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.

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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.

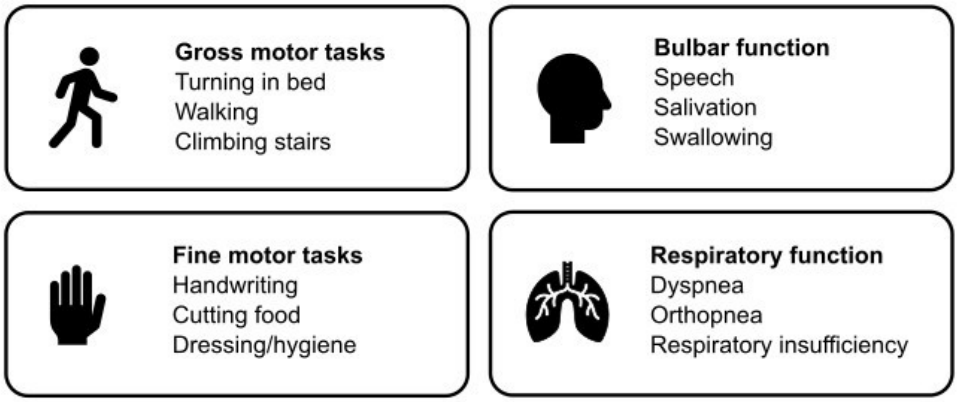

Figure 1: Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised (ALSFRS-R) questionnaire domains and their question topics.

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.

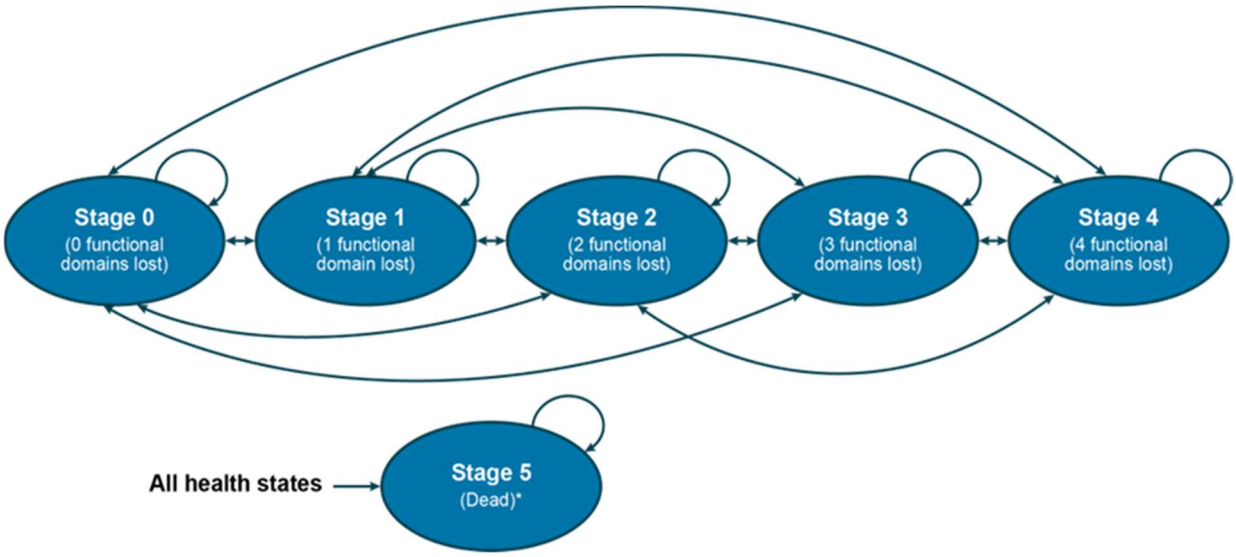

Figure 2: Markov model structure based on MiToS functional classification system (FCS).

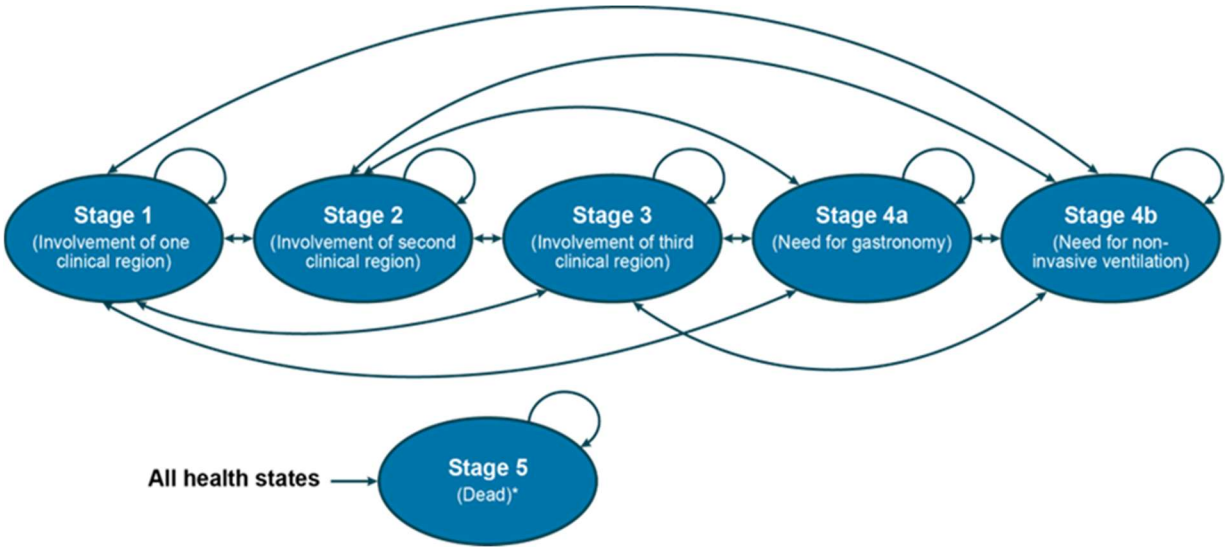

Figure 3: Markov model structure based on King's clinical staging system (CSS).

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).

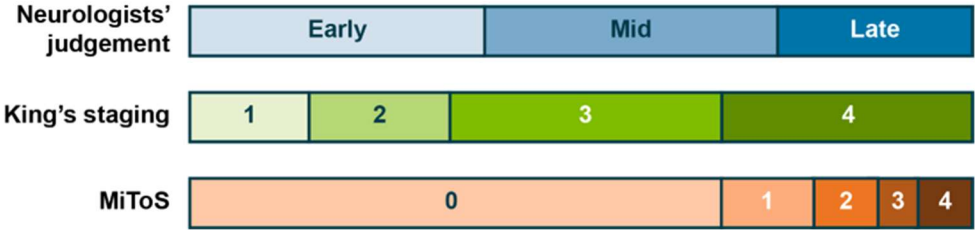

Figure 4: Illustration of How Staging Systems Correspond to Each Another

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).

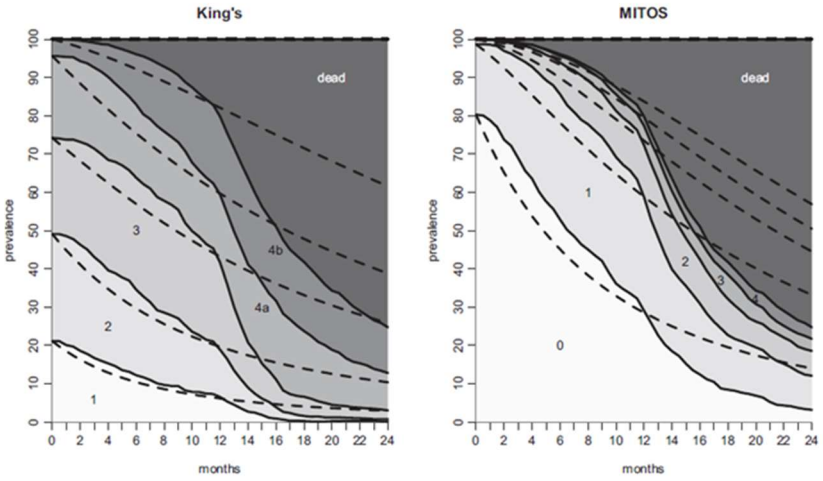

Figure 5: Stacked prevalence plots of stages and death for each system over the first 24 months of observation (49) before calibration. The shaded areas depict observed prevalences, whereas areas separated by dashed lines depict modeled prevalences employing time-homogeneous Markov models.

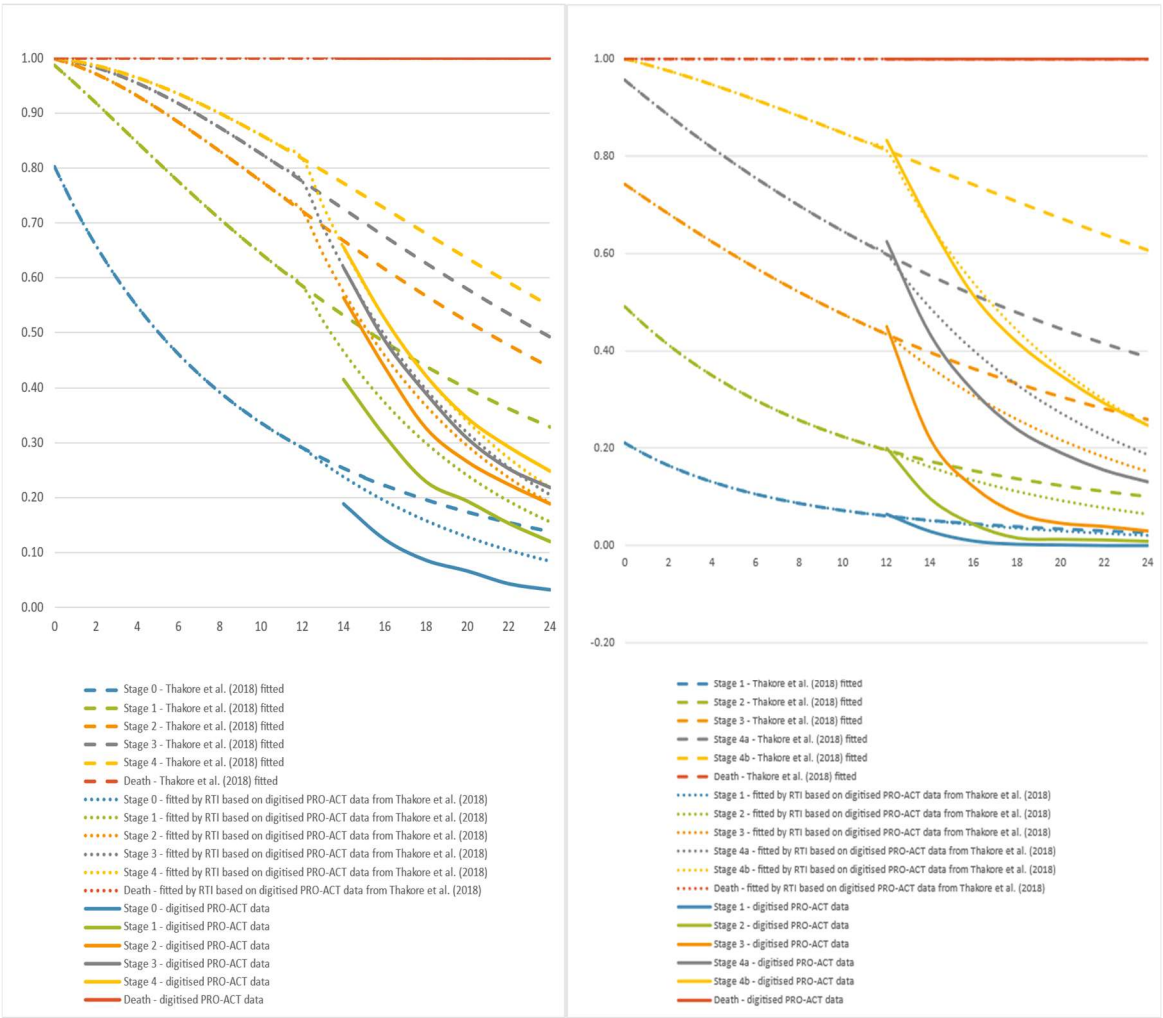

Figure 6: Stacked prevalence plots of stages and death estimated after calibration; MiToS on the left, King's on the right. The dashed lines depict modeled prevalences pre-calibration, the dotted lines depict modeled prevalences post-calibration, and the solid lines depict digitalized PRO-ACT data.

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.

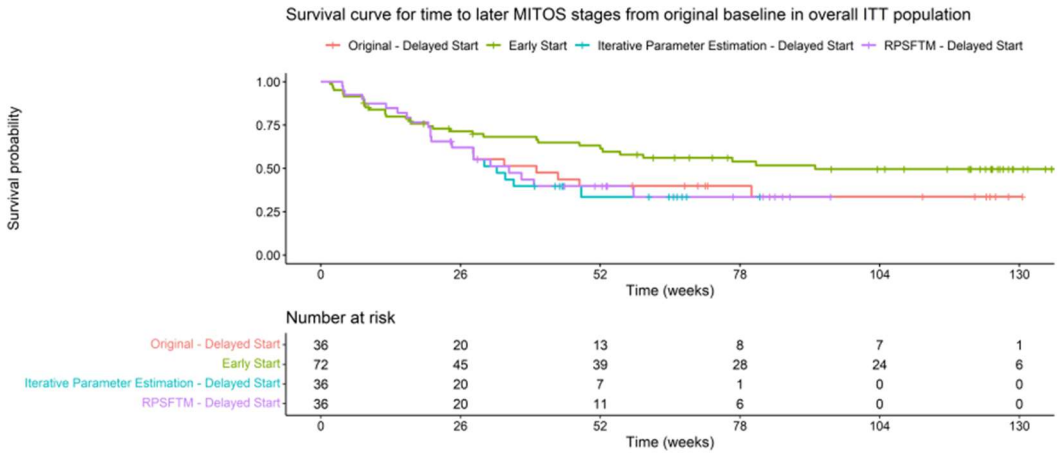

Figure 7: Survival curve for time to transition from VALOR baseline stage to later MiToS stages (excluding death), DCO 2022.

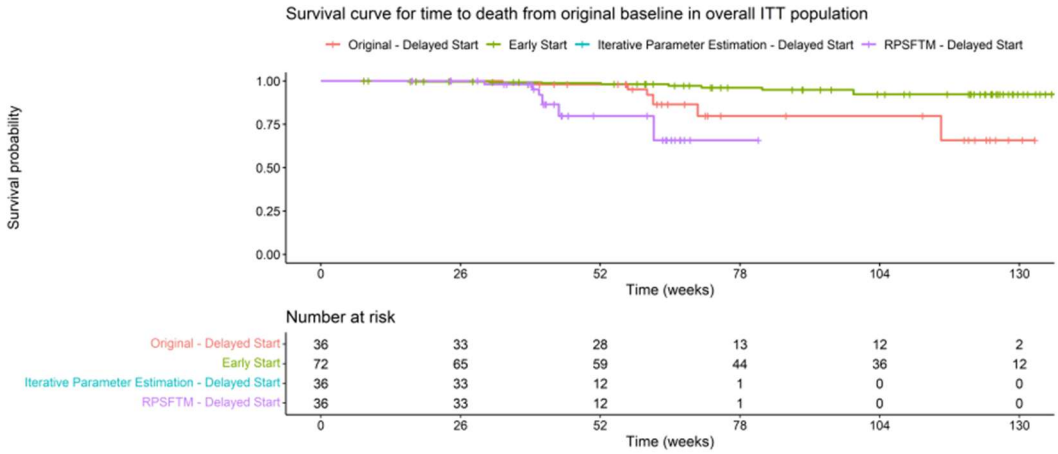

Figure 8: Survival curve for time to death from VALOR baseline, DCO 2022.

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).

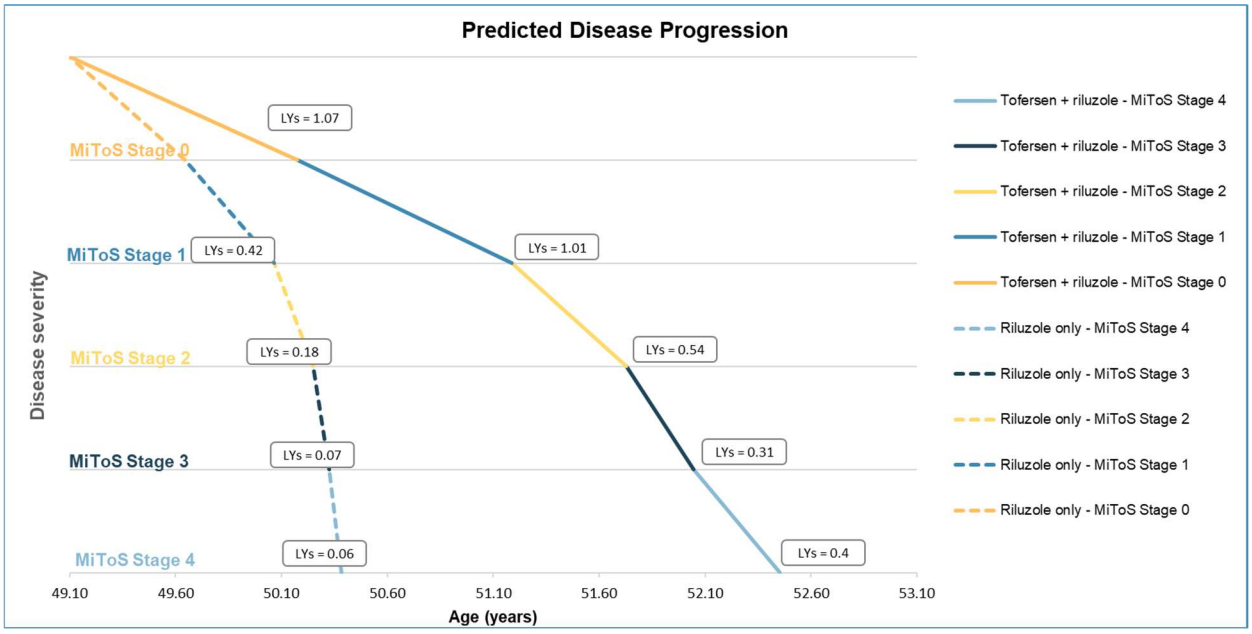

Figure 9: The predicted disease progression in the company's base case. It is calculated by adding the cumulative life years (LYs) accrued per stage to the mean baseline age. In the figure, the LYs accrued per stage are represented by each colored line section and are shown in grey outlined boxes.

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.

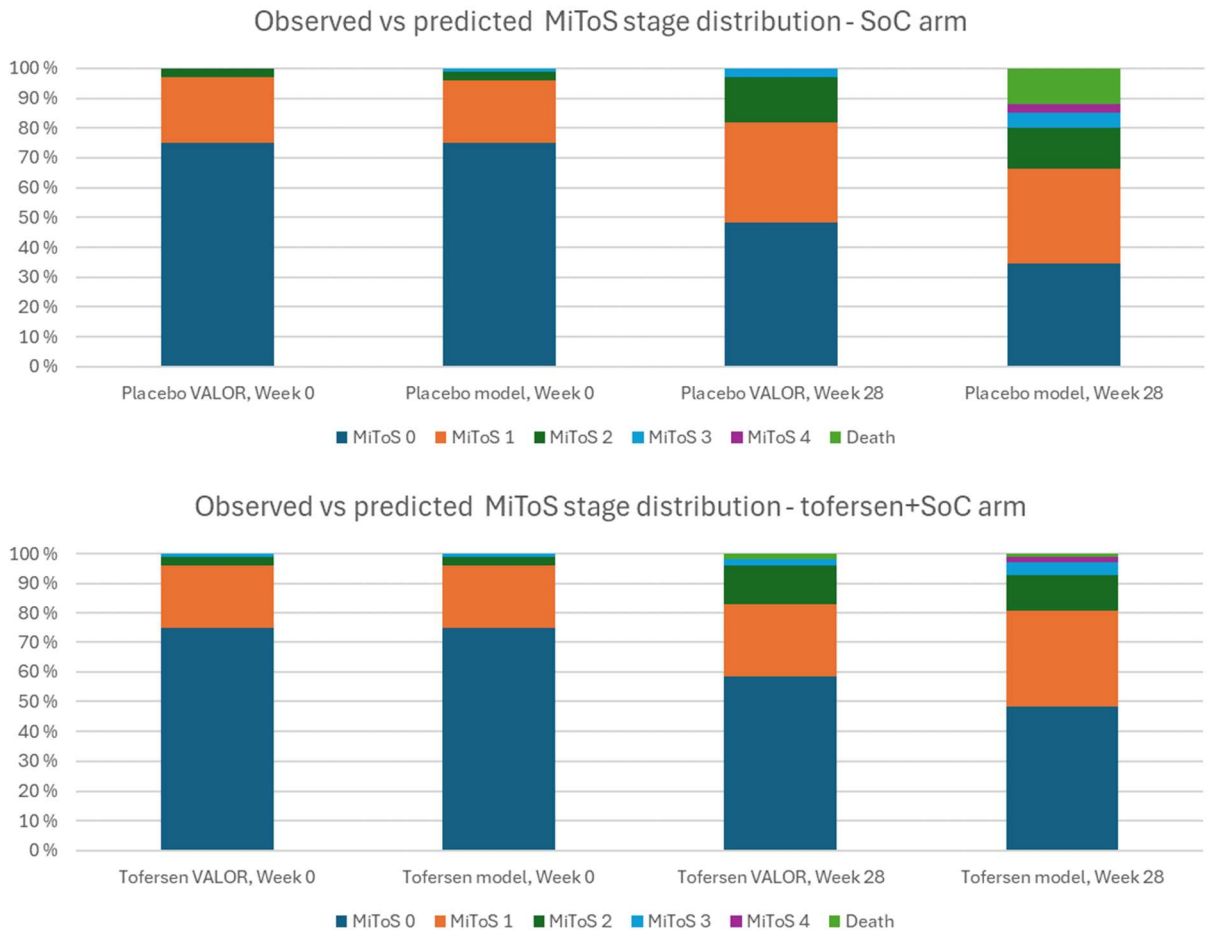

Figure 10: Validation of the model results with MiToS stage distribution observed in the VALOR Part C trial at week 0 and 28. Based on the company's base case.

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).

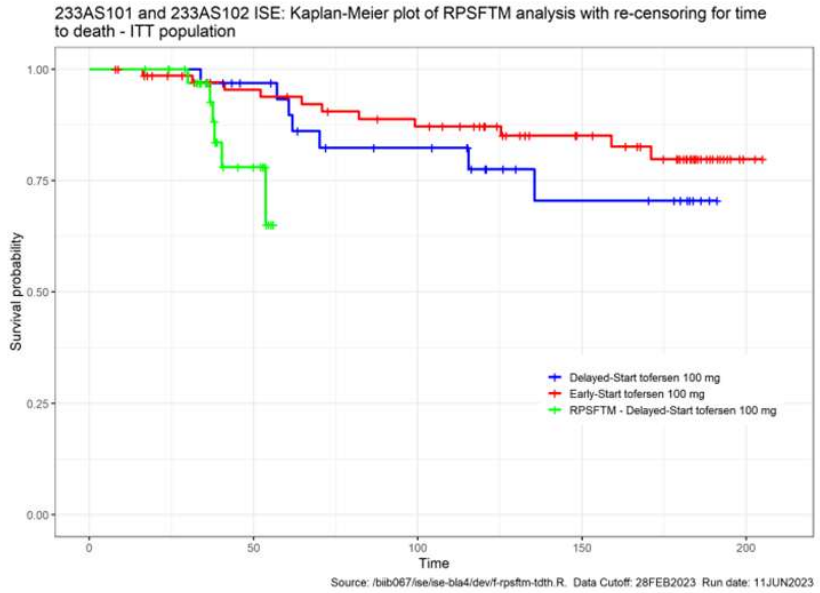

Figure 11: Overall survival observed in VALOR+OLE. Time in months. Datacut 18.02.2023.

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 $|Z| \leq 1.96$.

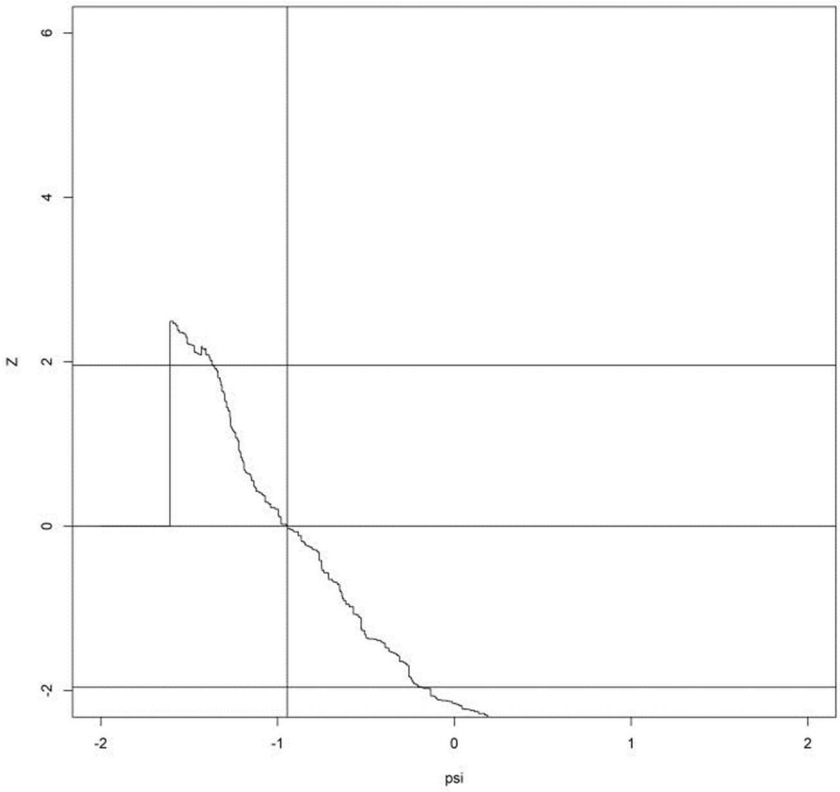

Figure 13 Z Graph plotting the z test statistic against the value of the multiplicative factor identified using RPSFTM for time to death from original baseline in overall ITT population.

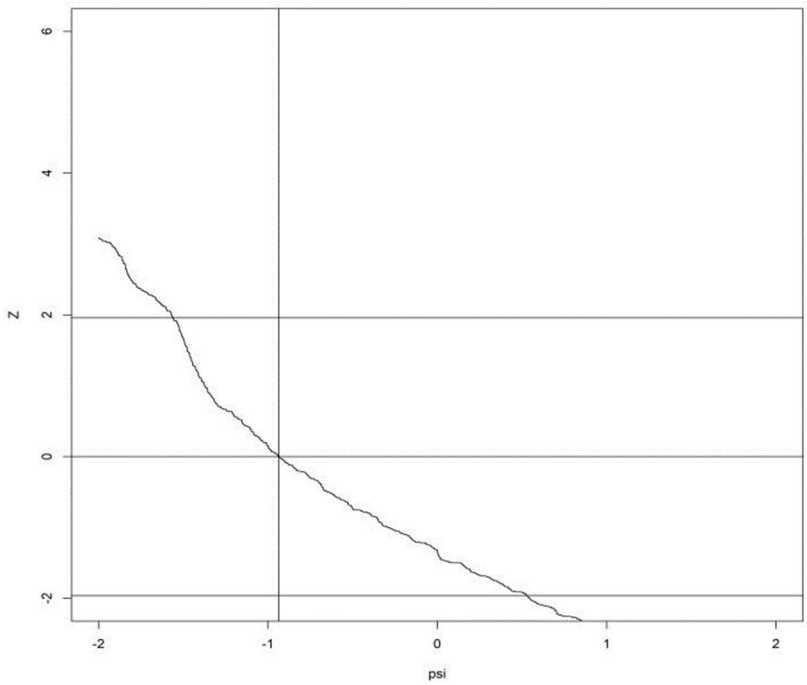

Figure 14 Z Graph plotting the z test statistic against the value of the multiplicative factor identified using RPSFTM for time to later MITOS stages from original baseline in overall ITT population.

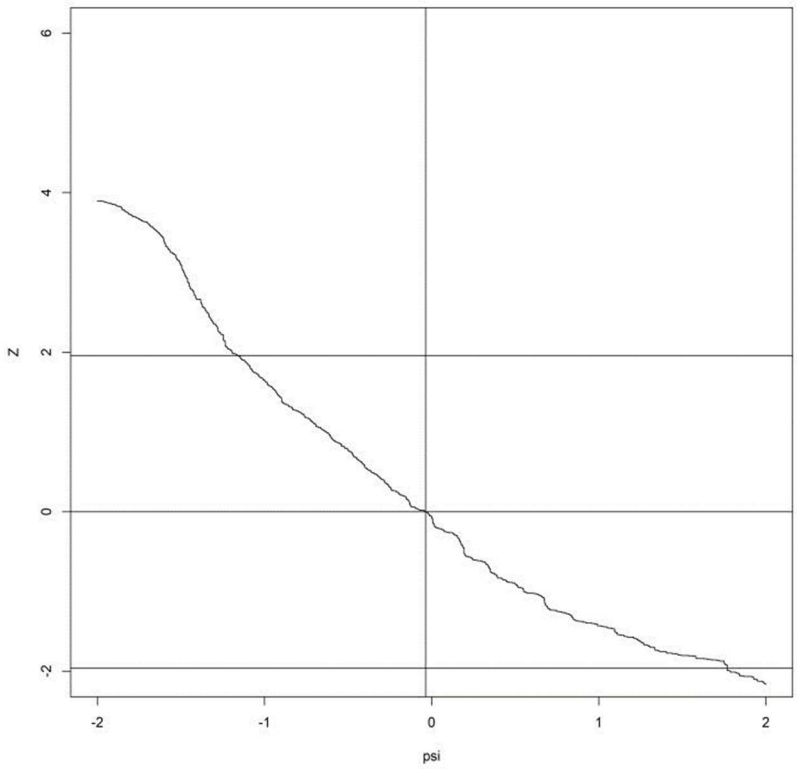

Figure 15 Z Graph plotting the z test statistic against the value of the multiplicative factor identified using RPSFTM for time to later King's stages from original baseline in overall ITT population.

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.

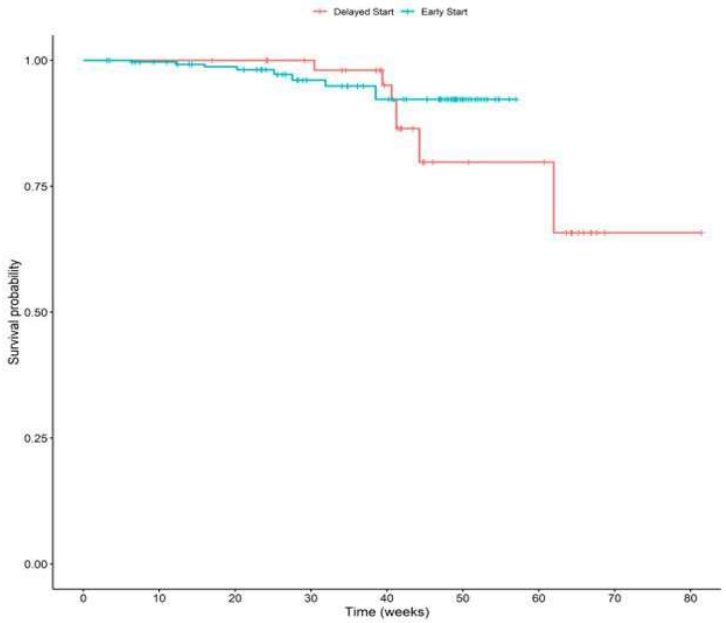

Figure 16 Counterfactual survival curves for time from baseline to death

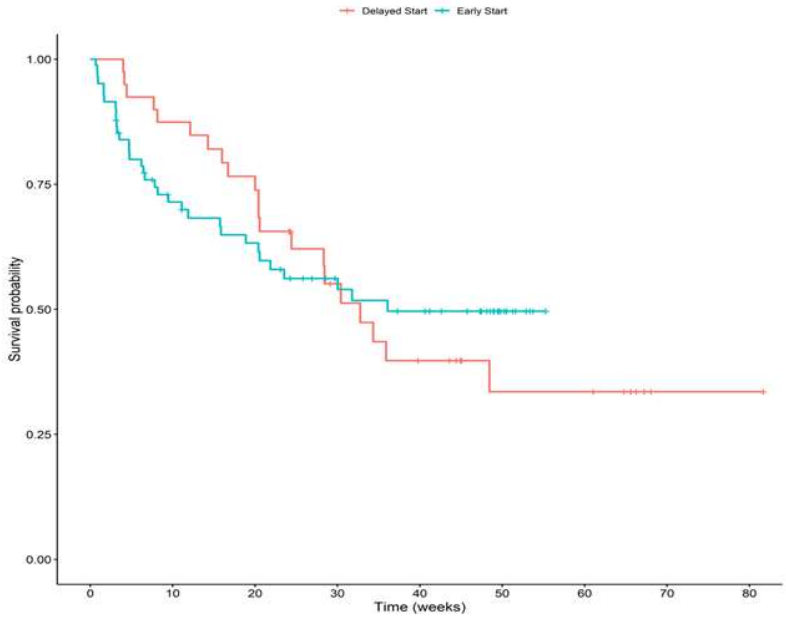

Figure 17 Counterfactual survival curves for time from baseline to later MITOS stages

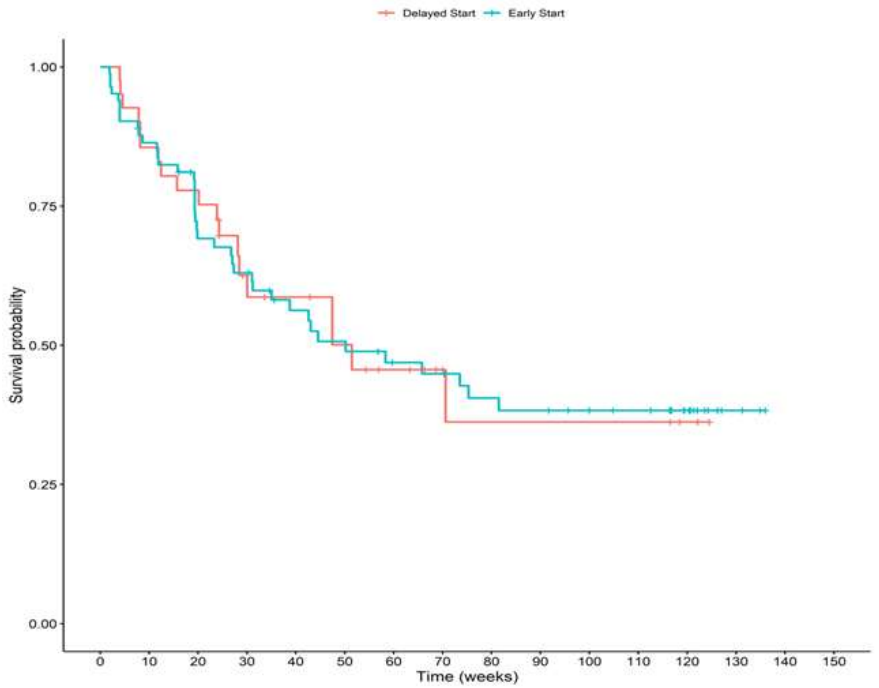

Figure 18 Counterfactual survival curves for time from baseline to later King's stages

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.