specifically, the review focused on outcomes such as transition probabilities and AEs, ALSFRS-R, and outcomes related to tracheostomy, ventilation, and overall survival.

Of the 82 studies extracted as part of the economic SLR (eSLR), 44 reported relevant outcomes in natural history and prognostics (Table 80). Of these 44 studies, 3 were based in the UK, 1 compared diaphragm pacing system plus standard care compared with SoC, where SoC was noninvasive ventilation (NIV) [244], another compared riluzole with placebo [260], and the third compared the multidisciplinary team with general care [170]. There were 2 additional multicountry studies that included patients from the UK, comparing riluzole with SoC [261] and dexpramipexole with placebo [159].

Three studies reported transition probabilities by health states, 2 of which were based on King's staging and PRO-ACT database, Thakore, Lapin [189] in the US (N = 3,199) was used to inform the CADTH [171] in Canada, and Thakore, Lapin [262] (abstract only) (N = 1,903). Tavakoli and Malek [261] was based on predefined health states from a randomized controlled trial (RCT) (N = 954) and reported results for the UK.

10.1. ALSFRS-R

ALSFRS-R outcomes were reported in 27 studies. One of these studies was based in the UK [244], 8 were in the US [159, 263-269], 1 was in Canada [263], and 1 was in Australia [270].

ALSFRS-R outcomes for riluzole, either as a comparator or as part of the placebo arm, were reported in 5 studies [267, 271-274], for which sample sizes ranged from 24 [267] to 1,540 [272]. Four studies reported ALSFRS-R outcomes for edaravone [269, 275-277], for which sample sizes ranged from 29 [276] to 205 [275].

10.2. Overall Survival

Overall survival was reported by 27 studies; 3 of which were UK studies based on treatment arms "DPS plus NIV vs. NIV only" [244], "multidimensional team vs. usual care" [170], and "riluzole vs. placebo" [260]. Two studies reporting overall survival for edaravone [269] and riluzole [278] were based in the US, and a study on ceftriaxone had a combined US and Canada population [263].

In addition to Stewart, Sandercock [260], 11 studies reported overall survival outcomes for riluzole, 9 of which used riluzole as a treatment arm [184, 272, 278-284] and 2 as part of the placebo arm [271, 273]. Overall survival for edaravone was reported in 3 studies in the US [269] and Japan [275, 277].

10.3. Ventilation and Tracheostomy

Four studies used NIV as a treatment arm [244, 283, 285, 286]. All these studies reported survival outcomes; however, only 1 reported ALSFRS-R, together with tracheostomy-free survival and AEs in a UK-based study [244]. Two of the studies had riluzole as part of the treatment arms [283, 286]. Outcomes related to NIV were reported in 2 other studies [170, 282]. One of these studies, which relied on a source paper with 417 patients diagnosed with MND for median time on NIV, was in the UK [170]. The other study on NIV (abstract only, Sabtos, Gromicho [282]) reported percentage of riluzole patients on NIV in a longitudinal, retrospective study in Portugal. For noninvasive positive

pressure ventilation (NPPV), percentage of edaravone patients were reported in a retrospective study in Japan [277].

Tracheostomy-related outcomes were reported in 2 studies in the form of combined survival from onset to death or tracheostomy [286], tracheostomy-free survival [244], and the number/percentage of patients who experienced tracheostomy [275].

The combined outcome of "death, tracheostomy, intubation with artificial ventilation, or 23-hour NPPV" was reported in a phase 2/3 RCT on omigapil (TCH346) [287]. Maximum voluntary ventilation outcomes were reported in 2 studies on tirasemtiv [267, 288] but were not extracted, because it was not an outcome of interest.

10.4. Adverse Events

Adverse event rates were reported in 20 studies, most of which have reported AE rates related to respiratory, gastrointestinal, and musculoskeletal systems. Two of these 20 studies were based in the UK [244, 260], 5 in the US [264, 265, 267, 269, 289], and 1 in Australia [270]; no study reported AE rates for Canada. The sample sizes of these studies ranged from 20 [270] to 108 [244].

Adverse events for riluzole (for 200 mg, 100 mg, and 50 mg doses) were reported in Stewart, Sandercock [260]; in addition, relevant outcomes were reported for riluzole as an add-on therapy in the placebo arms of 3 studies [Lenglet, Lacomblez [273] based on a multicountry RCT; Shefner, Watson [267] based on a randomized study in the US; Beghi, Pupillo [271] based on an RCT in Italy]. McDermott, Bradburn [244] was the other study based in the UK and reported adverse rates for NIV based on an RCT. Adverse events on edaravone were reported in retrospective studies in the US [269] and Japan [277], and in a cohort study in Germany [276].

10.5. Summary of studies

See Table 80.

Table 80. Summary Table for Studies Included at Level 2 Screening Reporting Natural History Outcomes

No.	Search ID	Reference	Country	Sample size	Interventions	ALSFRS-R	OS	Other outcomes reported	Staging system
1	96	Thakore, Lapin [189]	PRO-ACT database	3,199	NR			Transition probabilities	King's
2	133	Okada, Yamashita [277]	Japan	57	Edaravone vs. no edaravone	✓	✓	Discontinuation; NPPV use	
3	256	Fávero, Voos [280]	Brazil	578	Riluzole vs. no treatment		✓		
4	326	Calvo, Moglia [286]	Italy	2,648	Riluzole vs. no treatment; NIV vs. no NIV			Survival from onset to death or tracheostomy	
5	357	Chen, Liu [272]	China	1,540	Riluzole vs. no riluzole	✓	✓		
6	387	McDermott, Bradburn [244]	UK	108	DPS plus NIV vs. NIV only	✓	✓	AEs; tracheostomy-free survival	
7	446	Shamshiri, Fatehi [274]	Iran	358	Riluzole vs. no riluzole	✓			
8	516	Oh, An [186]	Korea	151	NR	✓			
9	543	Cetin, Rath [279]	Austria	911	Riluzole vs. no riluzole		✓		
10	692	Rudnicki, Berry [266]	US	92	Dexpramipexole (300 mg/day vs. 50 mg/day)	✓			
11	735	Dupuis, Dengler [290]	Germany	219	Pioglitazone vs. placebo	✓	✓	AEs	
12	957	Sivori, Rodriguez [283]	Argentina	97	Riluzole + NIV vs. riluzole + no NIV vs. no riluzole + NIV vs. no riluzole + no NIV		✓		
13	1047	Paillisse, Lacomblez [281]	France	2,069	Riluzole		✓		
14	1096	Traynor, Alexander [284]	Ireland	264	Riluzole vs. no riluzole		✓		
15	1147	Tavakoli and Malek [261]	Multicountry	954	Riluzole vs. usual care			Transition probabilities	Defined based on ALS HSS
16	1425	Meininger, Genge [256]	Multicountry	307	Ozanezumab vs. placebo		✓	AEs	
17	1667	Cudkowicz, Shefner [291]	US	300	Celecoxib vs. placebo	✓			

18	1670	Piepers, Veldink [292]	Netherlands	163	Valproic acid vs. placebo	✓	✓	AEs	
19	1683	Pascuzzi, Shefner [289]	US	59	Talampanel vs. placebo			AEs	
20	1684	Lauria, Dalla Bella [293]	Italy	200	rhEPO vs. placebo	✓	✓		
21	1687	Lenglet, Lacomblez [273]	Multicountry	512	Olesoxime vs. placebo (riluzole add-on)	✓	✓	AEs	
22	1690	Park, Vucic [270]	Australia	54	Flecainide vs. placebo	✓		AEs	
23	1697	Beghi, Chiò [294]	Switzerland	61	Interferon beta-1a vs. placebo			AEs	
24	1699	Nagata, Ogino [295]	Japan	36	Bromocriptine mesylate vs. placebo	✓		AEs	
25	1703	Cudkowicz, van den Berg [296]	Multicountry	934	Dexpramipexole vs. placebo	✓	✓	AEs	
26	1705	Shefner, Watson [267]	US	24	Tirasemtiv (with and without riluzole) vs. placebo (with and without riluzole)	✓		AEs; maximum voluntary ventilation	
27	1707	Edaravone ALS 16 Study Group [275]	Japan	205	Edaravone vs. placebo	✓	✓	Tracheotomy	
28	1711	Shefner, Wolff [288]	Multicountry	711	Tirasemtiv vs. placebo	✓		AEs; maximum voluntary ventilation	
29	1712	Cudkowicz, Titus [263]	US and Canada	541	Ceftriaxone vs. placebo	✓	✓		
30	1715	Ahmadi, Agah [297]	Iran	54	Nanocurcumin vs. placebo	✓	✓		
31	1716	Ludolph, Schuster [298]	Germany	252	Rasagiline vs. placebo	✓	✓	AEs	
32	1725	Beghi, Pupillo [271]	Italy	82	Acetyl-L-carnitine vs. placebo (riluzole add-on)	✓	✓	AEs	
33	1726	Weiss, Macklin [268]	US	60	Mexiletine vs. placebo	✓			
34	1727	Levine, Miller [265]	US	20	L-serine vs. placebo	✓		Withdrawals/AEs	
35	1733	Gordon, Cheung [264]	US	60	Celecoxib and creatine vs. minocycline and creatine	✓		AEs	

36	1743	Miller, Bradley [287]	Multicountry	553	Omigapil vs. placebo	✓	✓	AEs; death, tracheostomy, intubation with artificial ventilation, or 23-hour NPPV	
37	1787	Sabtos, Gromicho [282]	Portugal	1,162	Riluzole aged ≥ 80 vs. Riluzole aged < 80		✓	Percentage on NIV	
38	1792	Maier, Spittel [276]	Germany	29	Edaravone	✓		AEs	
39	1808	Thakore, Lapin [262]	PRO-ACT	1,903	Riluzole vs. not riluzole		✓	Transition probabilities	King's
40	1813	Wong and Hoerth [269]	US	53	Edaravone	✓	✓	AEs	
41	1849	Brooks, Bravver [285]	Unclear	51	NIV vs. no NIV		✓	Discontinuation	
42	IS14	National Clinical Guideline Centre UK [170]	UK		Multidimensional team vs. usual care		✓	Transition probabilities; median time by health state and on NIV	Defined based on literature
43	HS1	Brooks, Belden [278]	US	469	Riluzole-treated (1996 onwards vs. before 1996) vs. untreated		✓		
44	HS2	Stewart, Sandercock [260]	UK	NR	Riluzole vs. placebo		✓	AEs	
Total						27	27	29	4

AE = adverse event; ALS = amyotrophic lateral sclerosis; ALSFRS-R = Functional Rating Scale - Revised; DPS = diaphragm pacing stimulator; HSS = Health State Scale; ID = identifier; NIV = noninvasive ventilation; NPPV = noninvasive positive pressure ventilation; NR = not reported; OS = overall survival; PRO-ACT = Pooled Resource Open-Access ALS Clinical Trials; rhEPO = recombinant human erythropoietin; UK = United Kingdom; US = United States.

11. Appendix E. Clinical Systematic Literature Review

Please see attached file “cSLR of Tofersen in ALS”.

12. Appendix F – Key baseline characteristics stratified by NfL

Table 81. Baseline characteristics stratified by NfL

	"Faster progressing" ≥ median NfL population (N=60) (≥ median NfL=75.60 pg/mL)		"Slower progressing" < median NfL population (N=48) (<median NfL=75.60 pg/mL)	
	Placebo (n=16)	**tofersen 100 mg (n=38)**	**Placebo (n=20)**	**tofersen 100 mg (n=34)**
riluzole Use n (%)	11 (69)	21 (55)	11 (55)	24 (71)
Edaravone Use* n (%)	1 (6)	2 (5)	2 (10)	4 (12)
Time from symptom onset (m) median Range: min, max	10.3 2.4, 30.3	8.9 2.3, 59.9	31.7 3.0, 103.2	28.9 1.7, 145.7
Plasma NfL mean (SD) Range: min, max	160.3 (85.5) 78, 370	159.4 (73.7) 78, 329	33.1 (20.9) 8, 70	36.2 (21.9) 5, 74
ALSFRS-R baseline total score mean (SD)	34.5 (5.8)	36.4 (6.6)	39.6 (4.9)	37.5 (5.1)
% predicted SVC at baseline mean (SD)	81.8 (19.6)	82.6 (17.2)	87.8 (13.5)	81.5 (16.2)

Abbreviations: ALFFRS-R = The Revised Amyotrophic Lateral Sclerosis Functional Rating Scale; NfL = neurofilament; SD = standard deviation; SVC = slow vital capacity

Source: Miller et al. NEJM 2022;187:1099-110 [18].

13. Appendix G. Parameter distributions applied in the probabilistic sensitivity analyses

Parameter	Distribution	Alpha/Mean	Beta/SE
Mean age at baseline	Normal	49.10	1.19
Proportion female	Normal	0.43	0.04
HR for *SOD1* ALS	Lognormal	0.26	0.04
HR (Progression) - Tofersen vs. SoC - MiToS	Lognormal	-0.57	0.39
HR (Mortality) - Tofersen vs. SoC - MiToS	Lognormal	-3.12	1.28
Baseline distribution, % in HS0	Gamma/Dirichlet	100.00	75.00
Baseline distribution, % in HS1	Gamma/Dirichlet	100.00	21.30
Baseline distribution, % in HS2	Gamma/Dirichlet	100.00	2.78
Baseline distribution, % in HS3	Gamma/Dirichlet	100.00	0.93
Baseline distribution, % in HS4	Gamma/Dirichlet	100.00	0.00
Transition probability, month 0-12, HS0 → HS0	Gamma/Dirichlet	17,554.00	15,889.74
Transition probability, month 0-12, HS0 → HS1	Gamma/Dirichlet	17,554.00	1,369.38
Transition probability, month 0-12, HS0 → HS2	Gamma/Dirichlet	17,554.00	219.11
Transition probability, month 0-12, HS0 → HS3	Gamma/Dirichlet	17,554.00	32.47
Transition probability, month 0-12, HS0 → HS4	Gamma/Dirichlet	17,554.00	5.40
Transition probability, month 0-12, HS0 → HS5	Gamma/Dirichlet	17,554.00	37.90
Transition probability, month 0-12, HS1 → HS0	Gamma/Dirichlet	8,856.00	264.68
Transition probability, month 0-12, HS1 → HS1	Gamma/Dirichlet	8,856.00	7,725.61
Transition probability, month 0-12, HS1 → HS2	Gamma/Dirichlet	8,856.00	583.83
Transition probability, month 0-12, HS1 → HS3	Gamma/Dirichlet	8,856.00	116.03
Transition probability, month 0-12, HS1 → HS4	Gamma/Dirichlet	8,856.00	27.32
Transition probability, month 0-12, HS1 → HS5	Gamma/Dirichlet	8,856.00	138.53
Transition probability, month 0-12, HS2 → HS0	Gamma/Dirichlet	2,420.00	9.72
Transition probability, month 0-12, HS2 → HS1	Gamma/Dirichlet	2,420.00	129.77

Transition probability, month 0-12, HS2 → HS2	Gamma/Dirichlet	2,420.00	1,975.52
Transition probability, month 0-12, HS2 → HS3	Gamma/Dirichlet	2,420.00	140.79
Transition probability, month 0-12, HS2 → HS4	Gamma/Dirichlet	2,420.00	50.31
Transition probability, month 0-12, HS2 → HS5	Gamma/Dirichlet	2,420.00	113.88
Transition probability, month 0-12, HS3 → HS0	Gamma/Dirichlet	721.00	0.22
Transition probability, month 0-12, HS3 → HS1	Gamma/Dirichlet	721.00	5.59
Transition probability, month 0-12, HS3 → HS2	Gamma/Dirichlet	721.00	29.27
Transition probability, month 0-12, HS3 → HS3	Gamma/Dirichlet	721.00	558.84
Transition probability, month 0-12, HS3 → HS4	Gamma/Dirichlet	721.00	66.27
Transition probability, month 0-12, HS3 → HS5	Gamma/Dirichlet	721.00	60.81
Transition probability, month 0-12, HS4 → HS0	Gamma/Dirichlet	396.00	0.00
Transition probability, month 0-12, HS4 → HS1	Gamma/Dirichlet	396.00	0.24
Transition probability, month 0-12, HS4 → HS2	Gamma/Dirichlet	396.00	2.20
Transition probability, month 0-12, HS4 → HS3	Gamma/Dirichlet	396.00	12.75
Transition probability, month 0-12, HS4 → HS4	Gamma/Dirichlet	396.00	338.91
Transition probability, month 0-12, HS4 → HS5	Gamma/Dirichlet	396.00	41.89
Transition probability, month 12-24, HS0 → HS0	Gamma/Dirichlet	14,986.00	13,240.41
Transition probability, month 12-24, HS0 → HS1	Gamma/Dirichlet	14,986.00	1,138.39
Transition probability, month 12-24, HS0 → HS2	Gamma/Dirichlet	14,986.00	182.16
Transition probability, month 12-24, HS0 → HS3	Gamma/Dirichlet	14,986.00	27.00
Transition probability, month 12-24, HS0 → HS4	Gamma/Dirichlet	14,986.00	4.49
Transition probability, month 12-24, HS0 → HS5	Gamma/Dirichlet	14,986.00	393.55
Transition probability, month 12-24, HS1 → HS0	Gamma/Dirichlet	8,269.00	221.15
Transition probability, month 12-24, HS1 → HS1	Gamma/Dirichlet	8,269.00	6,518.55
Transition probability, month 12-24, HS1 → HS2	Gamma/Dirichlet	8,269.00	487.73
Transition probability, month 12-24, HS1 → HS3	Gamma/Dirichlet	8,269.00	96.96

Transition probability, month 12-24, HS1 → HS4	Gamma/Dirichlet	8,269.00	22.83
Transition probability, month 12-24, HS1 → HS5	Gamma/Dirichlet	8,269.00	921.79
Transition probability, month 12-24, HS2 → HS0	Gamma/Dirichlet	2,379.00	8.46
Transition probability, month 12-24, HS2 → HS1	Gamma/Dirichlet	2,379.00	112.87
Transition probability, month 12-24, HS2 → HS2	Gamma/Dirichlet	2,379.00	1,737.65
Transition probability, month 12-24, HS2 → HS3	Gamma/Dirichlet	2,379.00	122.45
Transition probability, month 12-24, HS2 → HS4	Gamma/Dirichlet	2,379.00	43.76
Transition probability, month 12-24, HS2 → HS5	Gamma/Dirichlet	2,379.00	353.82
Transition probability, month 12-24, HS3 → HS0	Gamma/Dirichlet	718.00	0.20
Transition probability, month 12-24, HS3 → HS1	Gamma/Dirichlet	718.00	4.94
Transition probability, month 12-24, HS3 → HS2	Gamma/Dirichlet	718.00	25.81
Transition probability, month 12-24, HS3 → HS3	Gamma/Dirichlet	718.00	498.48
Transition probability, month 12-24, HS3 → HS4	Gamma/Dirichlet	718.00	58.43
Transition probability, month 12-24, HS3 → HS5	Gamma/Dirichlet	718.00	130.14
Transition probability, month 12-24, HS4 → HS0	Gamma/Dirichlet	396.00	0.00
Transition probability, month 12-24, HS4 → HS1	Gamma/Dirichlet	396.00	0.21
Transition probability, month 12-24, HS4 → HS2	Gamma/Dirichlet	396.00	1.92
Transition probability, month 12-24, HS4 → HS3	Gamma/Dirichlet	396.00	11.10
Transition probability, month 12-24, HS4 → HS4	Gamma/Dirichlet	396.00	298.44
Transition probability, month 12-24, HS4 → HS5	Gamma/Dirichlet	396.00	84.33
Transition probability, month 24+, HS0 → HS0	Gamma/Dirichlet	14,986.00	13,240.41
Transition probability, month 24+, HS0 → HS1	Gamma/Dirichlet	14,986.00	1,138.39
Transition probability, month 24+, HS0 → HS2	Gamma/Dirichlet	14,986.00	182.16
Transition probability, month 24+, HS0 → HS3	Gamma/Dirichlet	14,986.00	27.00
Transition probability, month 24+, HS0 → HS4	Gamma/Dirichlet	14,986.00	4.49
Transition probability, month 24+, HS0 → HS5	Gamma/Dirichlet	14,986.00	393.55

Transition probability, month 24+, HS1 → HS0	Gamma/Dirichlet	8,269.00	221.15
Transition probability, month 24+, HS1 → HS1	Gamma/Dirichlet	8,269.00	6,518.55
Transition probability, month 24+, HS1 → HS2	Gamma/Dirichlet	8,269.00	487.73
Transition probability, month 24+, HS1 → HS3	Gamma/Dirichlet	8,269.00	96.96
Transition probability, month 24+, HS1 → HS4	Gamma/Dirichlet	8,269.00	22.83
Transition probability, month 24+, HS1 → HS5	Gamma/Dirichlet	8,269.00	921.79
Transition probability, month 24+, HS2 → HS0	Gamma/Dirichlet	2,379.00	8.46
Transition probability, month 24+, HS2 → HS1	Gamma/Dirichlet	2,379.00	112.87
Transition probability, month 24+, HS2 → HS2	Gamma/Dirichlet	2,379.00	1,737.65
Transition probability, month 24+, HS2 → HS3	Gamma/Dirichlet	2,379.00	122.45
Transition probability, month 24+, HS2 → HS4	Gamma/Dirichlet	2,379.00	43.76
Transition probability, month 24+, HS2 → HS5	Gamma/Dirichlet	2,379.00	353.82
Transition probability, month 24+, HS3 → HS0	Gamma/Dirichlet	718.00	0.20
Transition probability, month 24+, HS3 → HS1	Gamma/Dirichlet	718.00	4.94
Transition probability, month 24+, HS3 → HS2	Gamma/Dirichlet	718.00	25.81
Transition probability, month 24+, HS3 → HS3	Gamma/Dirichlet	718.00	498.48
Transition probability, month 24+, HS3 → HS4	Gamma/Dirichlet	718.00	58.43
Transition probability, month 24+, HS3 → HS5	Gamma/Dirichlet	718.00	130.14
Transition probability, month 24+, HS4 → HS0	Gamma/Dirichlet	396.00	0.00
Transition probability, month 24+, HS4 → HS1	Gamma/Dirichlet	396.00	0.21
Transition probability, month 24+, HS4 → HS2	Gamma/Dirichlet	396.00	1.92
Transition probability, month 24+, HS4 → HS3	Gamma/Dirichlet	396.00	11.10
Transition probability, month 24+, HS4 → HS4	Gamma/Dirichlet	396.00	298.44
Transition probability, month 24+, HS4 → HS5	Gamma/Dirichlet	396.00	84.33
Patient utility, HS0	Beta	1,403.29	573.17
Patient utility, HS1	Beta	375.24	406.51
Patient utility, HS2	Beta	63.64	113.14

Patient utility, HS3	Beta	66.67	135.36
Patient utility, HS4	Beta	5.63	16.89
Carer utility, HS0	Beta	100.78	18.49
Carer utility, HS1	Beta	20.75	5.52
Carer utility, HS2	Beta	29.86	11.85
Carer utility, HS3	Beta	16.61	5.54
Carer utility, HS4	Beta	8.74	3.45
Number of carers, HS0	Normal	1.00	0.10
Number of carers, HS1	Normal	1.00	0.10
Number of carers, HS2	Normal	1.00	0.10
Number of carers, HS3	Normal	1.00	0.10
Number of carers, HS4	Normal	1.00	0.10
AE disutility - Limb pain and back pain	Beta	99.27	13,688.62
AE disutility - Radiculitis	Beta	99.27	13,688.62
AE disutility - Myelitis	Beta	99.27	13,688.62
AE duration - Limb pain and back pain	Normal	7.00	0.70
AE duration - Radiculitis	Normal	7.00	0.70
AE duration - Myelitis	Normal	7.00	0.70