National Institute for Health and Care Excellence

Health Technology Evaluation

Tofersen for treating amyotrophic lateral sclerosis caused by SOD1 gene mutations [ID3767]

Response to stakeholder organisation comments on the draft remit and draft scope

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Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	ABN	High specialized Technology Evaluation is the appropriate route for this specialised targets genetic treatment for specific ALS due to SOD mutation as SOD1 ALS is a distinct disease with different neuropathology to ALS/MND in general	Thank you for your comment. The appraisal will be considered in NICE's Highly Specialised Technology program.
	University College London Hospitals NHS Foundation Trust (National Hospital for Neurology and Neurosurgery) /	We strongly support the proposal to evaluate this technology through the HST Evaluation Programme. SOD1-ALS is an ultra-rare condition, accounting for around 2% of all ALS cases. The complexity of intrathecal administration, the specific genetic sub-population, and the specialized multidisciplinary care required align perfectly with the HST criteria.	Thank you for your comment. The appraisal will be considered in NICE's Highly Specialised Technology program.

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	UCL Institute of Neurology		
	Motor Neurone Disease Association	We are content that the highly specialised technology (HST) evaluation is the most appropriate route.	Thank you for your comment. The appraisal will be considered in NICE's Highly Specialised Technology program.
	Biogen	Biogen considers it appropriate for tofersen to be referred to the National Institute for Health and Care Excellence (NICE) under the Highly Specialised Technology (HST) evaluation route. Further details on the rationale behind this decision can be found in the published HST checklist.1	Thank you for your comment. The appraisal will be considered in NICE's Highly Specialised Technology program.
	Genetic Alliance UK	Genetic Alliance UK welcomes the opportunity to comment on this draft scope for tofersen for treating amyotrophic lateral sclerosis (ALS) associated with SOD1 gene mutations. Based on our understanding, and through conversations with our member organisation, the Motor Neurone Disease (MND) Association, the Highly Specialised Technologies evaluation route appears appropriate for the following reasons: Tofersen is intended for a very small, genetically defined subgroup of people with ALS caused by SOD1 mutations, representing around 2% of ALS cases and an estimated 60–100 people living with SOD1-associated MND in the UK (**criterion 1**). SOD1-associated ALS is a rapidly progressive, life-limiting neurodegenerative condition with extremely limited condition-modifying treatment options, representing a high level of unmet clinical need (**criterion 2**). Further, progressive loss of motor function can lead to severe disability, loss of independence and ultimately respiratory failure (**criterion 3**), and	Thank you for your comment. The appraisal will be considered in NICE's Highly Specialised Technology program.

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		evidence shows that tofersen may slow disease progression by targeting the underlying genetic cause of SOD1-associated ALS – so offers a clinically meaningful benefit in a condition with otherwise limited therapeutic options (**criterion 4**).	
	My Name'5 Doddie Foundation	Highly relevant for the HST route, thank you	Thank you for your comment. The appraisal will be considered in NICE's Highly Specialised Technology program.
Wording	ABN	Yes reflects appropriately	Thank you for your comment. No action required.
	University College London Hospitals NHS Foundation Trust (National Hospital for Neurology and Neurosurgery) / UCL Institute of Neurology	The wording of the remit accurately reflects the clinical indication: treating adults with ALS associated with a mutation in the SOD1 gene.	Thank you for your comment. No action required.
	Motor Neurone Disease Association	We consider the wording appropriate.	Thank you for your comment. No action required.

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	Biogen	Biogen agrees with the wording of the remit in the draft scope and agrees that it accurately reflects any considerations around clinical and cost effectiveness regarding the licensing and marketing authorisation for tofersen.	Thank you for your comment. No action required.
	Genetic Alliance UK	No comments	Thank you. No action required.
	My Name'5 Doddie Foundation	It should be considered that as genetic testing coverage and timing improves (as does early diagnosis in general), people with SOD1 mutations will be identified earlier in the disease course, and tofersen can therefore be given much earlier, meaning they may have many more years before they reach a disabled state and begin to require much additional support (if at all). The ATLAS study which is currently ongoing is looking at this and it should be factored into thinking around cost effectiveness.	Thank you for your comment. The committee will consider if there are subgroups in which tofersen is expected to be more effective. The committee will consider all evidence relevant to the evaluation. No action required.
Timing Issues	ABN	Extremely urgent: this is a life limiting condition where most people die within 3 years of diagnosis so any delays in treatment are not acceptable. The incorrect initial routing has already delayed NICE consideration. The UK is outlying with the rest of Europe in not providing this urgent treatment to people living with SOD1 ALS. The FDA granted approval in 2023 and MHRA approval was granted in July 2025.	Thank you for your comment. The appraisal has been scheduled into the NICE work programme.
	University College London Hospitals NHS	The urgency of this evaluation for the NHS is extremely high. SOD1-ALS can be aggressively fast in its progression. Because Tofersen targets the underlying genetic driver of the disease, any delay in access results in	Thank you for your comment. The appraisal has been scheduled

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	Foundation Trust (National Hospital for Neurology and Neurosurgery) / UCL Institute of Neurology	irreversible motor neurone death and devastating functional decline for these patients.	into the NICE work programme.
	Motor Neurone Disease Association	ALS is a progressive, incurable terminal condition. The only disease-modifying therapy currently available through the NHS is riluzole, which has limited effectiveness. There is therefore an urgent unmet need for new therapies which can more effectively slow disease progression and the development of symptoms and extend life. Whilst tofersen has been made available to some people via an Early Access Programme, there are still people missing out. ALS can progress extremely rapidly in some cases, with a third of people dying within 12 months of diagnosis. Potential new therapies should therefore be evaluated as quickly as possible so that, if successful, a new therapy can be offered to as many eligible people as possible. The longer an evaluation is delayed, the more people will have symptoms that progress irreversibly and die from MND who may have benefited from access to the therapy.	Thank you for your comment. The appraisal has been scheduled into the NICE work programme.
	Biogen	There is a high degree of urgency for NICE to undertake a technology appraisal in patients with SOD1-ALS. Individuals with SOD1-ALS, caregivers, patient organisation representatives and clinicians have expressed an urgent need for new and better treatment	Thank you for your comment. The appraisal has been scheduled

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		options, as a subset of patients continue to deteriorate significantly despite receiving the current standard of care, emphasising the ongoing unmet need. This unmet need has been recognised through the designation of tofersen as a Promising Innovative Medicine (PIM) and approval from the Medicines and Healthcare products Regulatory Agency (MHRA) via the International Recognition Procedure (IRP).2 Similarly, the Food and Drug Administration (FDA) in the United States (US) granted tofersen a priority review, and it has subsequently been approved for patients with SOD1-ALS.3, 4 ALS is a progressive neurodegenerative disease that commonly presents as progressive muscle weakness, with SOD1-ALS a serious, debilitating and ultimately life-threatening disease associated with high morbidity and mortality.5-7 Symptoms typically arise in the lower limbs in 56–88% of SOD1 patients, but patients may also present with upper limb symptoms or speech or swallowing problems (bulbar onset).8-10 Motor weakness begins focally but eventually progresses to respiratory paralysis.5 After experiencing this considerable, life-limiting morbidity, ALS is ultimately fatal; for patients with SOD1-ALS, median survival is 2.7 years after disease onset.11 Currently, there is one licensed treatment (riluzole) recommended for individuals with ALS (NICE TA20).12 Despite the positive recommendation, NICE noted that the clinical efficacy results were associated with high levels of uncertainty, and both the statistical methods used and clinical significance of the results were challenged by NICE.12 TA20 concluded that "[..] there remains uncertainty as to the true benefit of riluzole; the confidence interval is wide and compatible with little or no difference between riluzole and placebo. [..]" Even under the most optimistic assumptions, riluzole at best only postpones death for a few months, and does not preclude the need for supportive care and practical help".12 Similar issues were noted in the EMA regulatory review, including "the failure to find any effect on functional endpoints".13 This was corroborated by a Cochrane systematic literature	into the NICE work programme

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		review, which concluded that riluzole had the possibility of prolonging median survival by 2–3 months in patients with ALS, whilst also noting that this improvement was in the absence of any noticeable improvements to strength and disability.14 Relatedly, clinicians consulted in the NICE HST scoping workshop for this submission stated that riluzole is not considered effective, and given the poor survival benefit, it cannot be classed as a satisfactory treatment option.12 Considering the minimal survival benefits, and notable uncertainty associated with riluzole, patients typically receive best supportive care (BSC), with or without riluzole use. BSC includes care from a multidisciplinary team (such as psychological and nutritional support) as well as a range of pharmacological treatments to manage symptoms, such as riluzole.15 Therefore, there is no cure for SOD1-ALS, highlighting the urgent need for an alternative treatment that can extend survival and alleviate the treatment burden.12	
	Genetic Alliance UK	We understand that there are currently very limited treatment options for ALS, and that riluzole is the only NICE-recommended medicine and has modest impact on disease progression. The timing of this evaluation for tofersen is therefore urgent, given the significance of a therapy that may alter the course of a progressive and life-limiting disease for a defined genetic subgroup. We also understand that there are already some people receiving tofersen through early access programmes, but access varies across regions and services, highlighting the need to address this inequity by timely evaluation of this therapy.	Thank you for your comment. The appraisal has been scheduled into the NICE work programme.
	My Name'5 Doddie Foundation	CRITICAL. There is currently a postcode lottery of who can access this life changing treatment. We as a charity have earmarked funding to support delivery infrastructure where required but this is not sustainable and the NHS needs to be in a position to deliver this now.	Thank you for your comment. The appraisal has been scheduled into the NICE work programme.

Section	Stakeholder	Comments [sic]	Action
Additional comments on the draft remit	Biogen	No further comments.	Thank you for your comment. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	ABN	Yes, accurate but “The rate of disease progression varies between individuals dependant on SOD1 gene mutations type.” is not completely accurate. The rate of disease progression in people with SOD1 ALS depends on a number of factors including (but not exclusively) the SOD1 gene variant – this is demonstrated in different rates of progression within the same family.	Thank you for your comment. The background information has been updated to reflect that rate of diseases progression depends on a number of factors including SOD1 gene mutation type.
	University College London Hospitals NHS Foundation Trust (National Hospital for Neurology and Neurosurgery) / UCL Institute of Neurology	The background accurately reflects the epidemiology, noting that SOD1 mutations cause around 15% of familial and 1% of sporadic ALS, totaling 2% of all ALS cases	Thank you for your comment. No action required.

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	Motor Neurone Disease Association	No comments - background information is appropriate. The MND Association estimates that approximately half of people with MND die within two years of diagnosis, and a third within one year. We estimate there are approximately 5000 people with MND in the UK at any one time. Tofersen is specifically targeted only at people living with ALS/MND who have SOD1 gene mutations. This is estimated to be c.2% of the total ALS population, or 60-100 people in the UK at any one time.	Thank you for your comment. No action required.
	Biogen	Biogen considers the information presented in the background section of the draft scope to be accurate for the overall ALS and SOD1-ALS population.	Thank you for your comment. No action required.
	Genetic Alliance UK	No comments	Thank you. No action required.
	My Name'5 Doddie Foundation	You state there is currently no cure. But actually, there aren't even any effective treatments – the only treatment riluzole extends life by only months and is not tolerated by some people with ALS. The unmet need for effective medicines for ALS cannot be over emphasised. More than half die within 2 years of diagnosis, not 3. https://pmc.ncbi.nlm.nih.gov/articles/PMC9068990/	Thank you for your comment. the scope is intended to be a brief summary of the disease and current treatment options. Further details about the effectiveness of current treatment will be gained during the appraisal process. The

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			disease progression statistics have been amended.
Population	ABN	50% die within 2.5 year of symptoms onset NOT 3 years after diagnosis as quoted – this can be significant as diagnostic delay of 12 months is not uncommon (noted in reference 8 in the draft remit).	Thank you for your comment. The disease progression statistics have been amended in the background section.
	University College London Hospitals NHS Foundation Trust (National Hospital for Neurology and Neurosurgery) / UCL Institute of Neurology	The population is appropriately defined as adults with ALS associated with a SOD1 mutation. This correctly focuses on symptomatic patients rather than asymptomatic gene carriers	Thank you for your comment. No action required.
	Motor Neurone Disease Association	This is appropriate	Thank you for your comment. No action required.
	Biogen	The patient population is consistent with the wording for the MHRA and EMA marketing authorisations, and it is consistent with the patient population used in the pivotal VALOR trial and its associated open-label extension (OLE).2, 16-18	Thank you for your comment. No action required.

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	Genetic Alliance UK	No comments	Thank you. No action required.
	My Name'5 Doddie Foundation	Yes. Only ALS patients with SOD1 mutations will be eligible for tofersen.	Thank you. No action required.
Subgroups	ABN	We do not think there are any clinically relevant subgroups Early treatment is likely to be more cost effective ensuring lower level of disability, less need for supportive care including NIV and gastrostomy and increasing likelihood of people remaining economically active.	Thank you for your comment. No action required
	University College London Hospitals NHS Foundation Trust (National Hospital for Neurology and Neurosurgery) / UCL Institute of Neurology	The scope correctly identifies "Stage/severity of the disease" as a subgroup. In clinical practice, the specific SOD1 mutation type dictates the rate of disease progression (e.g. rapid vs. slow progressors). Efficacy may vary depending on how early in the disease trajectory the treatment is initiated.	Thank you for your comment. The subgroups have been updated to include "SOD1 mutation type".
	Motor Neurone Disease Association	The subgroups listed are appropriate. Time to diagnosis should be included as an additional subgroup given the potential of SOD1 testing to aid more rapid diagnosis (and therefore earlier treatment initiation)	Thank you for your comment. Time to diagnosis should already be captured in the proposed "Stage/severity of the

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			disease" subgroup. No action required.
	Biogen	It is Biogen's position that tofersen would be appropriate for **all** patients with ALS associated with a SOD1 mutation (SOD1-ALS). The population of SOD1-ALS is very small, and it is therefore not appropriate to further reduce the population size by considering subgroups in terms of clinical outcomes or cost effectiveness. The background therapy subgroup suggested in the draft scope is inappropriate given that the VALOR trial design was stratified by background therapy and analyses were also adjusted for background therapy. For example, riluzole use was balanced between treatment arms and received by 61% of people in the placebo arm and 62% of people in the tofersen arm.17 Furthermore, as tofersen is expected to be given in addition to BSC (including riluzole) in clinical practice, this subgroup is not clinically relevant for this evaluation. To account for heterogeneity in the progression of SOD1-ALS, the overall intention-to-treat (ITT) population was adjusted for baseline plasma neurofilament light chain (NfL) level, which is a recognised prognostic biomarker of disease progression and survival.19 Additionally, the planned economic model for tofersen in SOD1-ALS will be based on an accepted disease staging system. Overall, the approach to the clinical and economic analyses, using disease stage-based health states with NfL-adjusted clinical efficacy data, ensures that population heterogeneity in SOD1-ALS stage/severity is captured.	Thank you for your comment. The committee will consider all relevant subgroups. No action required.
	Genetic Alliance UK	To our understanding working with the MND Association in our campaigns and advocacy work, that stage or severity of the condition that an individual present with is likely to be important. The progressive nature of ALS and the possibility that earlier intervention could affect outcomes differently from treatment started later in the disease course. We would encourage NICE to consider whether the evidence allows meaningful exploration of earlier and	Thank you for your comment. The committee will consider all relevant subgroups. No action required.

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		later treatment initiation, while recognising that subgroup analyses may be limited by small patient numbers.	
	My Name'5 Doddie Foundation	People diagnosed earlier in the disease course are expected to remain in a fitter state for longer	Thank you for your comment. The committee will consider all relevant subgroups. No action required.
Comparators	ABN	Best supportive care is the only comparator. Tofersen would be first line treatment for people SOD1 ALS	Thank you for your comment. No action required
	University College London Hospitals NHS Foundation Trust (National Hospital for Neurology and Neurosurgery) / UCL Institute of Neurology	Established clinical management without Tofersen, including best supportive care and riluzole, are the correct standard-of-care comparators in the UK	Thank you for your comment. No action required
	Motor Neurone Disease Association	Comparators listed are appropriate.	Thank you for your comment. No action required

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	Biogen	Biogen agrees with the inclusion of BSC (including riluzole if appropriate) as the main comparator to tofersen for patients with SOD1-ALS.	Thank you for your comment. No action required
	Genetic Alliance UK	The comparator appears appropriate. We understand current care to be established clinical management without tofersen, including best supportive care and riluzole where suitable.	Thank you for your comment. No action required
	My Name'5 Doddie Foundation	Yes, however as there is only one licenced drug (riluzole) for ALS, many patients resort to unlicenced medications and 'health compounds'	Thank you for your comment. No action required
Outcomes	ABN	Disease progression needs to be better defined e.g. is this a change in Kings staging, or change in ALSFRS-R or another milestone? Biomarker (serum neurofilament light) were in the VALOR trials and may be of utility as outcome measures to determine response to treatment in combination with clinical outcome measures. Whilst not a clinical outcome, the FDA consider neurofilament light "a surrogate endpoint that is reasonably likely to predict a clinical benefit to patients."	Thank you for your comment. The list of outcomes aims to capture the key aspects of the disease. But is not exhaustive. The committee will consider any additional outcomes included in submissions. No action required.
	University College London Hospitals NHS Foundation Trust (National Hospital for	The listed clinical outcomes (survival, disease progression, time to ventilation, respiratory/nutritional status) are appropriate. However, it is critical to include biomarker outcomes, specifically Neurofilament light chain in CSF and plasma. Tofersen's accelerated regulatory approvals were based on its ability to reduce NfL, which serves as a marker of reduced axonal degeneration.	Thank you for your comment. The list of outcomes aims to capture the key aspects of the disease. But is not exhaustive. The

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	Neurology and Neurosurgery) / UCL Institute of Neurology	Furthermore, standardised functional scales like the ALSFRS-R should be named under "disease progression"	committee will consider any additional outcomes included in submissions. No action required.
	Motor Neurone Disease Association	Outcomes listed are appropriate.	Thank you for your comment. No action required
	Biogen	Biogen considers the outcome measures listed in the draft scope to be appropriate and relevant to individuals with SOD1-ALS. Biogen would like to note that limited data are available on nutritional status following treatment with tofersen, as this was not a pre-specified outcome in the VALOR trial. Baseline body mass index (BMI) data are available from the VALOR trial but follow-up BMI data (as a proxy outcome for nutritional status) are not available. However, the primary endpoint in VALOR of Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised (ALSFRS-R) contains an assessment domain for bulbar function, which includes three items for speech, swallowing and salivation. As such, while nutritional status has not been captured directly, impairment in feeding and swallowing capacity is expected to be captured via the primary endpoint.	Thank you for your comment. No action required
	Genetic Alliance UK	The proposed outcomes are broadly appropriate. To our understanding, tofersen would be used in addition to established clinical management rather than as a replacement for it. Care would still include multidisciplinary support, symptom management, respiratory and nutritional support, mobility aids, communication support and riluzole, where appropriate. In practice, we would expect tofersen to sit within specialist neurology services for a very small subgroup of people with genetically confirmed SOD1-associated ALS.	Thank you for your comment. The committee will consider all health effects for patients and where relevant carers. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Do you consider that the use of tofersen can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? From the patient perspective, and the need for health and social care services use, that modest changes in progression are likely to avert, may still be highly meaningful in a condition where loss of function can be rapid and life-limiting. We would also recommend that NICE give appropriate weight to HRQoL that may not be fully reflected by standard measures alone, including effects on independence, ability to continue work or family roles and the experience of hope or reassurance where progression appears to slow. We would therefore encourage NICE to ensure that the evaluation captures outcomes that matter to people living with SOD1-associated ALS and their families, including whether treatment may stabilise a person's functional ability, slow further deterioration and help people living with the continuation manage and maintain independence for as long as possible.	
	My Name'5 Doddie Foundation	Yes – potentially also consider psychological status if not already included in QoL measurements, as we would expect less depression in treated population	Thank you for your comment. The committee will consider all health effects for patients. No action required
Equality	ABN	This treatment must be available to all living with SOD1 ALS who are consider clinically appropriate and wish to have treatment.	Thank you for your comment. The committee will consider equalities issues during the appraisal.

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		SOD1 ALS mutations are present in all ethnic origins so this diagnosis must be considered in all ethnic groups. There should be no barriers to treatment on the basis of geography and all people must have access to a safe and appropriately staffed neurology service able to deliver and monitoring intrathecal treatment irrespective of location.	
	University College London Hospitals NHS Foundation Trust (National Hospital for Neurology and Neurosurgery) / UCL Institute of Neurology	Given that Tofersen is administered via lumbar puncture, consideration must be given to patients with spinal deformities or respiratory failure who cannot lie flat for the procedure without respiratory support. Ensuring equal access may require provisions for interventional radiology-guided administration under sedation or resovoir ports.	Thank you for your comment. The committee will consider equalities issues during the appraisal.
	Motor Neurone Disease Association	No comments	Thank you for your comment. No action required
	Biogen	Biogen do not consider there to be any issues relating to equality of opportunity.	Thank you for your comment. No action required
	Genetic Alliance UK	We would encourage NICE to consider potential inequalities in access to specialist centres, genetic testing and treatment administration. As we recently highlighted in our Equity report for Rare Disease Day, which was	Thank you for your comment. The

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		synthethesised from a survey with almost 300 respondents from across our community, including people living with MND (see link below), access may be affected by a number of limitations on service provision, including geography and the capacity of local services, which could make it more difficult in practice for some people to receive treatment promptly. For a rapidly progressive neurodegenerative condition, delays in diagnosis, referral or treatment initiation may have a particularly significant impact on the quality of life for people living with this rare condition. https://geneticalliance.org.uk/campaigns-and-research/rare-disease-day/rare-disease-day-2026/	committee will consider equalities issues during the appraisal.
	My Name'5 Doddie Foundation	Tofersen can currently not be delivered if the patient cannot lie flat on their back for 1-2 hours after the treatment has taken place, therefore more disabled people may not be able to receive it. I am just flagging this as there may be a way to consider it.	Thank you for your comment. The committee will consider equalities issues during the appraisal.
Other considerations	ABN	1. The VALOR trial is likely to have significantly underestimated the real-world benefit of Tofersen for people living with SOD1 ALS. In clinical practice we will be treating people earlier in the disease course (incident cases), with Tofersen commenced as soon as possible after a diagnosis of SOD1 ALS is made. The VALOR trial treated enrolled prevalent cases, some of whom had ALS for several years and therefore established disability. This is accentuated by changes in genetic testing practice in the UK, whereby people diagnosed are offered genetic testing typically at the first appointment in the specialist MND clinic.	Thank you for your comments. No action required

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		2. Tofersen will result in substantial health-related benefits that are unlikely to be included in the QALY calculation. a) Clinical trial data from VALOR and the open label extend cover 12 months, but people are likely to experience benefits for longer. Due to the trial design, benefits at (or beyond) 12 months really consider early vs late treatment. b) There are broader benefits to families of people living longer, remained active in society both economically and who would otherwise be occupied in caring roles 3. Tofersen is an intrathecal (IT) treatment than needs to be delivered via lumbar puncture, this is need to be done in a neurosciences centre with experience of IT drug delivery and follow up for safety and efficacy monitoring in the neurosciences centre 4. Maximal benefit of this treatment is dependent on the early and wide access to genetic testing for those living with ALS and rapid turnaround of genetic testing results.	
	University College London Hospitals NHS Foundation Trust (National Hospital for Neurology and	The scope notes that economic modelling should include the costs of diagnostic testing for SOD1. It should be noted that genetic panel testing for ALS is standard practice via the NHS Genomic Medicine Service. Therefore, the marginal cost of identifying these patients is decreasing, though the associated cost and capacity for genetic counselling must be factored in.	Thank you for your comment. The committee will consider all relevant costs.

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	Neurosurgery) / UCL Institute of Neurology		
	Motor Neurone Disease Association	Nothing to add	Thank you for your comment. No action required
	Biogen	Not applicable.	Thank you for your comment. No action required
	Genetic Alliance UK	No comemnts	Thank you. No action required
	My Name'5 Doddie Foundation	Costs for genomic testing may not need to be included as this is already happening for MND patients	Thank you for your comment. The committee will consider all relevant costs.
Questions for consultation	University College London Hospitals NHS Foundation Trust (National Hospital for Neurology and Neurosurgery) / UCL Institute of Neurology	*Where will it fit in the pathway?* Tofersen will be a first-line disease-modifying therapy initiated as soon as a SOD1 diagnosis is confirmed, used alongside standard multidisciplinary care. *Prescribing setting:* C. Prescribed in secondary care with routine follow-up in secondary care. Due to the requirement for monthly intrathecal injections and complex monitoring, this will be strictly managed in tertiary Specialist Neuromuscular Centres.	Thank you for your comments. No action required

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		Managed Access: Yes, Tofersen would be an excellent candidate for a managed access agreement. This would allow immediate access for a small, rapidly deteriorating cohort while we collect vital real-world evidence (e.g. via a national registry) on long-term outcomes and biomarker responses. *Uncaptured QALY benefits:* Rapid-onset ALS causes profound, fast-moving psychological trauma and physical burden on caregivers. Stabilizing the disease not only benefits the patient but exponentially reduces the social care, nursing, and psychological burden on their families, which standard QALY models often fail to capture fully	
	Motor Neurone Disease Association	**Where do you consider tofersen will fit into the existing care pathway for amyotrophic lateral sclerosis (ALS), associated with a mutation in the superoxide dismutase 1 (SOD1) gene?** This will be the most important treatment for anybody with MND caused by a change in their SOD1 gene. People diagnosed with SOD1 MND should be given tofersen at the earliest possible opportunity. Given the current lack of effective treatment options for ALS (including riluzole which is of limited effectiveness) there is an urgent unmet need for more effective disease-modifying therapies. In addition, as potentially the first gene-targeted ALS therapy to become available through the NHS, tofersen represents a potential breakthrough and may be the first of multiple future therapies based on similar 'gene-targeting' strategies. Given the level of unmet need, the innovative nature of the therapy, and the devastating nature	Thank you for your comments. No action required

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		of the impacts of ALS, tofersen should be regarded as a potential step-change in the management of ALS. The use of tofersen should be integrated into the clinical pathway for MND and, if the patient is deemed eligible, be provided following receipt of genetic testing results as close to diagnosis as possible. The treatment should be used in combination with riluzole and in the care of the MND multidisciplinary team, particularly physiotherapy due to the potential to regain some mobility and strength. Others in the multidisciplinary team may be less relevant or needed if tofersen is given early and halts or significantly slows progression in the individual. **Are the patient subgroups listed in the scope relevant?** Yes. **Are there subgroups in which tofersen is expected to be more clinically or cost effective?** As SOD1 MND is often fast-progressing, the treatment should be offered as soon after diagnosis as possible. Evidence suggests that tofersen is most effective when given in the earlier stages of disease progression. The later the drug is provided, the more progressed the patient will be. There is also emerging evidence that some SOD1 mutations better respond to the treatment than others, however evidence for this is limited. **Please select from the following, will tofersen be:** A. Prescribed in primary care with routine follow-up in primary care B. Prescribed in secondary care with routine follow-up in primary care	

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		C. Prescribed in secondary care with routine follow-up in secondary care D. Other (please give details): **For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.** Tofersen is delivered intrathecally. This will be required every two weeks for the first three doses then once a month. Riluzole is the only other licenced treatment for MND but has a limited effect, extending life by just 6-19 months. Riluzole comes largely in tablet form, or oral suspension for those with swallowing difficulties. **Would tofersen be a candidate for managed access?** Our desired outcome is for tofersen to receive a positive recommendation and be routinely offered to all eligible patients via the NHS. We believe the evidence of efficacy is sufficiently strong to support this outcome. **Do you consider that the use of tofersen can result in any potential substantial health related benefits that are unlikely to be included in the QALY calculation?** The MND Association is in regular contact with people with SOD1 MND who have seen the progress of the disease halt or slow significantly after starting treatment with tofersen. People who would otherwise have likely died within 2-5 years have seen little or no progression in their symptoms, with many even experiencing improvements in their symptoms.	

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		Tofersen was granted UK marketing authorisation by the MHRA in July 2025, following data showing both sustained reductions in SOD1 protein and neurofilament light chain (NfL), which are key biomarkers of nerve damage, and clinical evidence that it slowed disease. Since then, evidence of efficacy has been strengthened by a paper published in Jama Neurology in December that found that people who started tofersen exhibited numerically less decline in function, strength, and risk of death-equivalent events. In addition to the published data, the Association is in regular contact with people with SOD1 MND who have seen the progress of the disease halt or slow significantly after starting tofersen. Many have reported a reduced reliance on multidisciplinary services, fewer face-to-face appointments, and a decreased need for respiratory or palliative services. Some have reported small improvements in their mobility, and some are even planning to return to work. Clinicians, facilitating access through the EAP, have reported manageable administration, low risk of serious side effects and acknowledge the clear positive impact tofersen is having on people living with SOD1 MND. Tofersen marks an unprecedented step forward in the treatment of MND. It represents the first ever treatment for an age-related neurodegenerative disease that has genuine disease-modifying potential. The data indicates it has a far greater impact on disease progression and life expectancy than any treatment previously developed for the disease.	

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		Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. • Data provided to MHRA • Clinical and patient-reported outcomes and neurofilament response during tofersen treatment in SOD1-related ALS-A multicenter observational study over 18 months • Long-Term Tofersen in SOD1 Amyotrophic Lateral Sclerosis • Quantitative and qualitative survey data and anecdotes from MND community	
	Biogen	**Where do you consider tofersen will fit into the existing care pathway for amyotrophic lateral sclerosis (ALS), associated with a mutation in the superoxide dismutase 1 (SOD1) gene?** As mentioned in the "Comparators" section of Comment 2, tofersen would be considered a first-line treatment, in addition to BSC (including riluzole if appropriate). **Are the patient subgroups listed in the scope relevant?** As mentioned in our response above in the "Subgroups" section of Comment 2, tofersen would be appropriate for all patients with ALS associated with a SOD1 mutation (SOD1-ALS). **Are there subgroups in which tofersen is expected to be more clinically or cost effective?** As mentioned above, tofersen would be appropriate for all patients with ALS associated with a SOD1 mutation (SOD1-ALS). Consequently, analyses of clinical outcomes and cost-effectiveness should not be stratified by	Thank you for your comments. No action required

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		subgroups. Also, since the SOD1-ALS population is small, further subdivision into subgroups for analyses of clinical outcomes or cost-effectiveness would be inappropriate, as these analyses would introduce unnecessary uncertainty. **Please select from the following, will tofersen be: A) Prescribed in primary care with routine follow-up in primary care; B) Prescribed in secondary care with routine follow-up in primary care; C) Prescribed in secondary care with routine follow-up in secondary care; D) Other (please give details):** Tofersen would be prescribed in secondary care with routine follow-up in secondary care (Option C), in line with the SmPC.16 **For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.** The comparator treatment is BSC, and there are no specified subsequent treatments following BSC. BSC involves care from a multidisciplinary team (such as psychological and nutritional support) as well as a range of pharmacological treatments to manage symptoms, including riluzole. This care can therefore be provided in a range of clinical settings, including primary and secondary care.15 **Would tofersen be a candidate for managed access?** Biogen has made tofersen available to patients through an Early Access Programme (EAP) since 2021.20 Biogen would welcome discussions about	

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		potential service models for implementation but believes that the clinical evidence currently available is sufficient for evaluation by NICE. **Do you consider that the use of tofersen can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** As SOD1-ALS is a very rare disease, there is currently a paucity of data on the social impact of disease experienced by patients and caregivers. In ALS more broadly, patients and their caregivers are less likely to be employed, with high levels of absenteeism.21, 22 This productivity loss may significantly impact the finances of patients with ALS and/or their caregivers, which would not otherwise be captured within the quality-adjusted life year (QALY) calculation. It is expected that, in light of the clinical improvements demonstrated in VALOR (and its subsequent OLE), treatment with tofersen will improve work impairment and absenteeism, leading to improved employment opportunities for patients and productivity gains more broadly.17, 18 A survey of individuals with ALS and their caregivers reported that 48% of the latter reported high levels of burden, as measured by the Zarit Burden Interview (ZBI).23 By improving clinical outcomes for patients, tofersen is also expected to reduce caregiver burden. **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** The pivotal VALOR trial (and its subsequent OLE) is expected to provide data on health-related benefits that are unlikely to be included in the QALY calculation (in addition to data on clinical effectiveness and the effect of	

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		tofersen on health-related QoL [HRQoL]). PROs were collected using a range of instruments in the VALOR trial, including the Work Productivity and Impairment (WPAI) and ZBI questionnaires. These PRO data may not be incorporated in economic modelling to align to NICE's reference case (NHS and Personal Social Services perspective). However, given the known societal impacts of SOD-1 ALS, it is reasonable to assume that additional potential benefits of tofersen are not captured in the QALY (and ICER) calculation. We would ask that these benefits be considered in the Committee's evaluation. **Please indicate if any of the treatments in the scope are used in NHS practice differently than advised in their Summary of Product Characteristics. For example, if the dose or dosing schedule for a treatment is different in clinical practice. If so, please indicate the reasons for different usage of the treatment(s) in NHS practice. If stakeholders consider this a relevant issue, please provide references for data on the efficacy of any treatments in the pathway used differently than advised in the Summary of Product Characteristics.** Tofersen dosage and administration frequency in NHS clinical practice will be in line with the SmPC, consistent with the dosing regimen used in the pivotal VALOR trial and its OLE.16-18 **NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:**	

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		o could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which tofersen is licensed; **o could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;** **o could have any adverse impact on people with a particular disability or disabilities.** **Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.** Biogen do not consider there to be any issues relating to equality of opportunity.	
	Genetic Alliance UK	**Please select from the following, will tofersen be:** To our understanding, tofersen would be prescribed in (B) secondary care with routine follow-up in secondary care, or through other highly specialised neurology services. We would not expect prescribing or routine follow-up to take place in primary care. **Would tofersen be a candidate for managed access?** Tofersen may be a candidate for managed access if this would help address uncertainty while enabling access for a very small group of people with high unmet need. This may be particularly relevant if longer-term evidence is still emerging.	Thank you for your comments. No action required
Additional comments on the draft scope	ABN	Please note original trial: Miller TM, Cudkowicz ME, Genge A, Shaw PJ, Sobue G, Bucelli RC, Chiò A, Van Damme P, Ludolph AC, Glass JD, Andrews JA, Babu S, Benatar M,	Thank you for your comments. No action required

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		McDermott CJ, Cochrane T, Chary S, Chew S, Zhu H, Wu F, Nestorov I, Graham D, Sun P, McNeill M, Fanning L, Ferguson TA, Fradette S; VALOR and OLE Working Group. Trial of Antisense Oligonucleotide Tofersen for *SOD1* ALS. N Engl J Med. 2022 Sep 22;387(12):1099-1110. doi: 10.1056/NEJMoa2204705. PMID: 36129998. Recent extended data: Miller TM, Cudkowicz ME, Shaw PJ, Genge A, Sobue G, Bucelli RC, Chiò A, Van Damme P, Ludolph AC, Glass JD, Andrews JA, Babu S, Benatar M, McDermott CJ, Salachas F, Bruneteau G, Al-Chalabi A, Amorin M, Nestorov I, Graham D, Lin L, Sun P, McNeill M, Malek S, Inra J, Garafalo S, Fradette S; VALOR and OLE Working Group. Long-Term Tofersen in SOD1 Amyotrophic Lateral Sclerosis. JAMA Neurol. 2026 Feb 1;83(2):115-125. doi: 10.1001/jamaneurol.2025.4946. PMID: 41661214; PMCID: PMC12723595. Real-world data: Wiesenfarth et al Effects of tofersen treatment in patients with SOD1-ALS in a “real-world” setting – a 12-month multicenter cohort study from the German early access program. eClinicalMedicine 2024 doi: 10.1016/j.eclinm.2024.102495 Smith et al Tofersen treatment leads to sustained stabilization of disease in SOD1 ALS in a “real-world” setting. Annals of Clinical and Translational Neurology 2024 doi: 10.1002/acn3.52264	

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	Motor Neurone Disease Association	On the economic analysis section: We have concerns regarding the following statement: The economic modelling should include the costs associated with diagnostic testing for SOD1 in people with ALS who would not otherwise have been tested. Updates to the National Genomic Test Directory in 2023 removed age and family history from genetic testing criteria for MND, making everyone with MND eligible for a genetic test already. SOD1 testing should aid prompt diagnosis (and therefore more rapid access with the likelihood of maintaining patients in early disease stages. Genetic testing in MND not only enables access to tofersen; it also enables understanding of potential risk to family members, as well as enabling participation in clinical trials for other precision medicines currently in development. We have received confirmation from 23 specialist MND clinics that the majority of people with MND in England and Wales are now routinely offered genetic testing to all newly diagnosed patients. These centres and networks care for 3500 people with MND in England, Wales and Northern Ireland. Genetic testing and counselling should be seen as a routine element of the MND diagnostic pathway. Consequently, we do not believe the costs associated with genetic testing should be attributed to tofersen as if that was the sole driver for genetic testing need.	Thank you for your comment. The committee will consider all relevant costs.
	Biogen	No further comments.	Thank you. No action required
	Genetic Alliance UK	We would also recommend that NICE consider carefully how the costs of SOD1 testing are handled in the economic analysis. To our understanding,	Thank you for your comment. The

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		genetic testing may already form part of standard diagnostic practice for some people with ALS, rather than being introduced solely because tofersen is available. Where testing would have happened regardless, it may be difficult to attribute the full cost of testing to the treatment. We therefore welcome the inclusion of a sensitivity analysis excluding diagnostic testing costs.	committee will consider all relevant costs.

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

N/A