Biogenin kommenttit Qalsody (toferseeni) ALS-taudin hoidossa suositusluonnosta koskien

Tiivistelmä osuuden suomennos

Päivämäärä: 19. joulukuuta 2025

Tiivistelmä

Qalsody hyväksyttiin käyttöön EU:ssa toukokuussa 2024. Euroopan lääkevirasto (EMA) katsoi, että lääkkeen hyödyt ovat suuremmat kuin sen riskit. Qalsody hyväksyttiin 'poikkeusolosuhteissa', koska lääkkeestä ei ollut mahdollista saada täydellistä tietoa taudin harvinaisuuden vuoksi, erityisesti SOD1-geenimutaatiosta johtuvan ALS:n muodon osalta, jota esiintyy vain 2 %:lla kaikista ALS-potilaista. Tämän vuoksi Biogen on velvoitettu toimittamaan lisätietoa pitkäaikaisesta turvallisuudesta ja tehosta osana hyväksyttyä myyntilupaa. Qalsodylla hoidettuja potilaita seurataan ja yritys toimittaa tietoja vuosittain. Joka vuosi EMA arvioi kaikkia uusia Qalsodysta saataville tulevia tietoja.

Avoimen jatkotutkimuksen ja tosielämän tutkimusten uudet tulokset ovat tukeneet näyttöä toferseenin tehosta ja turvallisuudesta aikuisilla. Keskeiset tulokset viikon 148 kohdalla verrattuna viikkoihin 52 ja 104 osoittavat toferseenin kliinisten hyötyjen jatkumisen ja vahvistumisen SOD1-ALS-tautia sairastavilla aikuisilla. Viikon 148 kohdalla potilaat, jotka aloittivat toferseeni-hoidon tutkimuksen alusta alkaen, osoittivat numeerisesti vähemmän ALSFRS-R (−9,9 vs −13,5 pistettä) ja hidas vitaalikapasiteetti (SVC) (−13,8 % vs −18,1 %) pisteiden laskua verrattuna niihin, jotka olivat aluksi lumelääkeryhmässä ja myöhemmin siirtyivät toferseeni-hoitoon. Mukautetut keskiarvoerot olivat vastaavasti 3,6 ja 4,3 pistettä. Tärkeää on, että noin 25 % osallistujista osoitti toiminnallisen tilan tai voiman parantuvan lähtötasosta, ja osuus oli suurempi aikaisemmin aloittaneiden ryhmässä. Kuoleman tai pysyvän hengityskoneen tarpeen riski oli myös pienempi aikaisemmin aloittaneiden ryhmässä, eikä uusia turvallisuussignaaleja ilmennyt pidemmän aikavälin seurannassa.

Geenimutaatioita, jotka vaikuttavat kaikkialla elimistössä ilmentyvään vapaita radikaaleja torjuvaan superoksididismutaasi-1 (SOD1) entsyymiin, esiintyy 2–6 %:lla amyotrofista lateraaliskleroosia sairastavista potilaista. Maailmanlaajuisesti yleisin SOD1-mutaatio on D90A, ja se on myös yleisin SOD1-mutaatio Skandinavian ALS-potilasjoukossa. PALKO toteaa, että suomalaisilla ALS-potilailla esiintyy tyypillisesti hyvin hitaasti etenevää taudin muotoa, jossa toferseeni-hoidon haitat ylittävät mahdolliset hyödyt. Suomessa esiintyvä homotsygoottinen D91A-variantti liittyy yleisesti merkittävästi pidempään elinaikaan. Fenotypin tunnusmerkki *SOD1*^{D90Ahom}-potilailla on hitaasti etenevä motorinen neuronisairaus, joka alkaa epäsymmetrisesti aina alaraajoista ja entenee hitaasti ylöspäin aiheuttaen pareesia. On kuitenkin tärkeää huomata, että potilaat, joilla on sama mutaatiotyyppi, voivat olla eri ikäisiä ensimmäisen oireen alkaessa ja sairauden kesto voi olla erilainen. Tämä tarkoittaa, että yksittäisellä potilaalla, jolla on SOD-1-variantti, joka yleensä liittyy hitaaseen taudin etenemiseen, tauti voi edetä odotettua nopeammin. Suomesta saatavilla olevien tietojen perusteella SOD1-ALS-taudin odotettu kesto on 11,4 vuotta. Valor-tutkimuksen alaryhmäanalyysi, jossa tarkasteltiin toferseenin vaikutusta

hitaasti etenevän fenotyypin SOD1-ALS-potilailla, osoittaa, että toferseeni oli tehokas myös tässä potilasryhmässä.

Vahvojen terveystaloudellisten arviointien tekemiseen harvinaisten ja erittäin harvinaisten sairauksien yhteydessä liittyy luontaisia menetelmällisiä ja todistusaineistoa koskevia haasteita. Qalsody on tarkoitettu erittäin harvinaiseen sairauteen, jossa rajallinen potilasmäärä yhdistettynä huomattavaan vaihteluun taudin ilmenemisessä ja etenemisessä rajoittaa merkittävästi perinteisten kustannusvaikuttavuustietojen tuottamisen mahdollisuuksia. Tämän heterogeenisyyden vuoksi kustannusvaikuttavuustulokset todennäköisesti vaihtelevat huomattavasti potilaiden välillä, mikä vaikeuttaa yhden koko potilasjoukkoon soveltuvan edustavan arvion laatimista. Näiden seikkojen valossa mahdollisen hyödyn yksilöllinen arviointi on tarkoituksenmukaisempaa kuin yleisiin kustannusvaikuttavuuden raja-arvoihin nojaaminen. Tällainen lähestymistapa noudattaa suhteellisuuden, tasa-arvon ja eettisen vastuun periaatteita erittäin harvinaisten sairauksien hallinnassa, joissa terapeuttiset vaihtoehdot ovat usein rajalliset tai olemattomat.

Executive Summary

Qalsody was authorised for use in the EU in May 2024. The European Medicines Agency (EMA) considered benefits are greater than its risks. Qalsody was authorised under 'exceptional circumstances', because it had not been possible to obtain complete information about the medicine due to the rarity of the disease, and the form of ALS associated with a mutation in the SOD1 gene in particular, as this is only found in 2% of all patients with ALS. Because of that, Biogen has been requested to provide further data on the long-term safety and effectiveness as part of the market authorization approval. Patients treated with Qalsody will be followed and the company will provide data on a yearly basis. Every year, EMA will review any new information that becomes available on Qalsody.

New results from open label extension study and real world evidence studies have shown to support efficacy and safety of tofersen in adults. Key findings at 148 weeks compared to 52 and 104 weeks show a continuation and strengthening of the clinical benefits of tofersen in adults with SOD1-ALS. At 148 weeks, patients who initiated tofersen from the start of the study demonstrated numerically less decline in ALSFRS-R scores (−9.9 vs −13.5 points) and slow vital capacity (−13.8% vs −18.1%) compared to those who were initially in the placebo arm and later switched to tofersen (treated with placebo-tofersen), with adjusted mean differences of 3.6 and 4.3 points respectively. Importantly, around 25% of participants showed functional or strength improvement from baseline, with a higher proportion in the early-start group. The risk of death or permanent ventilation was also lower in the early-start group, and no new safety signals emerged with longer-term follow-up.

Mutations in the gene encoding the ubiquitously expressed free radical scavenging enzyme superoxide dismutase-1 (SOD1) are found in 2–6% of amyotrophic lateral sclerosis patients. The most frequent SOD1 mutation worldwide is D90A, and it is also the most common SOD1 mutation in the Scandinavian ALS patient population. PALKO states that Finnish ALS patients typically experience a very slowly progressing form of the disease, where the harms of tofersen treatment outweigh the potential benefits. The homozygous D91A variant found in Finland is commonly associated with a significantly longer survival time. The hallmark of the phenotype in *SOD1*^{D90Ahom} individuals is a slowly progressing motor neuron disease beginning asymmetrically invariably in the lower limbs followed by slowly ascending paresis. It is however important to recognize that patients who have the same type of mutation can have different age at onset of first symptom and disease duration. This means that for an individual patient with a SOD-1 variant usually associated with slow progression the disease can also progress faster than expected. Based upon the data available for Finland, the expected disease duration for SOD1-ALS is 11.4 years. A subgroup analysis of the valor

study that examined the effect of tofersen in SOD1 ALS patients with the slowly progressive phenotype demonstrates that tofersen was efficacious also in this subgroup of patients,

Conducting robust health economic evaluations in the context of rare and ultra-rare diseases presents inherent methodological and evidentiary challenges. Qalsody targets an ultra-rare condition, where the limited patient population, combined with substantial heterogeneity in disease presentation and progression, significantly constrains the feasibility of generating conventional cost-effectiveness data. Due to this heterogeneity, cost-effectiveness results are likely to vary considerably across patients, making it difficult to derive a single, representative estimate applicable to the entire population. In light of these considerations, an individualized assessment of potential benefit is more appropriate than reliance on generalized cost-effectiveness thresholds. Such an approach aligns with the principles of proportionality, equity, and ethical responsibility in the management of ultra-rare diseases, where therapeutic alternatives are often limited or nonexistent.

Introduction

The Council for Choices in Health Care in Finland has prepared draft recommendation about “Toferseeni superoksididismutaasi 1 (SOD1)”. Biogen has been given the opportunity to comment on and within this report. The main concerns where we strongly disagree with the statement made by PALKO include:

1. Expected effect and safety of tofersen
2. The need of treatment in the Finnish ALS population
3. The relevance of cost-effectiveness in ultra-rare disease populations

Efficacy and safety

PALKO states that Finnish ALS patients typically experience a very slowly progressing form of the disease, where the harms of tofersen treatment outweigh the potential benefits. Also, there are concerns of safety issues and severe adverse events. Biogen does not agree with PALKO on this matter.

According to The European Medicines Agency (EMA), there were very limited treatment options for patients with ALS at the time of the authorisation of Qalsody. EMA also concluded that although the main results from a study in patients with ALS associated with a mutation in the SOD1 gene failed to show an effect of the medicine after 28 weeks of treatment, other measurements confirmed the way the medicine is expected to work and indicated that Qalsody may slow down the course of the disease. [8] In terms of safety, EMA stated that Qalsody can have serious side effects involving the nervous system, such as inflammation of the spinal cord; however, these can be managed with appropriate treatment. Based on this, **EMA therefore decided that Qalsody's benefits are greater than its risks**, quoting from the EPAR that *"The benefit/risk balance of tofersen for the treatment of patients with SOD1-ALS, a serious, relentlessly progressive and invariably fatal disease, is considered favourable based on the totality of evidence provided"*. Qalsody was authorised for use in the EU in May 2024. [8, 9] Experts shared their perspective on the EMA decision, published in Lancet Neurology, 2024. [31]

Qalsody was authorised under 'exceptional circumstances', because it had not been possible to obtain complete information about the medicine due to the rarity of the disease, and due to the form of ALS associated with a mutation in the SOD1 gene in particular, as this is only found in 2% of all patients with ALS. Because of that, Biogen has been requested to provide further data on the long-term safety and effectiveness of the medicine as part of the market authorization approval and to investigate the effect of the medicine in patients who do not yet have symptoms. Patients treated with Qalsody will be followed and the company will provide data on a yearly basis. Every year, EMA will review any new information that becomes available on Qalsody. [8]

The open label extension (OLE) study over 52 weeks in SOD1-ALS patients showed that starting tofersen earlier led to better outcomes in clinical function, respiratory performance, muscle strength, and quality of life, along with greater reductions in neurofilament and SOD1 protein levels [10]. Most adverse events were mild to moderate,

though serious neurological events occurred in 6.7% of participants [10]. Combined data from the phase 3 VALOR study and OLE indicate that tofersen slows functional decline [10, 11].

New results from the Phase 3 VALOR Trial and OLE, evaluating efficacy and safety of tofersen in adults with *SOD1*-ALS after 148 weeks of treatment were presented in the European Network for the Cure of ALS (ENCALS) meeting in June 2025 [12]. The key findings were that tofersen-driven reductions in plasma NfL were maintained over time (Figure 1), consistent with sustained slowing of neurodegeneration and that earlier initiation of tofersen was associated with a trend of numerically less decline in measures of clinical function, respiratory function, muscle strength, and QoL, as well as reduced risk of death or permanent ventilation (PV) (Figures 2-4) [12].

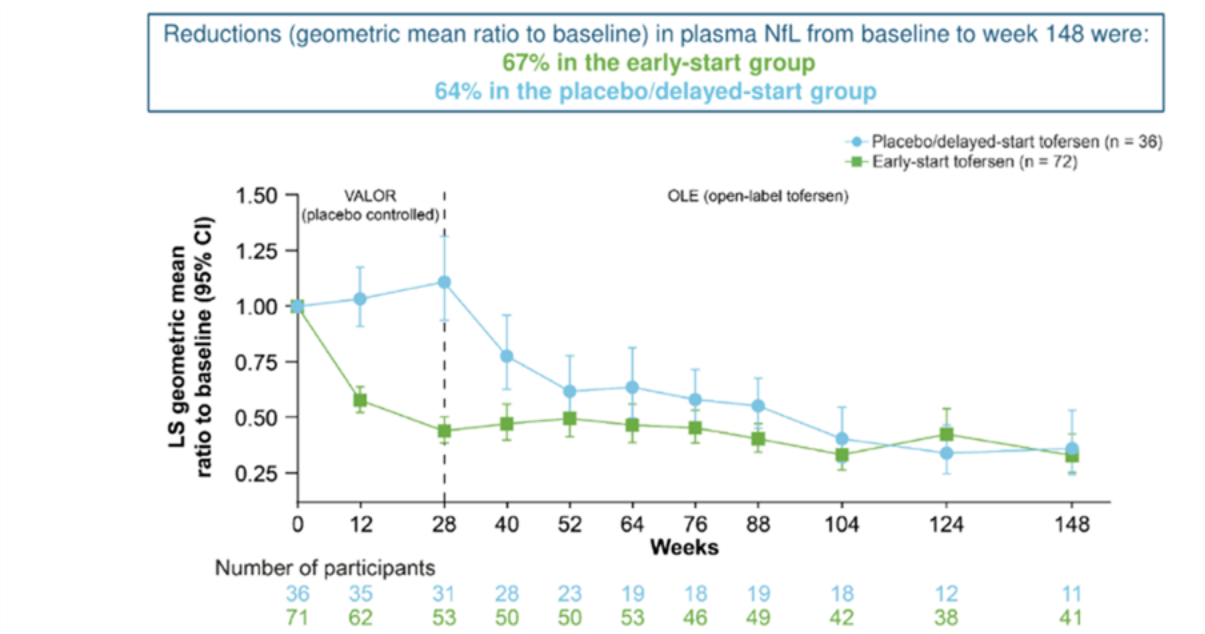

Figure 1. Tofersen-driven reductions in plasma NfL were sustained over time. Abbreviations: CI = confidence interval; LS = least squares; NfL = neurofilament light chain; OLE = open-label extension. Data cut: 148 weeks. Source: Miller et al. 2025 [12].

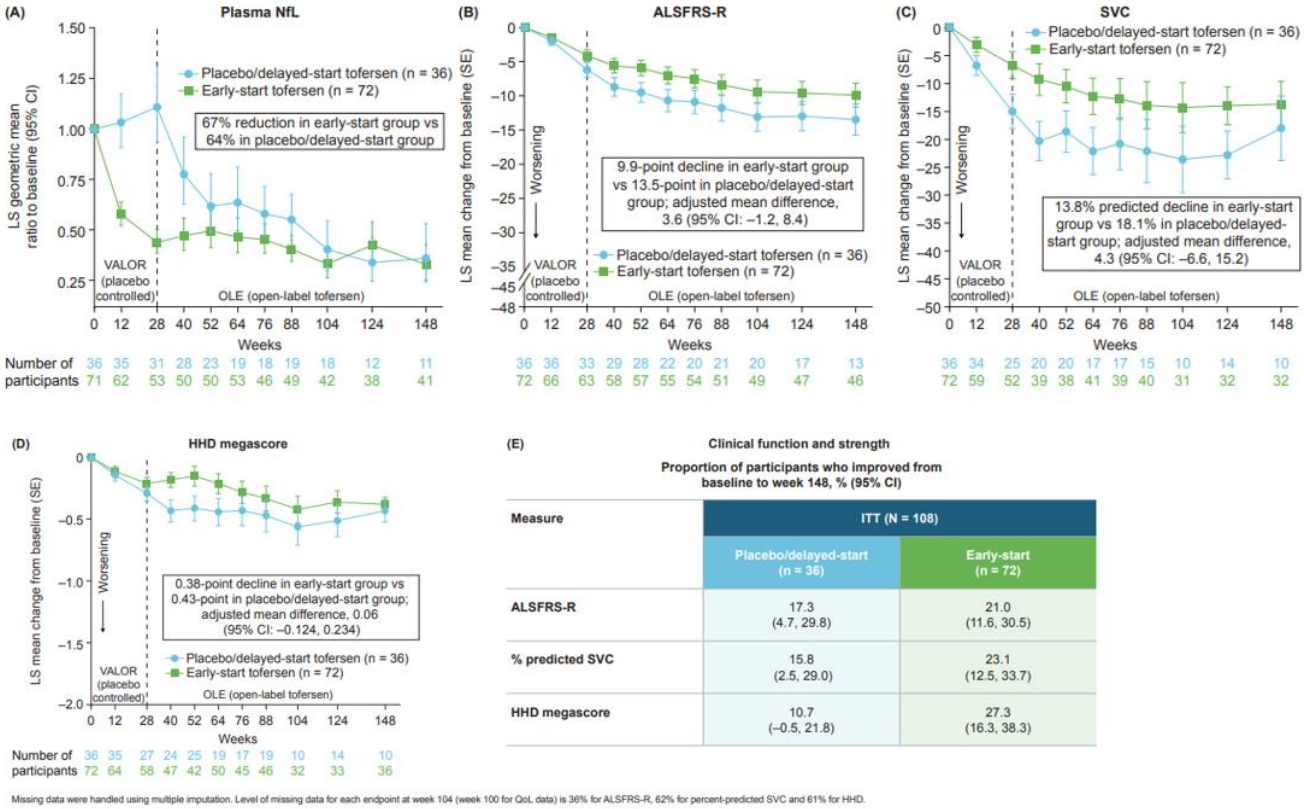

Figure 2. Change in key efficacy measures from baseline to week 148. Earlier initiation of tofersen was associated with numerically less decline in function and strength. Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised; CI = confidence interval; HHD = handheld dynamometry; LS = least squares; OLE = open-label extension; SE = standard error; SVC = slow vital capacity. Data cut: 148 weeks. Source: Miller et al. 2025 [12].

Proportion of participants who improved from baseline to week 148, % (95% CI)						
	ITT (N = 108)		Faster-progressing subgroup (NfL-based[a]) (n = 54)		Slower-progressing subgroup (NfL-based[a]) (n = 54)	
Measure	Early start (n = 72)	Placebo/ delayed start (n = 36)	Early-start (n = 38)	Placebo/ delayed-start (n = 16)	Early-start (n = 34)	Placebo/ delayed-start (n = 20)
ALSFRS-R	21.0 (11.6, 30.5)	17.3 (4.7, 29.8)	16.2 (4.3 to 28.0)	12.5 (−3.7 to 28.7)	26.5 (11.6 to 41.3)	21.0 (2.8 to 39.3)
SVC	23.1 (12.5, 33.7)	15.8 (2.5, 29.0)	12.1 (1.0 to 23.1)	18.8 (−0.4 to 37.9)	35.5 (17.8 to 53.2)	13.4 (−4.8 to 31.5)
HHD megascore	27.3 (16.3, 38.3)	10.7 (−0.5, 21.8)	6.9 (−2.0 to 15.8)	7.7 (−6.3 to 21.7)	50.0 (31.9 to 68.1)	13.1 (−3.3 to 29.4)

Figure 3. Proportion of participants who improved from baseline to week 148, in percentage (95% CI). Abbreviations: ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised; CI = confidence interval; HHD = handheld dynamometry; ITT = = intention-to-treat; NfL = neurofilament light chain; SVC = slow vital capacity. Data cut: 148 weeks. Source: Miller et al. 2025 [36].

[a] *NfL-based subgroups are based on median baseline NfL (i.e., slower-progressing subgroup).*

Table S3. Estimated proportion of participants (%) with improvement or stabilization/improvement from baseline to week 148 in the faster- and slower-progressing subgroups

Endpoint	Analysis	Faster-progressing subgroup		Slower-progressing subgroup	
		Placebo/ delayed-start (n = 16)	Early-start (n = 38)	Placebo/ delayed-start (n = 20)	Early-start (n = 34)
ALSFRS-R	Improvement, %	12.5	16.2	21.1	26.5
	Stabilization or improvement, %	12.5	16.2	31.1	39.0
% predicted SVC	Improvement, %	18.8	12.1	13.4	35.5
HHD megascore	Improvement, %	7.7	6.9	13.1	50.0

Improvement was defined as a change from baseline >0 and stabilization/improvement was defined as a change from baseline ≥0.

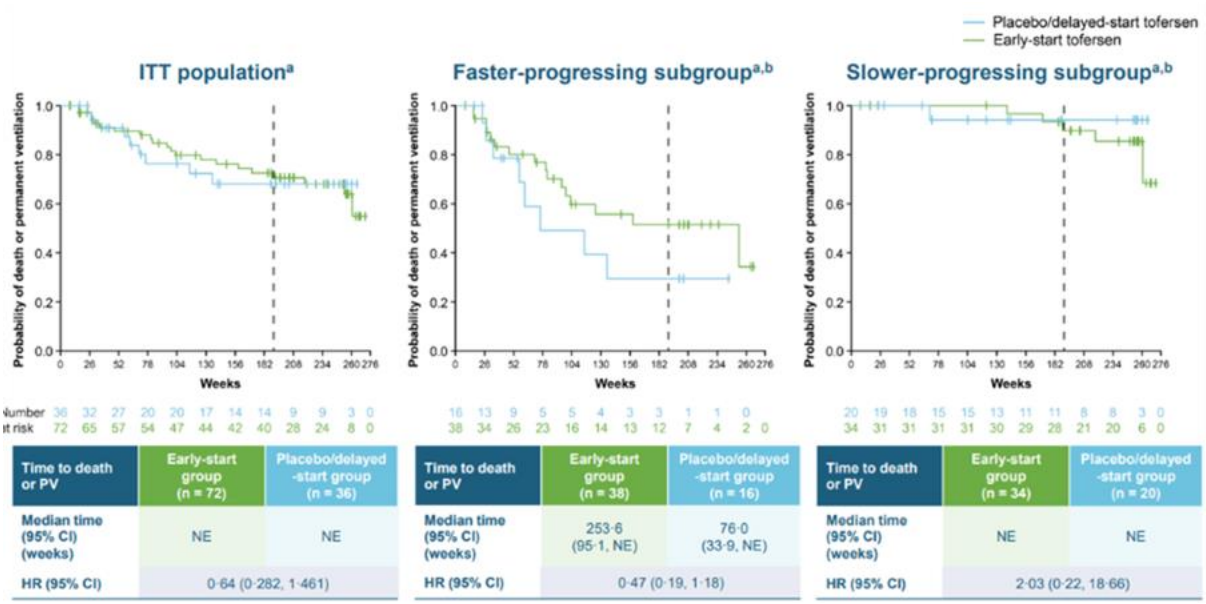

Figure 4. Earlier initiation of tofersen was associated with a lower risk of death or PV. Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat; NE = not estimable; PV = permanent ventilation. Data cut: 148 weeks. Source: Miller et al. 2025 [12].

[a]The dotted line corresponds to week 192, the time point when the last participant enrolled reached the end of the study.

[b]NfL-based subgroups are based on median baseline NfL (ie, slower-progressing subgroup <75·6 pg/mL; faster-progressing subgroup ≥75·6 pg/mL).

Additionally, no new safety signals were identified with longer-term follow-up at 148 weeks. Most adverse events were consistent with ALS progression or known procedural side effects, while all serious neurologic events were reversible, and few led to discontinuation of tofersen (Figure 5) [12].

Participants, n (%)[a]	VALOR and OLE (tofersen 100 mg) (n = 104)
Any AE	103 (99.0)
AE related to trial agent[b]	66 (63.5)
AE related to lumbar puncture[b]	87 (83.7)
Serious AE (any grade ≥3)	58 (55.8)
Serious AE related to trial agent[b]	10 (9.6)
AE with fatal outcomes	22 (21.2)
AE leading to discontinuation	28 (26.9)
Serious neurologic events[c]	9 (8.7)
Myelitis	4 (3.9)
Papilloedema	3 (2.9)
Aseptic meningitis	2 (1.9)
Radiculitis	1 (1.0)

Figure 5. No new safety signals were identified with longer-term follow-up. Abbreviations: AE = adverse event; OLE = open-label extension; PT = preferred term. Data cut: 148 weeks. Source: Miller et al. 2025 [12].

[a]A participant could appear in more than one category.

[b]The relatedness of an event to the trial agent or lumbar puncture was assessed by the investigator.

[c]Myelitis includes the PT Myelitis transverse, Papilloedema includes the PT Intracranial pressure increased, Aseptic meningitis includes the PTs Meningitis chemical and Meningitis aseptic.

In summary, the key findings at 148 weeks compared to 52 [10] and 104 weeks [13] show a continuation and strengthening of the clinical benefits of tofersen in adults with SOD1-ALS. At 148 weeks, patients who initiated tofersen early demonstrated numerically less decline in ALSFRS-R scores (−9.9 vs −13.5 points) and slow vital capacity (−13.8% vs −18.1%) compared to those who started later, with adjusted mean differences of 3.6 and 4.3 points respectively. Importantly, around 25% of participants showed functional or strength improvement from baseline, with a higher proportion in the early-start group. The risk of death or permanent ventilation was also lower in the early-start group, and no new safety signals emerged with longer-term follow-up. These findings reinforce the value of early tofersen initiation and suggest sustained disease-modifying effects over nearly three years of treatment.

Presymptomatic treatment

As is the case for other neurodegenerative diseases [14], there is emerging evidence for a presymptomatic phase of ALS, including *SOD1*-ALS, based on a natural history and biomarker study of unaffected individuals at elevated genetic risk for ALS (the Pre-

Symptomatic Familial ALS, Pre-fALS study) [15]. The ATLAS study (NCT04856982), a Phase 3 study designed to evaluate the ability of tofersen to delay clinical onset and/or slow disease progression when initiated in presymptomatic individuals with a *SOD1* mutation and biomarker evidence of disease activity, was initiated on May 17, 2021 [16]. The study enrolled 158 participants, including 1 patient from Sweden. An interim readout from ATLAS is expected between late 2025 - early 2026 and the study's estimated primary completion date is August 7, 2027. As part of the conditions of the marketing authorisation, Biogen (as MAH) as committed to providing the final results of this study by 31 December 2028.

Tofersen Early Access Programme (EAP) and Real-world Evidence (RWE) data

In the light of the critical unmet medical need, Biogen provided free access to tofersen as part of an Early Access Programme (EAP) prior to marketing authorization [17]. The EAP provided more than 700 patients world-wide (36 countries) access to treatment. From the Nordics and Baltics, 8 patients were included in EAP (Sweden: 1 patient, Norway: 2 patients, Denmark: 2 patients, Lithuania: 2 patients, Estonia: 1 patient).

New data from a recent multicentre, retrospective cohort study (based on secondary use of clinical data), non-interventional, conducted in France, named FORSLA, will soon be published. The data is particularly relevant to Finland, due to similarity of mutation types to the Finnish population (most frequent variant was in this study p.Asp91Ala (alias: D90A)) and due to an analysis with natural history as a comparator. This study is based on the combination of data from the tofersen EAP and data extracted from patients' medical records to constitute a cohort of treated patients and data extracted from the national ALS database, used to constitute a historical cohort of untreated patients.

A growing body of evidence from other real-world settings points in favour of tofersen. The studies presented in the table below (Table 1), reveal a consistent pattern of biological efficacy and variable clinical outcomes. Across multiple countries and study designs - from randomised controlled trials to observational cohorts and case reports - tofersen was shown to reduce biomarkers such as SOD1 in cerebrospinal fluid and neurofilament light chain (NfL) in plasma and serum. While early trials like Miller 2022 and 2020 demonstrated biochemical effects without significant clinical improvement, later observational studies in France, Germany, Italy, Sweden, Poland, and Iceland reported stabilisation or slowed disease progression, improved ALSFRS-R scores, and high patient satisfaction. Notably, adverse events such as myelitis were rare and manageable. These findings constitute a cohort of approximately 265 patients treated with tofersen for varying lengths of time, and

they collectively suggest that tofersen may offer meaningful benefits, particularly when initiated early, with effects observable in both fast and slow progressors.

Table 1: Characteristics of the published studies and their participants, along with the key findings of each report (adapted from Hamad et al. 2025 [18]), as of October 2025.

Study	Country	Study design	n	Males	Age, mean (SD)	Mutation types - similarity to Finnish population?	Key findings
Miller 2022 [10]	10 countries	Phase 3 RCT	Tof: 72 & plac: 38	Tof: 43 & plac: 19	Tof: 48.1 (12.6) & plac: 51.2 (11.6)	YES	Tofersen reduced concentrations of SOD1 in CSF and NfL in plasma but did not significantly improve the disease progression at 6 months. In OLE at 52 weeks, the change in the ALSFRS-R score from the VALOR baseline was −6.0 points for early-start participants and −9.5 points for delayed-start participants.
Miller 2020 [11]	6 countries	Phase 2 ascending-dose RCT	Tof: 38 & plac: 12	21 & plac: 7	Tof: 48.32 (10.82) & plac: 49.2 (11.0)	YES	CSF SOD1 concentrations decreased at the highest concentration of tofersen, and adverse events were documented and managed.
Wiesenfarth 2024 [19]	Germany	Multicenter observational cohort	24	12	51.8 (15.4)	YES	There was reduction of NfL serum levels (p=0.02), and pNfH CSF levels (p=0.02).
Sabatteli 2024 [20]	Italy	Multicenter observational cohort	17	12	58.6 (6.8)	YES	During treatment, a significant statistical change was observed in the disease progression rate compared to the pre-treatment period. Cumulative evaluation of the ALSFRS-R and MRC progression rates showed a statistically significant change during treatment with respect to the period prior to therapy (p = 0.023 and p = 0.007, respectively).
Meyer 2024 [21]	Germany	Multicenter observational cohort	16	7	53 (9.3)	YES	ALS progression rate was reduced by 25%. ALSFRS-R was increased in 7 patients. Most patients reported high treatment satisfaction.
Weishaupt 2024 [22]	Germany	Multicenter observational cohort	11	4	54.4	YES	Tofersen decreased serum NfL in both homozygous and heterozygous patients. Tofersen decreased serum NfL in both homozygous ($p < 0.05$ after fouth injection) and heterozygous patients ($p < 0.05$

							after fouth injection, but $p > 0.05$ after the fifth).
Vinceti 2024 [23]	Italy	Multicenter observational cohort	10	5	Median: 58.6	Not reported	Total selenium and key species increased significantly post-intervention. While the study did not assess clinical efficacy or safety, the authors hypothesised that these may reflect neuronal or blood–brain barrier effects. There was a relevant decrease in the CSF concentrations of light chain neurofilaments following the drug treatment, confirming its biological activity.
Meyer 2023 [24]	Germany	Case series	2	2	53.3 (7.5)	YES	There was reduction of NfL in both serum and CSF in all patients.
Gianferrari 2023 [25]	Italy	Case report	2	2	61 & 53	NO	There was a reduction in the ALSFRS-R decline in both patients after starting on tofersen administration.
Reilich 2024 [26]	Germany	Case report	1	0	56	NO	The study reports a case of myelitis as a side effect of tofersen therapy.
Vidovic 2024 [27]	Sweden	Case report	1	0	39	YES	Tofersen treatment was associated with mild pleocytosis, as well as increased total protein and albumin concentrations since treatment month 3, but no serious adverse events.
Forsberg 2024 [28]	Sweden	Case report	1	1	In 30s	YES	After four years on tofersen, the patient showed significant reduction in toxic SOD1 species and improved ALSFRS-R decline course, with active social lifestyle.
Kuźma-Kozakiewicz 2025 [29]	Poland	Multicenter observational cohort (EAP, 8 sites)	20	14	49	Not reported	Early results from Tofersen treatment (8-18 months) showed stabilization of patients (ALSFRS-R no significant difference from treatment initiation at the data cut)/decreased disease progression in 79% of cases and decreased NFL concentration in 86% of cases. The effect was present in both fast- and slow-progressors. Treatment-related SAEs were found in 2 patiens, who presented with myelitis which was treatable with IV methylprednisolone.
Þórarinsson2025 [30]	Iceland	Case report	4	3	49	Not reported	None of the patients have shown significant deterioration since the treatment began; on the contrary, three have experienced improvements that could be confirmed with previous comparison measurements by a physiotherapist, coupled with a decrease in NfL levels in CSF. In all

							patients, the decrease began immediately in the first months of treatment and was mostly evident after 6 months. No SAEs were reported.

Abbreviations: ALS, Amyotrophic Lateral Sclerosis; n, sample size; ALSFRS-R, ALS Functional Rating Scale–Revised; CSF, Cerebrospinal Fluid; NfL, Neurofilament Light Chain; pNfH, Phosphorylated Neurofilament Heavy Chain; SOD1, Superoxide Dismutase 1; Tof, tofersen; plac, placebo; SAE, serious adverse event; IV, intravenous.

Clarification of the data - relevant for Finland

PALKO state that since the clinical studies of tofersen does not include an analysis based on genetic variations, there is no information on whether the response is better for any specific genetic variant. Within the recommendation, PALKO also notes that the SOD1 gene variants of the participants in the study do not represent the variants found in Finland, and therefore, the study results are not directly transferable to Finnish patients. Again, PALKO states that Finnish ALS patients typically experience a very slowly progressing form of the disease, where the harms of tofersen treatment outweigh the potential benefits. Biogen does not agree with PALKO on this matter.

Mutations in the gene encoding the ubiquitously expressed free radical scavenging enzyme superoxide dismutase-1 (SOD1) are found in 2–6% of amyotrophic lateral sclerosis patients. The most frequent SOD1 mutation worldwide is D90A and is the most common SOD1 mutation in the Scandinavian population [1]. It is important to clarify that the Human Genome Variation Society nomenclature was used to name the different SOD1 variants, i.e., using one amino acid shift compared to past nomenclature. For example, this former D90A mutation was then named D91A. [2] The homozygous D91A variant found in Finland is commonly associated with a significantly longer survival time (11.4 years on average), Figure 6 [3, 4].

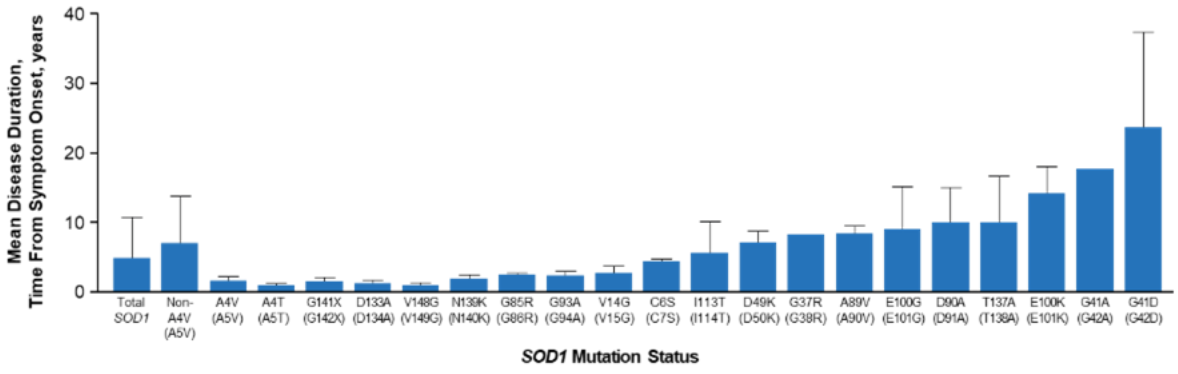

Figure 6. *Mean disease duration reported for each mutation population with a minimum n=2. There was no statistical significance between all SOD1 patients (n=162), non-A4V patients (n=105), SOD1A4V patients (n=57; p=0.7217, Kruskal-Wallis). Error bars represent SD. Adapted from Bali, et al. 2016, Opie-Martin, et al. 2022 [3, 4].*

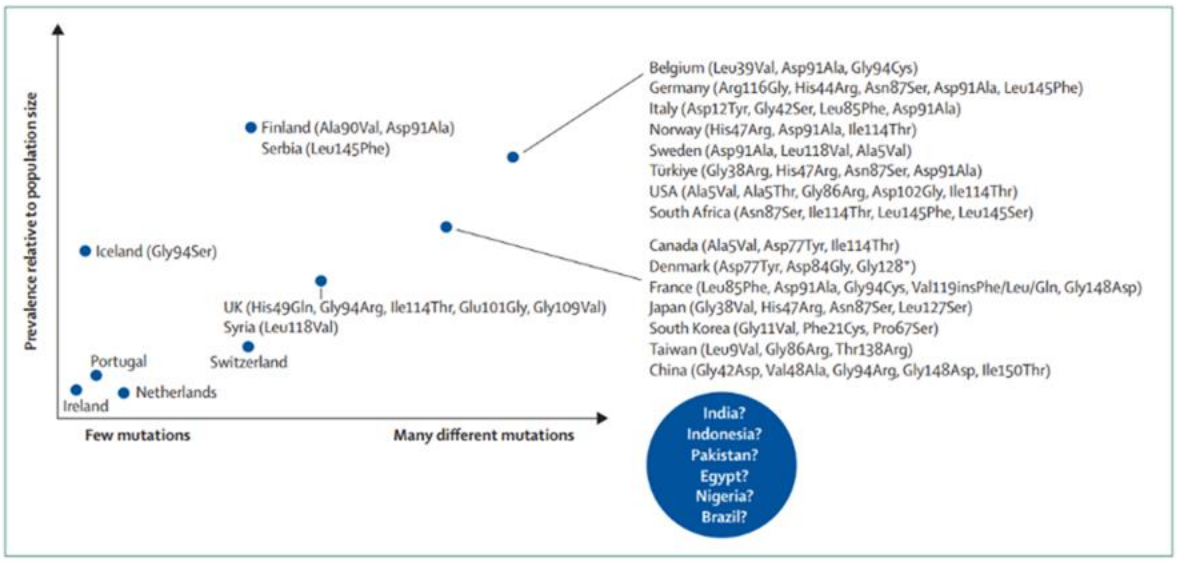

Figure 7. *Worldwide distribution of carriers of SOD1 variants adapted from Benatar et al. 2025 [5]. The relationship between SOD1-ALS prevalence relative to population size and the number of mutations.*

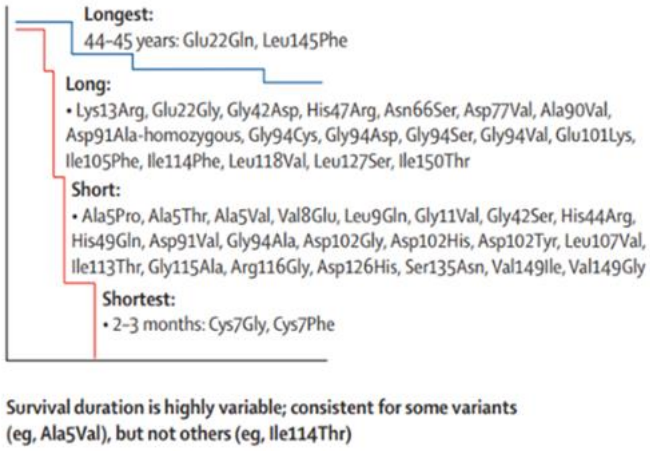

Figure 8. *SOD1-ALS phenotype–genotype associations with survival time. Adapted from Benatar et al. 2025 [5]. Asp91Ala (alias: D90A) is common in Finland.*

In most populations, ALS caused by *SOD1*^{D90A} is inherited as a recessive trait, and heterozygous members in these families do not develop ALS. In D90A *SOD1*-homozygous individuals (*SOD1*^{D90Ahom}), the disease penetrance is high, with ages of onset ranging from 20 to 94 years (median of 46 years) [6, 7]. The hallmark of the phenotype in *SOD1*^{D90Ahom} individuals is a slowly progressing motor neuron disease beginning asymmetrically invariably in the lower limbs followed by slowly ascending paresis. Forsberg, K. et al., 2022 collected tissues from nine ALS patients homozygous for the D90A *SOD1* mutation at the

Department of Neurology, Umeå University Hospital [7]. **Table 2 shows that even if the patients have the same type of mutation, in this case D90A (homozygous) that is associated with slow progression, these nine patients have a range in patient age at onset of first symptom from 38 to 60 years (mean 49 years), and a disease duration ranged from 5 to 33 years (mean 17 years). This means that for an individual patient with an SOD-1 variant that is usually associated with slow progression, the disease can also progress faster than expected.** The three patients in Table 1 with the shortest survival were all heavy cigarette smokers. Patients #3 and #5 both had a history of chronic ulcer of the stomach, and patient #4 was diagnosed with diabetes mellitus type 1 at the time the first paresis appeared. [1]. Assessing the results on the slowly progressing patients, many of these patients demonstrate an improvement during treatment with tofersen (Figure 4). [12]

Table 2. Clinical features

Patient Number	1	2	3	4	5	6	7	8	9
Sex	Female	Male	Female	Male	Male	Female	Male	Female	Female
Age at onset[a] (y)	38	58	53	38	55	38	51	54	50
Age at death[a] (y)	43	66	64	53	70	55	75	81	82
Disease duration[a] (y)	5	8	11	15	15	17	24	26	33

[a]Age and disease duration are presented in full years

Health economic assessment

PALKO state that tofersen is not cost-effective in any modeled scenario in Finland, with an incremental cost-effectiveness ratio (ICER) of €1.3 million per QALY. Care giver utility is not considered.

Conducting robust health economic evaluations in the context of rare and ultra-rare diseases presents inherent methodological and evidentiary challenges. Qalsody (tofersen) targets an ultra-rare condition, where the limited patient population, combined with substantial heterogeneity in disease presentation and progression, significantly constrains the feasibility of generating conventional cost-effectiveness data.

Due to this heterogeneity, cost-effectiveness results are likely to vary considerably across patients, making it difficult to derive a single, representative estimate applicable to the entire

population. The variation in disease progression is particularly pronounced, with some patients experiencing a relatively stable course while others deteriorate rapidly.

In the assessment by FIMEA, a significantly lower disease progression rate was assumed for the Finnish patients. However, as described, disease progression varies substantially between individuals, and the potential QALY gain will not be uniform across patients. It will depend on individual disease dynamics, baseline function, and timing of intervention. Therefore, a generalized assumption risks underestimating the value of treatment for those patients most likely to benefit.

It is important to emphasize that it is not appropriate to assume that all Finnish patients will experience a slow disease progression, assuming that such patient are not in need of a medical therapy based solely on genotype. There are considerable intra-genotypic variations, and clinical trajectories differ markedly even among patients with similar genetic profiles as demonstrated. Therefore, a patient-by-patient assessment is a more appropriate and clinically based approach, taking into account individual disease severity, expected progression, and treatment need. This approach ensures that patients with the most urgent clinical profiles are not excluded based on population-level assumptions.

Furthermore, ALS is a disease of profound severity, not only in terms of its clinical trajectory and prognosis, but also in its psychosocial and functional impact on both patients and caregivers. Multiple studies have demonstrated that the burden on informal caregivers—often family members—is substantial, affecting their mental health, quality of life, and ability to remain in the workforce. To fully capture the societal value of treatment, caregiver utility should be included in the health economic analysis. However, FIMEA has chosen to exclude caregiver effects, which risks underestimating the broader benefits of treatment in this highly burdensome condition.

In light of these considerations, we propose that individualized assessment of potential benefit is more appropriate than reliance on generalized cost-effectiveness thresholds. Such an approach aligns with the principles of proportionality, equity, and ethical responsibility in the management of ultra-rare diseases, where therapeutic alternatives are often limited or nonexistent.

Importantly, the safety profile of the product is being closely monitored through post-marketing surveillance and structured follow-up, in accordance with regulatory expectations. Emerging real-world evidence (RWE) further supports the product's favorable safety profile, reinforcing its suitability for continued use in this vulnerable population.

We respectfully request that the agency consider these factors when evaluating the product, and apply a flexible, context-sensitive approach that reflects the realities of ultra-rare

disease management and the ethical imperative to provide access where evidence generation is inherently constrained.

References

1. Forsberg, K., et al., *Widespread CNS pathology in amyotrophic lateral sclerosis homozygous for the D90A SOD1 mutation*, Acta Neuropathol., 2022, 16;145(1):13–28
2. Den Dunnen, et al., *HGVS Recommendations for the Description of Sequence Variants: 2016 Update*. Hum. Mutat. 2016, 37, 564–569
3. Bali, T., et al., *Defining SOD1 ALS natural history to guide therapeutic clinical trial design.* J Neurol Neurosurg Psychiatry, 2017. 88(2): 99-105
4. Opie-Martin, S., et al., The SOD1-mediated ALS phenotype shows a decoupling between age of symptom onset and disease duration. Nat Commun, 2022. 13(1):6901
5. Benetar, M., et al., *Amyotrophic lateral sclerosis caused by SOD1 variants: from genetic discovery to disease prevention*. The Lancet Neurology, 2025. 24(1):77-86
6. Andersen PM, et al. *Autosomal recessive adult-onset amyotrophic lateral sclerosis associated with homozygosity for Asp90Ala CuZn-superoxide dismutase mutation. A clinical and genealogical study of 36 patients.* Brain. 1996;119:1153–1172
7. Andersen PM, et al. *Amyotrophic lateral sclerosis associated with homozygosity for an Asp90Ala mutation in CuZn-superoxide dismutase.* Nat Genet. 1995;10:61–66
8. European Commission decision, Qalsody, 2024:Qalsody | European Medicines Agency (EMA)
9. Qalsody European Public Assessment Report (EPAR), 07/2025, https://www.ema.europa.eu/en/documents/overview/qalsody-epar-medicine-overview_en.pdf
10. Miller TM, et al., *Trial of Antisense Oligonucleotide Tofersen for SOD1 ALS.* New England Journal of Medicine, 2022. 387(12):1099-1110
11. Miller, T., et al., *Phase 1–2 trial of antisense oligonucleotide tofersen for SOD1 ALS.* New England Journal of Medicine, 2020. 383(2):109-119

12. Miller TM, et al., *Final Results from the Phase 3 VALOR Trial and Open-Label Extension Evaluating Efficacy and Safety of Tofersen in Adults with SOD1-ALS, in European Network to Cure ALS (ENCALS)*. June 3-6, 2025: Turin, Italy.

13. Qalsody Orphan Maintenance Assessment Report, 07/2025, https://www.ema.europa.eu/en/documents/orphan-maintenance-report/qalsody-orphan-maintenance-assessment-report-initial-authorisation_en.pdf

14. Crawford, T.O., et al., *Continued benefit of nusinersen initiated in the presymptomatic stage of spinal muscular atrophy: 5-year update of the NURTURE study.* Muscle Nerve, 2023. 68(2):157-170.

15. Benatar, M. and J. Wuu, *Presymptomatic studies in ALS: rationale, challenges, and approach*. Neurology, 2012. 79(16):1732-9

16. Benatar, M., et al., *Design of a Randomized, Placebo-Controlled, Phase 3 Trial of Tofersen Initiated in Clinically Presymptomatic SOD1 Variant Carriers: the ATLAS Study.* Neurotherapeutics, 2022. 19(4):1248-1258

17. Biogen Press Release: *Biogen Receives European Commission Approval for QALSODY® (tofersen), the First Therapy to Treat a Rare, Genetic Form of ALS*, 05/2024, https://investors.biogen.com/news-releases/news-release-details/biogen-receives-european-commission-approval-qalsodyr-tofersen.

18. Hamad, A.A., et al., *Tofersen for SOD1 amyotrophic lateral sclerosis: a systematic review and meta-analysis*. Neurol Sci, 2025. 46(5):1977-1985

19. Wiesenfarth, M., 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. 69.

20. Sabatelli, M., et al., *Long-term treatment of SOD1 ALS with tofersen: a multicentre experience in 17 patients*. Journal of Neurology, 2024. 271(8):5177-5186.

21. Meyer, T., et al., *Clinical and patient-reported outcomes and neurofilament response during tofersen treatment in SOD1-related ALS-A multicenter observational study over 18 months*. Muscle Nerve, 2024. 70(3):333-345

22. Weishaupt, J.H., et al., *Tofersen decreases neurofilament levels supporting the pathogenesis of the SOD1 p.D91A variant in amyotrophic lateral sclerosis patients*. Communications Medicine, 2024. 4(1):150.

23. Vinceti, M., et al., *Changes in Cerebrospinal Fluid Concentrations of Selenium Species Induced by Tofersen Administration in Subjects with Amyotrophic Lateral Sclerosis Carrying SOD1 Gene Mutations*. Biol Trace Elem Res, 2025. 203(4):2355-2364.

24. Meyer T, et al., *Neurofilament light-chain response during therapy with antisense oligonucleotide tofersen in SOD1-related ALS: Treatment experience in clinical practice*. Muscle & Nerve, 2023. 67: p. 515-521.

25. Gianferrari, G., et al., *Case report: p.Glu134del SOD1 mutation in two apparently unrelated ALS patients with mirrored phenotype*. Frontiers in Neurology, 2023. Volume 13 - 2022.

26. Reilich, P., et al., *Myelitis as a side effect of tofersen therapy in SOD1-associated ALS*. Journal of Neurology, 2024. 271(4): p. 2114-2118.

27. Vidovic, M., et al., *Macrophage inclusions in cerebrospinal fluid following treatment initiation with antisense oligonucleotide therapies in motor neuron diseases*. Neurol Res Pract, 2024. 6(1): p. 11.

28. Forsberg, K., et al., *Fallbeskrivning: Precisionsmedicinsk genterapi har bromsat utveckling av ALS - Tofersen minskar syntesen av SOD1-protein*. Läkartidningen, 2024. 121: p. 24044.

29. Kuźma-Kozakiewicz, M., *Presentation as part of Scientific Panel Meeting on ALS and Frontotemporal Dementia, in European Academy of Neurology (EAN)*. 21 June 2025.

30. Björn Logi Þórarinsson, K.E.H., et al., *Case study. Treatment of hereditary ALS disease with the drug tofersen* (Original: Sjúkratilfelli. Meðferð við ættlægum ALS-sjúkdómi með lyfinu tofersen). Læknablaðið (The Icelandic Medical Journal), 2025. 111(0708).

31. Haberkamp et al., *Tofersen for SOD-1-associated amyotrophic lateral sclerosis*, Lancet Neurol, 2024, 23(8): p. 772-773