European Journal of Pharmaceutical Sciences 223 (2026) 107563

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Review

Tofersen in SOD1-associated amyotrophic lateral sclerosis: From molecular mechanisms to regulatory milestones

Antonio J. Braza [a,*], Montserrat Viñas-Bastart [a,*], Maria Sureda-Rosich [a], Beliu García-Parra [a,b], Josep M. Guiu-Segura [a], Pilar Modamio [a]

[a] Clinical Pharmacy and Pharmaceutical Care Unit. Department of Pharmacy and Pharmaceutical Technology, and Physical Chemistry. Faculty of Pharmacy and Food Sciences. University of Barcelona. Barcelona, Spain
[b] Clinical Neurophysiology Section – Neurology Service. Bellvitge University Hospital. L'Hospitalet de Llobregat, Spain

ARTICLE INFO

Keywords:
Amyotrophic lateral sclerosis
Tofersen
SOD1 mutation
Antisense oligonucleotide therapy
Biomarkers
Regulatory approval
Neurofilament light chain

ABSTRACT

Background: Amyotrophic Lateral Sclerosis (ALS) is a progressive and ultimately fatal neurodegenerative disorder characterized by degeneration of upper and lower motor neurons. Mutations in the superoxide dismutase 1 (SOD1) gene account for approximately 2% of ALS cases and are associated with toxic protein misfolding and aggregation. Tofersen is an antisense oligonucleotide therapy designed to reduce the synthesis of mutant SOD1 protein through targeted mRNA degradation. While this strategy represents a gene-specific therapeutic approach for a subset of ALS patients, evidence regarding its efficacy, effectiveness and long-term outcomes continues to be evaluated in clinical trials and post-marketing studies.

Objective: First, to describe the molecular mechanisms underlying SOD1-associated ALS and second, to analyze the therapeutic development, clinical outcomes, and regulatory evolution of tofersen.

Methods: A narrative review was conducted in PubMed on preclinical and clinical studies published from 2016 through late 2025, complemented by an analysis of public registries and regulatory documentation. Clinical trials were identified through ClinicalTrials.gov and the Clinical Trials Information System (CTIS), and official reports from the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) were reviewed to contextualize their development and regulatory evaluation.

Results: Fifty-three publications were identified, of which 20 met predefined inclusion criteria after screening and full-text review. Preclinical studies showed reduced mutant SOD1 expression and prolonged survival in transgenic models. Phase I-II trials demonstrated safety, favorable pharmacokinetics, and dose-dependent reductions in SOD1 in the cerebrospinal fluid and plasma neurofilament light chain (NfL) levels. Although the phase III VALOR trial did not meet the primary ALSFRS-R endpoint (a validated questionnaire-based functional rating scale-revised for determining ALS disease progression) at 28 weeks, significant reductions in the surrogate biomarker NfL indicated target engagement and supported accelerated regulatory approval. Extension data suggested potential clinical benefit with early treatment. Ongoing studies, including ATLAS in presymptomatic carriers, and real-world European data support continued evaluation, alongside accelerated regulatory approvals by FDA and EMA.

Conclusion: Tofersen marks a paradigm shift in ALS management, establishing the foundation for precision medicine in neurodegenerative diseases. Its ongoing evaluation in the ATLAS trial will determine whether early intervention can prevent or delay disease onset in presymptomatic SOD1 mutation carriers.

1. Introduction

Amyotrophic Lateral Sclerosis (ALS) is a relentlessly progressive and fatal neurodegenerative disease characterized by the selective degeneration of upper and lower motor neurons, leading to muscle atrophy, progressive weakness, and eventual paralysis (Moriyama and Yokota, 2024; Hamad et al., 2025). Despite significant advances in molecular biology and neurogenetics, the precise pathophysiology of

* Corresponding authors.
E-mail addresses: braza@ub.edu (A.J. Braza), mvinasbastart@ub.edu (M. Viñas-Bastart), jmguiu@ub.edu (M. Sureda-Rosich), beliu.bellvitge@gmail.com (B. García-Parra), mariasureda@ub.edu (J.M. Guiu-Segura), pmodamio@ub.edu (P. Modamio).

https://doi.org/10.1016/j.ejps.2026.107563
Received 23 March 2026; Received in revised form 12 May 2026; Accepted 20 May 2026
Available online 21 May 2026

ALS remains unknown, with current models pointing to a complex interplay between genetic susceptibility, environmental factors, and age-related cellular decline (Zufiría et al., 2016; Al-Chalabi et al., 2017; Masrori and Van Damme, 2020).

Epidemiologically, ALS is a rare disease with a global incidence of approximately 2–2.7 cases per 100,000 people per year and a grim prognosis, with a median survival of approximately 3 to 5 years after diagnosis (Vidal Notari et al., 2024; Hamad et al., 2025). It primarily affects adults aged 40–70 years and shows a slight male predominance (ratio ~1.3:1) (Vidal Notari et al., 2024). Approximately 5–10% of cases are classified as familial (fALS), while the remaining 90–95% are considered sporadic (sALS). This clinical distinction, however, is increasingly blurred, as pathogenic mutations are also identified in patients without a clear family history, a phenomenon attributed to reduced penetrance or lack of diagnosed relatives.

To date, mutations in more than 40 genes have been associated with ALS, implicating diverse cellular pathways. Among these, the most common contributors – C9orf72, SOD1, TARDBP, and FUS – collectively account for 48% of familial cases and about 5% of sporadic cases (Akçimen et al., 2023; Everett and Bucelli, 2024). The first ALS-linked gene, identified in 1993, was superoxide dismutase 1 (SOD1). Mutations in SOD1 are responsible for 10–20% of fALS and 1–2% of sALS (Huang et al., 2024; Nguyen, 2024). The SOD1 gene encodes a critical antioxidant enzyme. Importantly, over 100 identified pathogenic variants in SOD1 are associated primarily with a toxic gain-of-function mechanism, leading to protein misfolding and aggregation, rather than a simple loss of enzymatic activity (Huang et al., 2024). This genetic heterogeneity translates into marked clinical variability, where specific variants like A4V or G93A are linked to rapid disease progression, while others like H46R follow a more indolent course (Nguyen, 2024; Smith et al., 2024).

The diagnosis of ALS remains primarily clinical, relying on the identification of combined upper and lower motor neuron signs and the exclusion of other disorders, supported by electromyography (EMG), neuroimaging, and laboratory tests (NINDS, 2024). Disease progression is quantitatively monitored using validated functional scales, most notably the ALS Functional Rating Scale-Revised (ALSFRS-R). This 12-item scale, scored from 0 (worst) to 4 (best) across bulbar, fine motor, gross motor, and respiratory domains (maximum score 48), is the most widely used instrument for assessing functional decline in both clinical practice and trials (Cedarbaum et al., 1999). Its role is so pivotal that recent consensus calls advocate for its standardized use as a primary outcome measure, including the evaluation of its correlation with biomarkers like neurofilament light chain (NfL), to ensure high-quality data in clinical trials on ALS (Genge et al., 2024).

In this context, tofersen has emerged as a gene-targeted therapeutic approach for patients with ALS associated with mutations in the SOD1 gene. Tofersen is an antisense oligonucleotide (ASO) therapy designed to reduce the production of mutant SOD1 protein by targeting its messenger RNA (mRNA) (Moriyama and Yokota, 2024). The therapy received accelerated approval from the U.S. Food and Drug Administration (FDA) in April 2023 and was granted conditional marketing authorization by the European Commission in May 2024, following a recommendation from the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA), based primarily on biomarker evidence rather than conclusive clinical outcomes (FDA, 2023; EMA, 2024). These regulatory decisions reflect growing interest in precision medicine approaches for genetically defined subgroups of ALS, while further evidence is being generated to clarify the magnitude and durability of clinical benefit.

The rapid evolution of knowledge regarding SOD1 pathogenesis, coupled with the clinical development and regulatory trajectory of tofersen, has generated a substantial and rapidly expanding body of literature. However, an integrated and up-to-date synthesis linking molecular mechanisms to therapeutic rationale, clinical evidence, and regulatory milestones remains lacking. This narrative review seeks to address this gap by connecting the molecular basis of SOD1-ALS with the development and clinical application of tofersen, providing a resource for researchers and clinicians.

2. Objective

The present study aims to: (1) describe the molecular mechanisms underlying the pathogenesis of SOD1-associated ALS; and (2) examine the therapeutic development and regulatory pathway of tofersen as the first antisense oligonucleotide (ASO) specifically targeting mutant SOD1.

3. Material and methods

The narrative review encompassed peer-reviewed publications indexed in PubMed from 2016 through late 2025, including studies on tofersen (BIIB067). All available clinical trials during this period were analyzed to reconstruct the historical development of tofersen, examine their main methodological characteristics, and evaluate their scientific contributions to the treatment of SOD1-ALS. In parallel, the chronology of its clinical and regulatory development—from preclinical research to evaluation by regulatory agencies such as the FDA and the EMA—was compiled to provide a comprehensive overview of its therapeutic relevance.

Clinical trials were identified through a stepwise search of international registries. First, “tofersen” was used as a keyword in the Clinical Trials Information System (CTIS), managed by the EMA, to retrieve trials authorized or ongoing in the European Union member states and European Economic Area, including international multicenter studies involving European sites. Subsequently, a complementary search was performed in ClinicalTrials.gov, managed by the U.S. National Library of Medicine, to capture studies conducted in the United States, the Americas, and other regions, as well as global multicenter trials.

In parallel, a structured bibliographic search was conducted in PubMed using the terms “tofersen” and “trials,” which were combined and refined to identify publications corresponding to the clinical trials previously retrieved from public registries. This approach enabled direct linkage between each scientific publication and its associated registered trial, ensuring consistency and methodological coherence across sources. Study selection and screening were performed independently by two reviewers, with discrepancies resolved by consensus to minimize bias and enhance the objectivity of the analysis.

In addition, a structured comparative analysis of the trials was conducted, focusing on aspects such as study phase (I–III), methodological design (randomized, double-blind, open-label, placebo-controlled), planned and actual number of participants, target population characteristics (symptomatic and presymptomatic patients according to SOD1 variant), duration of follow-up, primary and secondary endpoints, safety measures, treatment discontinuation rates, and statistical methods employed.

Finally, a regulatory analysis was conducted based on the review of official documents and communications issued by regulatory agencies. For the EMA, reports from the CHMP and the status of the conditional marketing authorization in the European Union were analyzed. For the FDA, the accelerated approval process for tofersen was reviewed, including its approved indications, conditions of use, and post-marketing monitoring requirements. This approach allowed the integration of scientific and clinical perspectives with the regulatory evolution of the medicine, providing a comprehensive overview of its development process and current positioning as a targeted therapy for SOD1-ALS.

4. Results

A total of 53 publications were initially identified through the bibliographic search. The selection process followed a structured and

reproducible methodology.

In the first phase, duplicate records were removed. Subsequently, two reviewers independently screened the titles and abstracts of all retrieved articles according to predefined eligibility criteria. Studies were selected based on their scientific relevance, inclusion of original data, and methodological value for understanding the preclinical and clinical development of tofersen. Each reviewer independently assessed methodological quality, robustness of results, clarity of reporting, and the specific contribution to the pharmacological, clinical, or regulatory knowledge of the drug. Discrepancies were resolved through discussion until consensus was reached.

Potentially eligible articles were then evaluated in full text. Inclusion criteria emphasized methodological rigor and thematic relevance. Priority was given to original studies reporting primary data on efficacy, safety, biomarkers—particularly neurofilaments—as well as pharmacokinetic and pharmacodynamic parameters and relevant regulatory information. Redundant publications, secondary subanalyses without substantial new data, and preliminary reports later consolidated into more comprehensive articles were excluded. After this screening and critical appraisal process, 20 articles were finally selected and constituted the core bibliography used to reconstruct the sequence of preclinical and clinical studies of tofersen and to analyze its methodological and regulatory evolution.

Once the final selection was completed, the correspondence between included publications and their respective registered clinical trials was verified to ensure consistency between sources. Regarding study types, one publication specifically describing the initial preclinical development of tofersen was identified. For phase I and II trials, including studies that transitioned into phase III, a single integrative article compiling the available clinical data was selected. In addition, two publications specifically addressing long-term follow-up and biomarker validation were included, reflecting the growing importance of neurofilament dynamics and extended efficacy and safety outcomes in the therapeutic evaluation of tofersen.

A flowchart (Fig. 1) summarizing the identification, screening, eligibility, and inclusion process would be appropriate to visually represent the study selection pathway and enhance methodological transparency.

Regarding pivotal phase III trials—including the VALOR and ATLAS studies and their corresponding open-label extensions (OLEs)—seven publications were identified that addressed clinical outcomes, secondary analyses, and methodological considerations, thereby enabling a comprehensive evaluation of both functional endpoints and biomarker evolution, as well as long-term follow-up data.

Separately, before specifically addressing evidence in real-world clinical settings, phase IV and prospective and retrospective observational studies conducted post-authorization were included. These studies were designed to assess safety, effectiveness, and benefit-risk profiles in less controlled environments than pivotal trials. Finally, in the context of real-world evidence, four publications were selected analyzing cohorts of patients treated in routine clinical practice, providing complementary information on usage patterns, adherence, tolerability, and clinical outcomes in more heterogeneous populations. This sequential integration of evidence—from preclinical studies to post-authorization observational data—allowed for a structured and chronologically coherent overview of tofersen's pharmacological and clinical development.

The results of this review are structured into two main subsections corresponding to the study objectives: first, a brief characterization of the pathogenic mechanisms underlying SOD1-associated ALS (Section 4.1); and second, the analysis of tofersen's therapeutic development and regulatory evolution, from initial studies to evaluation by international regulatory agencies (Section 4.2).

4.1. *Pathogenic mechanisms of SOD1-associated ALS*

The SOD1 gene encodes the enzyme superoxide dismutase 1, which catalyses the conversion of the superoxide radical ($O_2^{\bullet -}$) into molecular oxygen and hydrogen peroxide, protecting cells from oxidative damage. Its correct function depends on appropriate Cu^{2+} and Zn^{2+} ion binding, the formation of a stabilizing disulphide bond (Cys^{57}–Cys^{146}), and proper dimerization (Nguyen, 2024). In the context of ALS, SOD1 mutations do not primarily lead to loss of enzymatic activity, but rather to a toxic gain of function. These mutations destabilize the protein, reduce its metal-binding affinity, expose hydrophobic residues, and induce misfolding and aggregation into intracellular inclusions. Many mutant variants maintain partial catalytic activity, reinforcing that neurotoxicity arises from newly acquired harmful properties rather than enzymatic inactivity (Huang et al., 2024; Berdyński et al., 2025). In addition, mutant SOD1 appears to propagate its misfolded conformation in a prion-like manner, facilitating disease spread across motor neurons. This prion-like propagation may begin before clinical manifestations become apparent, providing a strong mechanistic rationale for early therapeutic intervention strategies, such as presymptomatic treatment approaches evaluated in the ATLAS trial, with the aim of limiting neuronal spread and cumulative neurotoxicity (Huang et al., 2024; Berdyński et al., 2025).

Once misfolded, mutant SOD1 triggers multiple pathogenic mechanisms (Tafuri et al., 2015; Huang et al., 2024; Smith et al., 2024). These include oxidative stress due to ROS accumulation with consequent lipid, protein, and DNA damage, exacerbated by reduced antioxidant defences (Moriyama and Yokota, 2024). Mitochondrial dysfunction is also prominent: mutant SOD1 accumulates in the mitochondrial intermembrane space, alters membrane integrity, reduces membrane potential,

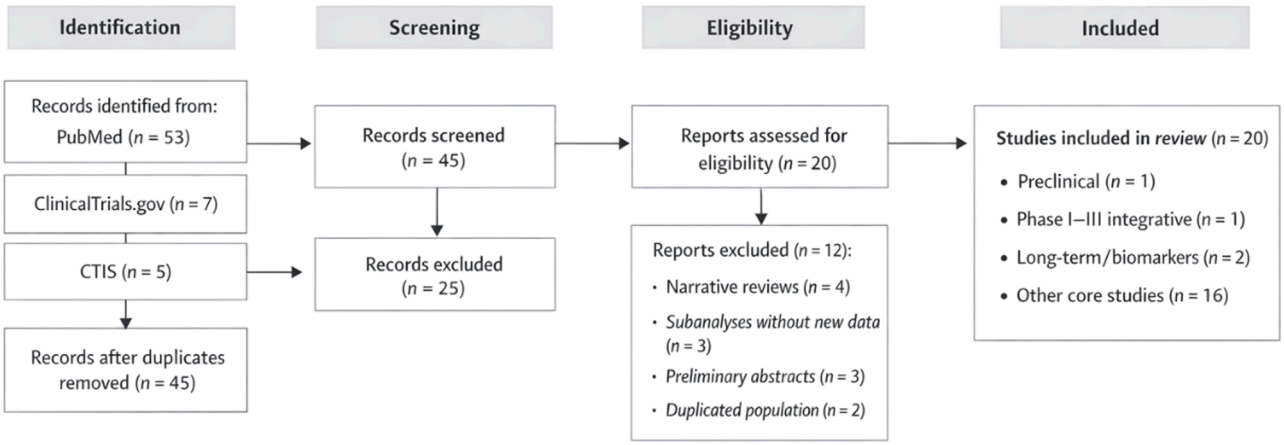

Fig. 1. Flow diagram of the study selection process.

decreases ATP production, and promotes cytochrome c release (Tsekrekou et al., 2024; Martinelli et al., 2025). Another important mechanism is impaired axonal transport, as mutant SOD1 disrupts microtubule-dependent trafficking of vesicles and organelles, causing axonal congestion and degeneration (Smith et al., 2024). Proteostasis is significantly compromised: SOD1 aggregates overload the ubiquitin–proteasome system and impair autophagy, promoting the accumulation of abnormal proteins (Woo et al., 2021). Neuroinflammation further contributes to disease progression, since mutant SOD1 activates microglia and astrocytes, inducing the release of pro-inflammatory cytokines; notably, selective removal of SOD1 in glial cells slows disease progression in animal models, indicating that ALS is not purely cell-autonomous (Huang et al., 2024). A more recently described mechanism is the inhibition of mitochondrial-derived vesicle formation, an essential quality-control pathway for removing damaged mitochondrial proteins; its disruption accelerates mitochondrial dysfunction (Guo et al., 2024).

All these pathological processes have been effectively modelled in SOD1 transgenic mice, such as the G93A line, which reproduce key clinical and molecular features of human ALS (Tafuri et al., 2015). This mechanistic knowledge has guided the development of targeted therapies. Among them, the ASO tofersen reduces the expression of mutant SOD1 and mitigates its toxic downstream effects, while additional molecules designed to stabilize the native conformation of SOD1 and prevent aggregation are also under investigation (Woo et al., 2021; Hamad et al., 2025).

The development of tofersen began between 2013 and 2016 through discovery and preclinical studies, during which its mechanism of action was validated and robust reductions in mutant SOD1 were demonstrated in cellular and animal models, together with a favourable safety profile that enabled progression to clinical trials (Ionis Pharmaceuticals, 2018).

The development of tofersen was initially supported by preclinical studies conducted in transgenic murine models carrying SOD1 mutations. In this context, McCampbell et al. (2018) demonstrated that intrathecal administration of ASOs targeting SOD1 mRNA significantly reduced mutant SOD1 protein levels in the spinal cord, improved muscular responses, and prolonged survival in SOD1-ALS animal models. Tofersen partially reversed functional decline when administered in early symptomatic stages, providing evidence of disease-modifying potential and establishing the mechanistic rationale for transitioning to clinical studies.

4.2. Clinical development evolution of tofersen

Prior to the initiation of interventional clinical trials, a characterization of the natural history of SOD1-associated ALS was performed. Bali et al. (2017) analyzed clinical progression, phenotypic heterogeneity, and survival in patients with SOD1-ALS, providing robust estimates of functional decline rates and interindividual variability. These data were critical for the methodological planning of subsequent clinical trials, particularly regarding the selection of primary endpoints, sample size calculation, and the definition of inclusion criteria.

The clinical development of tofersen began with a phase I–II trial the results of which were published (Miller et al., 2020), which evaluated safety, tolerability, pharmacokinetics, and pharmacodynamic effects following intrathecal administration. The study demonstrated a dose-dependent reduction of SOD1 protein levels in cerebrospinal fluid (CSF), along with decreased NfL, a biomarker associated with axonal damage. Although not designed to establish definitive clinical efficacy, preliminary signals of slowed functional decline were observed in higher-dose groups, supporting progression to subsequent trials.

The clinical development of tofersen followed a systematic approach, including phase III trials (VALOR), OLE studies, preventive studies in presymptomatic carriers (ATLAS), and observational studies under real-world clinical practice conditions (Table 1).

4.2.1. Phase I-II (Study 233AS101 parts A and B)

Study 233AS101 (Parts A and B) constituted the initial evaluation phase (Phase I-II). It was designed as a randomized, double-blind, placebo-controlled trial, including a single ascending dose phase (Part A) and a multiple ascending dose phase (Part B) in adult patients with confirmed SOD1-mutant ALS. Participants received intrathecal injections of tofersen at doses ranging from 10 to 100mg, or a matching placebo. The primary objectives focused on assessing safety, tolerability, and pharmacokinetics.

Results showed that the 100mg dose achieved the highest drug exposure in CSF and produced the most pronounced reduction in total SOD1 protein levels in CSF, a key pharmacodynamic marker. Pharmacokinetic analysis revealed an effective CSF half-life of approximately one month, which informed the subsequent dosing regimen. While adverse events related to the lumbar puncture procedure (such as back pain and headache) were observed, the overall safety profile was considered manageable, allowing progression to subsequent efficacy trials. A notable safety finding was the occurrence of elevated white blood cell counts in CSF, observed more frequently and with greater magnitude in the tofersen group, prompting the implementation of strict blinding measures in subsequent studies (Miller et al., 2020).

4.2.2. Phase III (VALOR, 233AS101 part C)

Part C of Study 233AS101 (VALOR) constituted the pivotal phase III trial. This 28-week, randomized (2:1), double-blind, placebo-controlled study enrolled 108 patients, with stratification of a prognostically enriched rapid progression subgroup (modified intention-to-treat population) for the primary analysis. Importantly, the primary efficacy analysis focused on this “fast progressors” subgroup, representing patients with an anticipated accelerated disease course, thereby establishing a carefully defined context for detecting meaningful functional improvement within the relatively short 28-week study period. The dosing regimen established in earlier phases consisted of three 100mg loading doses administered every 14 days, followed by maintenance doses every 28 days. The primary endpoint was the change from baseline in ALSFRS-R score at week 28 in the modified intention-to-treat population.

Although the primary outcome did not reach statistical significance (difference of 1.2 points; $p = 0.97$), post hoc analyses adjusting for baseline NfL levels showed a greater difference of 2.1 points ($p = 0.0904$). Robust efficacy was observed at the biomarker level, with statistically significant reductions of 38% in CSF SOD1 and 67% in plasma NfL in the tofersen group versus placebo. Favorable trends were also noted in other clinical measures, including vital capacity and select quality-of-life parameters.

Regarding safety, the profile was consistent with prior phases, highlighting intrathecal administration-related events and neuroaxial inflammatory events (e.g., myelitis/radiculitis). These inflammatory complications, although infrequent, are clinically relevant because they generally require prompt recognition, temporary treatment interruption, and management with corticosteroid therapy and supportive neurological monitoring, with most reported cases showing partial or complete resolution after intervention. Their consideration is particularly important when evaluating the benefit–risk balance in presymptomatic SOD1 mutation carriers who may otherwise remain clinically stable for prolonged periods. The main limitation of the study was its relatively short duration, insufficient to clearly detect a clinical benefit in a disease with heterogeneous progression. Parts A, B, and C of Study 233AS101 have now been completed (Benatar et al., 2022).

4.2.3. Open-label extension (OLE, 233AS102)

The pivotal clinical study 233AS102 is an ongoing long-term OLE, designed to evaluate the safety and sustained effect of tofersen in participants who completed study 233AS101. This multicenter study is conducted in Belgium, Canada, Denmark, France, Germany, Israel, Japan, Italy, New Zealand, the United Kingdom, and the United States.

Table 1
Chronological evolution of tofersen clinical trials (2013–present). AE: adverse event; AESI: adverse event of special interest; ANCOVA: analysis of covariance; ANOVA: analysis of variance; CSF: cerebrospinal fluid; MAD: multiple ascending dose; MAR: missing at random; MI: multiple imputation; MMRM: mixed-model repeated measures; NfL: neurofilament light chain; NOAEL: no observed adverse effect level; NR: not reported; N/A: not applicable; OLE: open-label extension; PK/PD: pharmacokinetics/pharmacodynamics; pNfH: phosphorylated neurofilament heavy chain; PV: pharmacovigilance. SAD: single ascending dose; SAE: serious adverse event; SVC: slow vital capacity; TEAE: treatment-emergent adverse event.

Years	Study / Milestone	Trial phase	Study design	Number of participants (planned / actual)	Target population	Duration of follow-up	Primary efficacy endpoint(s)	Primary endpoint results	Secondary / exploratory endpoint(s)	Safety measures & discontinuations	Statistical analysis	Key references
2015–2018	233AS101 – Parts A & B	Phase I-II	Multicenter, randomized, double-blind, placebo-controlled SAD (Part A) and MAD (Part B)	Part A: 20 (15 tofersen / 5 placebo) Part B: 50 (38 tofersen / 12 placebo)	Symptomatic ALS with confirmed SOD1 mutation	~8 weeks (SAD); ~24 weeks (MAD)	Safety and tolerability	Tolerated at all doses; no dose-limiting toxicities	PK/PD; CSF SOD1; plasma NfL; exploratory clinical measures	TEAEs, SAEs, labs, neurological exams; low discontinuation	Descriptive; exploratory ANOVA/ ANCOVA; mixed models	(Miller et al., 2020).
2016–2021	233AS101 – Part C (VALOR pivotal study)	Phase III	Multicenter, randomized, double-blind, placebo-controlled	Planned/ Actual: 108 (72 tofersen / 36 placebo)	Symptomatic ALS-SOD1 patients (enriched for faster progression)	28 weeks double-blind	Change from baseline to Week 28 in ALSFRS-R (mITT population)	Mean ALSFRS-R decline reduced vs placebo (−1.2vs −3.0 points); not statistically significant primary endpoint	CSF SOD1; plasma NfL; SVC; HHD; time to death or permanent ventilation (exploratory)	TEAEs, SAEs, AESIs; ~7% discontinuation	ANCOVA with MI; MMRM; predefined mITT; post hoc analyses adjusting for baseline NfL	(Benatar et al., 2022)
2017–ongoing	233AS102 – OLE	Phase III (OLE)	Multicenter, randomized, double-blind, placebo controlled, OLE of 233AS101	Enrolled: 139 (from Parts A, B, and C)	Symptomatic ALS-SOD1 patients previously treated	Up to ~7 years (depending on entry). 28 weeks DB; 52 weeks extended	Long-term safety and tolerability. Change in ALSFRS-R at week 28	Slower ALSFRS-R decline in early-start group vs delayed-start; maintained safety profile	ALSFRS-R slope; SVC; CSF SOD1; plasma NfL; survival (exploratory)	Cumulative TEAEs/SAEs; long-term safety monitoring. TEAEs, SAEs, AESIs; ~7% discontinuation	Descriptive; mixed-effects longitudinal models; integrated analyses with study 101. ANCOVA; MMRM; MI (MAR); early vs delayed start	(Benatar et al., 2022;NLMa, 2025).
2019–ongoing	233AS303 – ATLAS	Phase III (preventive)	Multicenter, randomized, double-blind, placebo-controlled with natural history run-in and OLE	Part A: ~150 planned (observational) Part B: 28 randomized	Presymptomatic carriers of highly penetrant SOD1 mutations with elevated plasma ↑ NfL	Up to 2 years (interventional) + OLE. ≥5 years or until ALS onset	Time to emergence of clinically manifest ALS	Preliminary data: delayed ALS onset in NfL-guided early intervention cohort	NfL/pNfH dynamics; functional decline after symptom onset; safety	Continuous AE/ SAE monitoring; blinded safety reviews	Cox proportional hazards; Kaplan–Meier; longitudinal models	(Brown et al., 2021; Benatar et al., 2022; Oliveria-Santos and de Carvalho 2024; McGuigan and Blair, 2025).
2024–2025	Real-world studies	Phase IV	Multicenter observational (retro/ prospective) Locations: Italy, Germany, Sweden.	Planned: NR Actual: 20–80 per country	Symptomatic ALS-SOD1 (routine practice)	6–24 months	Real-world effectiveness (ALSFRS-R)	ALSFRS-R stabilized or slowed decline vs historical control	Respiratory function, NfL/pNfH, survival proxies	PV-based AE reporting	Descriptive; adjusted longitudinal	(Meyer et al., 2024; Wiesenfarth et al., 2024; Hamad et al., 2025; Smith et al., 2025).
2026–2027	Long-term follow-up & biomarker validation	Phase IV / post-authorisation	Multicenter longitudinal	N/A	ALS-SOD1 (treated & presymptomatic)	Long-term (≥5 years)	Durability of biomarker response	Stable CSF SOD1 suppression; correlations with slowed functional decline	Correlation with function, survival	Long-term safety monitoring	Longitudinal correlation & survival analyses	(Benatar et al., 2022; NLMb, 2025; Simonini et al., 2025).

The design incorporates a blinded loading period, carefully conceived to preserve the integrity of the pivotal study blinding.

Integrated data from the VALOR and long-term extension studies, with a cut-off at week 52, have provided valuable insights. Analyses extended to 52 weeks showed that biomarker changes correlated with slowed motor and respiratory decline, as well as improvements in quality of life (Miller et al., 2022). Reductions in SOD1 and NfL biomarkers remained stable over the long term, and the safety profile remained consistent, with serious adverse events observed in approximately 7% of patients, including myelitis, radiculitis, aseptic meningitis, and intracranial hypertension.

Furthermore, comparative analysis between patients who initiated tofersen early (in VALOR) and those who started later (placebo in VALOR, active in long-term extension) revealed clinically meaningful differences favoring early initiation: a 3.5-point difference in ALSFRS-R, a 9.2% increase in predicted vital capacity, and a 64% reduction in the risk of death or permanent ventilation (Hazard Ratio = 0.36). These findings suggest that prolonged treatment may translate observed biological effects into clinical benefits. The safety profile during this extended phase has remained consistent, with no new signals, although neuroaxial inflammatory events continue to require monitoring (NLMa, 2025).

The OLE (233AS102) incorporated Part C, allowing tofersen administration to all participants, including those who initially received placebo. In the combined analysis of VALOR and OLE at 12 months, patients who started treatment early demonstrated significant improvements: a +3.5-point increase in ALSFRS-R, a 9% improvement in vital capacity, gains in muscle strength and quality of life, as well as sustained reductions in SOD1 (33% → 21%) and NfL (51% → 41%) biomarkers, demonstrating both biological and clinical benefits of early administration (Brown and Al-Chalabi, 2017; Brown et al., 2021).

4.2.4. Preventive study ATLAS (233AS303)

Finally, study 233AS303 (ATLAS) represents a Phase III preventive approach. This ongoing, blinded trial is recruiting presymptomatic carriers of high-risk SOD1 mutations. Its design includes an initial observational "run-in" phase to establish the natural history, followed by a two-year randomized, placebo-controlled intervention phase. The primary objective is to evaluate whether tofersen can delay or prevent the onset of clinical manifestations of ALS. Given its current status, no efficacy data are yet available. tofersen is administered following the 100mg intrathecal regimen. Safety assessment in this asymptomatic population is of paramount importance, requiring careful consideration of known procedural and drug-related risks versus the potential benefit of preventing a devastating disease (Benatar et al., 2022; Oliveira-Santos and de Carvalho, 2024; McGuigan and Blair, 2025).

Subsequently, other observational studies under real-world clinical practice conditions were conducted in Italy, Germany, and Sweden, including small cohorts (11–17 patients) with ≥12 months follow-up. These studies confirmed reductions in phosphorylated neurofilament heavy chain (pNfH) and NfL in serum and CSF, stabilization or slight improvement of ALSFRS-R scores in some patients, and a safety profile consistent with clinical trials, with mild inflammatory events and no significant increase in serious adverse events (Meyer et al., 2024; Wiesenfarth et al., 2024).

4.2.5. Evidence from real-world clinical practice

To further characterize the long-term benefit-risk profile of tofersen in real-world settings, phase IV observational studies were planned for 2024–2025. These multicenter, retrospective and prospective studies were conducted in countries including Italy, Germany, and Sweden, aiming to recruit 20–80 patients per country with symptomatic SOD1-ALS receiving routine care. With a planned duration of 6 to 24 months, the primary objective is to assess drug effectiveness under real-world clinical conditions, using change in ALSFRS-R score as the primary endpoint. Secondary objectives included evaluation of respiratory function, biomarker levels (NfL and pNfH), and indirect survival parameters. Safety has been monitored through adverse event reporting based on pharmacovigilance procedures. Statistical analyses are primarily descriptive, complemented by adjusted longitudinal models. These studies are essential to understand how benefits observed in controlled clinical trials translate into less structured and more heterogeneous clinical settings (Meyer et al., 2024; Wiesenfarth et al., 2024; Hamad et al., 2025; Smith et al., 2025).

4.2.6. Long-term follow-up studies (233AS401)

In parallel, long-term follow-up and biomarker validation studies are planned for 2026–2027, constituting a post-authorization phase. These longitudinal, multicenter studies aim to follow patients with SOD1-ALS—including symptomatic patients under treatment and presymptomatic carriers from the ATLAS study—over periods of 5 years or more. The primary objective is to evaluate the durability of responses in key biomarkers (SOD1, NfL) over extended treatment durations. Additionally, the studies aim to establish stronger correlations between biomarker changes and long-term clinical outcomes, such as functional decline and survival. Long-term safety monitoring will also be a central component. Analyses will be based on longitudinal correlation methods and survival analyses, providing critical evidence on the sustainability of disease-modifying effects and the prognostic utility of biomarkers over extended time horizons (Benatar et al., 2022; Miller et al., 2022; ECa, 2024; NLMb, 2025; Simonini et al., 2025).

In conclusion, the clinical development program of tofersen illustrates a comprehensive pathway from initial safety and pharmacology characterization, through a pivotal trial with mixed results on the primary clinical endpoint but robust effects on pathogenic biomarkers, to evidence suggestive of longer-term benefit and the pioneering exploration of a preventive treatment paradigm. Planned phase IV and very long-term follow-up studies are designed to close remaining knowledge gaps, particularly regarding effectiveness and the durability of response, thereby strengthening the evidence base for this innovative therapy. The collective evidence highlights the central role of biomarkers in the development of therapies for neurodegenerative diseases and underscores the importance of treatment duration and prolonged observation to fully evaluate disease-modifying potential in ALS (Meyer et al., 2024; Wiesenfarth et al., 2024; Hamad et al., 2025; Smith et al., 2025).

4.3. International regulatory approval

Table 2 summarizes the main regulatory assessments and approvals of tofersen by the European Union and U.S. drug regulatory agencies.

The marketing authorization of tofersen was granted under special regulatory frameworks, reflecting both the severity of SOD1-associated ALS and the lack of effective therapeutic alternatives. In the FDA granted an accelerated approval on 25 April 2023, primarily based on the significant reduction in NfL, considered a reasonably likely surrogate biomarker for predicting clinical benefit. This approval was conditional on subsequent confirmation of clinical benefit through post-

Table 2
Evaluation and regulatory approval of tofersen by FDA and EMA.

Month/ Year	Agency/Region	Key Details
Apr 2023	FDA (United States)	Expedited approval based on NfL biomarker reduction for genetically confirmed ALS-SOD1. Post-marketing surveillance required (ATLAS as confirmatory) (FDA, 2023; Lisi et al., 2023).
Feb 2024	EMA CHMP	Positive recommendation under "exceptional circumstances." Conditions: Annual benefit-risk assessments, continuous safety/efficacy data (EMA, 2024).
May 2024	European Commission	Formal approval (ECb, 2024).

authorization studies, including the ATLAS program (FDA, 2023; Lisi et al., 2023).

Concurrently, other international regulatory agencies, such as Health Canada and the Therapeutic Goods Administration (TGA) of Australia, approved tofersen in 2023 under conditional or standard frameworks, respectively, subject to pharmacovigilance commitments and the future availability of confirmatory evidence from pivotal and long-term extension studies, as well as the ATLAS confirmatory trial (EMA, 2024; ECa, 2024; NLMb, 2025).

In Europe, the CHMP of the EMA issued a positive opinion in February 2024 for the marketing authorization of tofersen under the "exceptional circumstances" scheme, in accordance with Article 14(8) of Regulation (EC) No 726/2004. This recommendation was based on the robust and consistent effect of the drug on key pathogenic biomarkers, despite the pivotal VALOR trial (233AS101, Part C) not reaching statistical significance on its primary clinical endpoint (ALSFRS-R) (EMA, 2024; ECa, 2024).

The CHMP recommendation was formalized by the European Commission on 30 May 2024, granting marketing authorization in the European Union under exceptional circumstances. This authorization requires annual evaluations of the benefit–risk balance, continuous submission of safety and efficacy data, and enhanced regulatory oversight by the EMA and competent authorities (ECa, 2024; EMA, 2024).

Given that the marketing authorization of tofersen was granted under special regulatory frameworks—accelerated approval in the United States and exceptional circumstances authorization in the European Union—its commercialization is subject to a specific set of post-authorization obligations. These conditions reflect both the severity of SOD1-associated ALS and the need to definitively confirm long-term clinical benefit beyond the biomarker effects observed. In this context, regulatory agencies have established strict commitments, including confirmatory studies, extended safety monitoring, and periodic reassessments of the benefit–risk balance. Table 3 provides a structured summary of these requirements, associated timelines, and the oversight mechanisms that govern the maintenance of tofersen authorization across different jurisdictions.

5. Discussion

Based on the information selected, the discussion is structured into four sections, allowing integration of the drug's biological rationale, clinical and regulatory evidence, limitations associated with its use, and its current positioning.

5.1. Accelerated approval and mechanism of action of tofersen

Tofersen is an intrathecally administered ASO that specifically binds to SOD1 mRNA, reducing its translation and consequently lowering mutant SOD1 protein levels (Moriyama and Yokota, 2024). This mechanism of action directly aligns with the molecular pathophysiology of SOD1-ALS, which is characterized by a toxic gain-of-function of the mutant protein, responsible for inducing oxidative stress, mitochondrial dysfunction, impaired axonal transport, neuroinflammation, and disruption of neuronal proteostasis (Tafuri et al., 2015; Woo et al., 2021; Huang et al., 2024; Tsekrekou et al., 2024; Martinelli et al., 2025).

This biological rationale explains the consistency and magnitude of the effects observed on key pathogenic biomarkers. In clinical studies, tofersen has been associated with significant and sustained reductions in CSF SOD1 protein and plasma NfL levels (Miller et al., 2022). The decrease in NfL is particularly relevant given its value as a marker of axonal damage and its association with ALS clinical progression, suggesting a potential neuroprotective effect and providing a robust mechanistic basis for regulatory consideration.

5.2. Clinical evidence and key regulatory milestones

In April 2023, the FDA approved tofersen as the first targeted treatment for SOD1-associated ALS through an accelerated approval pathway (FDA, 2023). Subsequently, in May 2024, the European Commission granted authorization under the "exceptional circumstances" scheme (EMA, 2024; ECb, 2024). These decisions were primarily based on the consistent reduction of SOD1 and NfL, considered reasonably likely surrogate biomarkers for clinical benefit in a context of high unmet medical need (Miller et al., 2022; Lisi et al., 2023).

However, the pivotal VALOR trial did not reach statistical significance on its primary clinical endpoint, assessed by the ALSFRS-R score at 28 weeks (Benatar et al., 2022). This outcome should be interpreted considering the study's limited duration and the high heterogeneity in ALS functional progression, factors that hinder the detection of meaningful clinical changes over a short period. In this context, data from the

Table 3
Commitments & Future Monitoring to maintain the commercialization of Tofersen in the European Union, the United States and others contries.

Regulatory Agency	Approval Status	Date	Indication Approved	Post-Authorization Requirements	Short-Term / Annual Reassessments	Long-Term Confirmatory Milestones	References
EMA (European Union)	Conditional approval	2022–2023	Adults with ALS associated with confirmed SOD1 mutation	Annual benefit-risk assessments; continuous submission of safety and efficacy data; annual observational record (study 233AS401); results of the pivotal study and long-term follow-up (study 233AS102 – VALUE); integrated final survival analyses (treated vs. untreated); completion of the ATLAS confirmatory study (233AS303)	Annual reassessment reports; 30 September 2025 (VALUE results)	**30 June 2027 (integrated survival analyses); 31 December 2028 (ATLAS completion)**	(ECa, 2024; EMA, 2024; NLMb, 2025).
FDA (United States)	Accelerated Approval	25 April 2023	Adults with ALS associated with confirmed SOD1 mutation	Confirmation of clinical benefit through post-approval studies (including ATLAS); enhanced pharmacovigilance	Ongoing pharmacovigilance reporting	Aligned with VALOR extension and ATLAS completion milestones	(ECa, 2024; NLMb, 2025).
Health Canada	Approved with conditions	2023	Adults with ALS associated with confirmed SOD1 mutation	Post-marketing pharmacovigilance commitments and possible additional confirmatory evidence	Periodic pharmacovigilance updates	Dependent on ATLAS end results and integrated survival analyses	(EMA, 2024; ECa, 2024; NLMb, 2025).
TGA (Australia)	Approved	2023	Adults with ALS associated with confirmed SOD1 mutation	Standard post-authorisation pharmacovigilance	Routine safety monitoring	International confirmatory evidence follow-up (ATLAS long-term extension)	(EMA, 2024; NLMb, 2025).

OLE acquire key interpretative value. Integrated 12-month analyses showed that patients who initiated tofersen early exhibited slowed functional and respiratory decline, improvements in strength and quality-of-life measures, and a clinically meaningful reduction in the composite risk of death or permanent ventilation (Miller et al., 2022; Meyer et al., 2024;NLMa, 2025).

The consistency of these findings is reinforced by a recent meta-analysis, which show significant slowing of functional decline measured by ALSFRS-R and reduced loss of vital capacity (Hamad et al., 2025), as well as by real-world clinical practice studies conducted in several European countries, where consistent reductions in NfL and, in some cases, stabilization of clinical progression were confirmed in less controlled care settings (Meyer et al., 2024; Wiesenfarth et al., 2024). Although these observational studies have inherent limitations, their concordance with clinical trial data provides external robustness to the overall body of evidence.

5.3. Limitations and challenges associated with tofersen treatment

Despite these advances, the implementation of tofersen presents relevant limitations and challenges. SOD1 mutations are rare, accounting for only 2% of ALS cases, which limits the direct population impact and highlights the need for systematic genetic diagnostic strategies to identify eligible patients early (Vázquez-Costa et al., 2022; Huang et al., 2024).

From a regulatory perspective, approval is primarily based on biomarker reduction, which, while aligned with current trends in rare diseases, requires the generation of robust long-term confirmatory clinical evidence. In this context, the ATLAS trial is pivotal for assessing whether early treatment initiation in presymptomatic carriers can prevent or delay the onset of clinical disease (Benatar et al., 2022; NLMb, 2025).

From a logistical standpoint, intrathecal administration via lumbar puncture requires specialized infrastructure, trained personnel, and dedicated care pathways, which may limit accessibilityin certain centers (Cerillo and Parmar, 2023; Medscape, 2024; AEMPS, 2025).

Regarding safety, although the overall profile is considered manageable, serious neurological adverse events have been reported in approximately 7% of patients, including myelitis, radiculitis, aseptic meningitis, and intracranial hypertension (Miller et al., 2022; Cerillo and Parmar, 2023; Qalsody®, 2025). These events warrant close monitoring and careful benefit–risk assessment, particularly in presymptomatic populations. Additionally, regulatory obligations associated with authorization under "exceptional circumstances," such as annual benefit–risk reassessments and submission of definitive results from ongoing studies, pose further challenges in terms of economic sustainability and healthcare planning. Furthermore, the high acquisition and administration costs associated with tofersen may generate reimbursement and cost-effectiveness challenges for national healthcare systems, particularly in countries with centralized public funding models such as Spain, where long-term clinical benefit confirmation may influence future funding and access decisions (ECa, 2024; SMH, 2025).

5.4. International variability in regulatory approval and access to tofersen

The regulatory pathway of tofersen highlights substantial differences between countries and regulatory agencies regarding the evaluation of clinical benefit, the role of biomarkers, and the management of uncertainty in rare, high-severity diseases. These divergences reflect not only distinct regulatory frameworks but also heterogeneous approaches to benefit–risk assessment and unmet medical need.

In the United States, the FDA granted accelerated approval in April 2023 primarily based on biomarker reductions, particularly NfL, which are considered reasonably likely predictors of clinical benefit in the context of SOD1-ALS (FDA, 2023). This approach aligns with a more flexible regulatory tradition for rare and potentially fatal diseases, where a higher degree of initial clinical uncertainty is accepted in exchange for early patient access, conditioned on the completion of post-authorization confirmatory studies.

In contrast, the European Comission adopted a more restrictive approach, granting authorization under "exceptional circumstances" in May 2024—a regulatory mechanism that explicitly acknowledges the limitations of available evidence and the difficulty of generating complete data in an ultra-rare population (EMA, 2024; ECb, 2024). This framework imposes additional obligations, such as periodic reassessments of the benefit–risk balance and continuous submission of data from ongoing studies, which condition both the maintenance of authorization and its implementation across member states.

These regulatory differences translate into different access across European countries, where centralized authorization does not automatically ensure reimbursement or clinical availability. In countries such as Italy and Germany, early-access programs and real-world studies coordinated at the national level have been initiated, facilitating the generation of additional evidence and controlled clinical use of the medicine (Meyer et al., 2024; Wiesenfarth et al., 2024). In other countries, like Spain, the reimbursement of tofersen by the national healthcare system is subject to national evaluation, budget impact, and resource prioritization, which may delay effective access (AEMPS, 2025).

The international experience with tofersen illustrates how the same dataset can lead to different regulatory decisions depending on institutional contexts and healthcare priorities, while highlighting the growing convergence between molecular biology, biomarkers, and regulatory evaluation processes. This scenario underscores the importance of post-authorization studies and real-world evidence in reducing uncertainty and promoting equitable access to innovative therapies for rare, high-risk diseases. It also anticipates a structural shift in ALS therapeutic development, where conditional early access and progressive validation of surrogate endpoints may redefine classical criteria for clinical efficacy in neurodegenerative disorders.

In this context, the development and regulatory trajectory of tofersen may serve as a precedent for future gene-targeted therapies in neurodegenerative diseases, illustrating how biomarker-driven strategies can reshape both clinical trial design and regulatory evaluation in precision medicine.

Although this review provides a comprehensive and up-to-date overview of the clinical development of tofersen in SOD1-ALS, several limitations should be acknowledged. First, as this is a narrative review rather than a systematic review or meta-analysis, there is a risk of selection and interpretation bias. In addition, the search strategy was limited to publications indexed in PubMed and publicly available registries, which may have led to the exclusion of unpublished studies, gray literature, conference abstracts, or non-indexed articles, thereby introducing potential publication bias. Furthermore, the heterogeneity among the included studies (sample size, follow-up duration, and outcome measures) limits the generalizability of the conclusions. Nevertheless, the review also presents several methodological strengths that enhance its robustness, including the use of multiple international information sources (PubMed, CTIS, and ClinicalTrials.gov), the inclusion of regulatory documentation from the FDA and EMA, and the independent selection and extraction of data by two reviewers, which reduces the risk of selection bias and increases methodological rigor. Moreover, the integration of clinical, methodological, and regulatory evidence provides a well-rounded perspective on the current state of tofersen research in SOD1-ALS.

6. Conclusions

The clinical development program of tofersen illustrates a pathway from initial safety and pharmacology characterization, through a pivotal trial with mixed results on the primary clinical endpoint but robust

effects on pathogenic biomarkers, to evidence suggestive of longer-term benefit and the pioneering exploration of a preventive treatment paradigm. The collective evidence highlights the key role of biomarkers in the development of therapies for neurodegenerative diseases and underscores the importance of treatment duration in assessing disease-modifying potential in ALS.

Tofersen is a targeted therapy for SOD1-associated ALS that acts on a molecular mechanism directly implicated in disease pathogenesis. Its development is grounded in accumulated knowledge of SOD1-ALS pathophysiology, characterized by oxidative stress, mitochondrial dysfunction, axonal transport disturbances, neuroinflammation, and loss of neuronal proteostasis.

Although the pivotal VALOR trial did not reach statistical significance for the primary clinical endpoint over the short term, it demonstrated consistent reductions in relevant biomarkers, particularly mutant SOD1 protein and NfL, supporting a potential neuroprotective effect. Data from the OPL suggest that early treatment initiation may be associated with slower functional and respiratory decline, as well as a reduction in the composite risk of death or permanent ventilation.

Accelerated approvals by regulatory agencies reflect the high unmet medical need and the growing acceptance of biomarkers as surrogate endpoints in severe diseases. Nevertheless, confirmation of long-term clinical benefit, especially in presymptomatic carriers, will depend on ongoing studies.

Overall, tofersen represents a step forward toward personalized medicine in hereditary neurodegenerative diseases, although its clinical implementation requires specialized centers and close safety monitoring

CRediT authorship contribution statement

Antonio J. Braza: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Montserrat Viñas-Bastart:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Maria Sureda-Rosich:** Writing – review & editing, Writing – original draft, Visualization, Investigation, Formal analysis, Data curation. **Beliu García-Parra:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Investigation, Conceptualization. **Josep M. Guiu-Segura:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Conceptualization. **Pilar Modamio:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Data availability

Data will be made available on request.

References

AEMPS Spanish Agency for Medicines and Health Products, 2025. Therapeutic positioning report IPT-369/V1/19052025 therapeutic positioning report of tofersen (Qalsody®) for the treatment of adults with amyotrophic lateral sclerosis (ALS) associated with a mutation in the superoxide dismutase 1 (SOD1) gene (In Spanish) (cited 2026/03/17). Available at the web address https://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/docs/2025/IPT-369-Qalsody-tofersen.pdf.

Akçimen, F., Lopez, E.R., Landers, J.E., Nath, A., Chiò, A., Chia, R., Traynor, B.J., 2023. Amyotrophic lateral sclerosis: translating genetic discoveries into therapies. Nat. Rev. Genet. 24 (9), 642–658. https://doi.org/10.1038/s41576-023-00592-y.

Al-Chalabi, A., van den Berg, L.H., Veldink, J., 2017. Gene discovery in amyotrophic lateral sclerosis: implications for clinical management. Nat. Rev. Neurol. 13 (2), 96–104. https://doi.org/10.1038/nrneurol.2016.182.

Bali, T., Self, W., Liu, J., Siddique, T., Wang, L.H., Bird, T.D., Ratti, E., Atassi, N., Boylan, K.B., Glass, J.D., Maragakis, N.J., Caress, J.B., McCluskey, L.F., Appel, S.H., Wymer, J.P., Gibson, S., Zinman, L., Mozaffar, T., Callaghan, B., McVey, A.L., Jockel-Balsarotti, J., Allred, P., Fisher, E.R., Lopate, G., Pestronk, A., Cudkowicz, M.E., Miller, T.M., 2017. Defining SOD1 ALS natural history to guide therapeutic clinical trial design. J. Neurol. Neurosurg. Psychiatry 88 (2), 99–105. https://doi.org/10.1136/jnnp-2016-313521.

Benatar, M., Wuu, J., Andersen, P.M., Bucelli, R.C., Andrews, J.A., Otto, M., Farahany, N. A., Harrington, E.A., Chen, W., Mitchell, A.A., Ferguson, T., Chew, S., Gedney, L., Oakley, S., Heo, J., Chary, S., Fanning, L., Graham, D., Sun, P., Liu, Y., Wong, J., Fradette, S., 2022. Design of a randomized, placebo-controlled, phase 3 trial of Tofersen initiated in clinically presymptomatic SOD1 variant carriers: the ATLAS study. Neurotherapeutics 19 (4), 1248–1258. https://doi.org/10.1007/s13311-022-01237-4. Erratum in: Neurotherapeutics. 19(5), 1686. 10.1007/s13311-022-01286-9.

Berdyński, M., Safranow, K., Andersen, P.M., Żekanowski, C., 2025. Phenotypic characterization of ALS-causing SOD1 mutations affecting polypeptide length. Hum. Mutat. 2025 (16), 9792233. https://doi.org/10.1155/humu/9792233.

Brown, R.H., Al-Chalabi, A., 2017. Amyotrophic lateral sclerosis. N. Engl. J. Med. 377 (2), 162–172. https://doi.org/10.1056/NEJMra1603471.

Brown, C.A., Lally, C., Kupelian, V., Flanders, W.D., 2021. Estimated prevalence and incidence of amyotrophic lateral sclerosis and SOD1 and C9orf72 genetic variants. Neuroepidemiology 55 (5), 342–353. https://doi.org/10.1159/000516752.

Cedarbaum, J.M., Stambler, N., Malta, E., Fuller, C., Hilt, D., Thurmond, B., Nakanishi, A., 1999. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS study group (Phase III). J. Neurol. Sci. 169 (1–2), 13–21. https://doi.org/10.1016/s0022-510x(99)00210-5.

Cerillo, J.L., Parmar, M., 2023. Tofersen: treatment & management. NCBI Bookshelf, 2023. (cited 2026/03/17). Available at the web address https://www.ncbi.nlm.nih.gov/books/NBK594270/.

ECa (European Commission), 2024. Qalsody, annex I: technical data shhet or summary of product characteristics (in Spanish) (cited on 2026/03/17). Available at the web address https://www.ema.europa.eu/es/documents/product-information/qalsody-epar-product-information_es.pdf.

ECb (European Commission), 2024. Qalsody, technical data shhet or summary of product characteristics (in Spanish) (cited on 2026/03/17). Available at the web address https://ec.europa.eu/health/documents/community-register/2024/20240529162142/anx_162142_es.pdf.

EMA (European Medicines Agency), 2024. Committee for medicinal products for human use (CHMP) positive opinion: tofersen (cited on 2026/03/17). Available at the web address: https://www.ema.europa.eu/en/search?keywords=anyword&search_api_fulltext=qalsody&f%5B0%5D=ema_search_entity_is_document%3ADocument.

Everett, W.H., Bucelli, R.C., 2024. Tofersen for SOD1 ALS. Neurodegener. Dis. Manage 14 (5), 149–160. https://doi.org/10.1080/17582024.2024.2402216.

FDA (Food and Drug Administration), 2023. FDA approves treatment of amyotrophic lateral sclerosis associated with a mutation in the SOD1 gene (cited on 2026/03/17). Available at the web address: https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-treatment-amyotrophic-lateral-sclerosis-associated-mutation-sod1-gene.

Genge, A., Cedarbaum, J.M., Shefner, J., Chio, A., Al-Chalabi, A., Van Damme, P., McDermott, C., Glass, J., Berry, J., van Eijk, R.P.A., Fournier, C., Grosskreutz, J., Andrews, J., Bertone, V., Bunte, T.M., Couillard, M., Cummings, C., Kittle, G., Polzer, J., Salmon, K., Straub, C., van den Berg, L.H., 2024. The ALSFRS-R Summit: a global call to action on the use of the ALSFRS-R in ALS clinical trials. Amyotroph. Lateral. Scler. FrontotempOral Degener. 25 (3–4), 382–387. https://doi.org/10.1080/21678421.2024.2320880.

Guo, Y., Guan, T., Yu, Q., Sanghai, N., Shafiq, K., Li, M., Jiao, X., Na, D., Zhang, G., Kong, J., 2024. ALS-linked SOD1 mutations impair mitochondrial-derived vesicle formation and accelerate aging. Redox. Biol. 69, 102972. https://doi.org/10.1016/j.redox.2023.102972.

Hamad, A.A., Alkhawaldeh, I.M., Nashwan, A.J., Meshref, M., Imam, Y., 2025. Tofersen for SOD1 amyotrophic lateral sclerosis: a systematic review and meta-analysis. Neurol. Sci. 46 (5), 1977–1985. https://doi.org/10.1007/s10072-025-07994-2.

Huang, M., Liu, Y.U., Yao, X., Qin, D., Su, H., 2024. Variability in SOD1-associated amyotrophic lateral sclerosis: geographic patterns, clinical heterogeneity, molecular alterations, and therapeutic implications. Transl. Neurodegener. 13 (1), 28. https://doi.org/10.1186/s40035-024-00416-x.

Ionis Pharmaceuticals, Inc, 2018. Biogen Exercises Option with Ionis to Develop and Commercialize Investigational Treatment BIIB067 for a Subtype of Familial Amyotrophic Lateral Sclerosis (ALS) Based on Positive Phase 1 Data (cited 2026/03/17). Available at the web address https://ir.ionis.com/news-releases/news-release-details/biogen-exercises-option-ionis-develop-and-commercialize.

Lisi, D.M., 2023. Tofersen gains accelerated approval for ALS. US. Pharm. 48 (11), 37–41, 2023(cited 2026/03/17). Available at the web address: https://www.uspharmacist.com/article/tofersen-gains-accelerated-approval-for-als.

Martinelli, I., Mandrioli, J., Ghezzi, A., Zucchi, E., Gianferrari, G., Simonini, C., Cavallieri, F., Valzania, F., 2025. Multifaceted superoxide dismutase 1 expression in amyotrophic lateral sclerosis patients: a rare occurrence? Neural Regener. Res. 20 (1), 130–138. https://doi.org/10.4103/NRR.NRR-D-23-01904.

Masrori, P., Van Damme, P., 2020. Amyotrophic lateral sclerosis: a clinical review. Eur. J. Neurol. 27 (10), 1918–1929. https://doi.org/10.1111/ene.14393.

McCampbell, A., Cole, T., Wegener, A.J., Tomassy, G.S., Setnicka, A., Farley, B.J., et al., 2018. Antisense oligonucleotides extend survival and reverse decrement in muscle response in ALS models. J. Clin. Invest. 128 (8), 3558–3567. https://doi.org/10.1172/JCI99081.

McGuigan, A., Blair, H.A., 2025. Tofersen: a review in amyotrophic lateral sclerosis associated with SOD1 mutations. CNS. Drugs 39 (9), 903–912. https://doi.org/10.1007/s40263-025-01204-5.

Medscape Drug Reference, 2024. Qalsody (tofersen) dosing, indications … administration (cited 2026/03/17). Available at the web address https://reference.medscape.com/drug/qalsody-tofersen-4000306.

Meyer, T., Schumann, P., Weydt, P., Petri, S., Weishaupt, J.H., Weyen, U., Koch, J.C., Günther, R., Regensburger, M., Boentert, M., Wiesenfarth, M., Koc, Y., Kolzarek, F., Kettemann, D., Norden, J., Bernsen, S., Elmas, Z., Conrad, J., Valkadinov, I., Vidovic, M., Dorst, J., Ludolph, A.C., Hesebeck-Brinckmann, J., Spittel, S., Münch, C., Maier, A., Körtvélyessy, P., 2024. Clinical and patient-reported outcomes and neurofilament response during tofersen treatment in SOD1-related ALS-A multicenter observational study over 18 months. Muscle Nerve 70 (3), 333–345. https://doi.org/10.1002/mus.28182.

Miller, T., Cudkowicz, M., Shaw, P.J., Andersen, P.M., Atassi, N., Bucelli, R.C., Genge, A., Glass, J., Ladha, S., Ludolph, A.L., Maragakis, N.J., McDermott, C.J., Pestronk, A., Ravits, J., Salachas, F., Trudell, R., Van Damme, P., Zinman, L., Bennett, C.F., Lane, R., Sandrock, A., Runz, H., Graham, D., Houshyar, H., McCampbel, l A., Nestorov, I., Chang, I., McNeill, M., Fanning, L., Fradette, S., Ferguson, T.A., 2020. Phase 1-2 trial of antisense oligonucleotide tofersen for *SOD1* ALS. N. Engl. J. Med. 383 (2), 109–119. https://doi.org/10.1056/NEJMoa2003715.

Miller, T.M., Cudkowicz, M.E., Genge, A., Shaw, P.J., Sobue, G., Bucelli, R.C., Chiò, A., Van Damme, P., Ludolph, A.C., Glass, J.D., Andrews, J.A., Babu, S., Benatar, M., McDermott, C.J., Cochrane, T., Chary, S., Chew, S., Zhu, H., Wu, F., Nestorov, I., Graham, D., Sun, P., McNeill, M., Fanning, L., Ferguson, T.A., Fradette, S., 2022. Trial of antisense oligonucleotide tofersen for SOD1 ALS. N. Engl. J. Med. 387 (12), 1099–1110. https://doi.org/10.1056/NEJMoa2204705.

Moriyama, H., Yokota, T., 2024. Recent progress of antisense oligonucleotide therapy for superoxide-dismutase-1-mutated amyotrophic lateral sclerosis: focus on Tofersen. Genes. (Basel) 15 (10), 1342. https://doi.org/10.3390/genes15101342.

Nguyen, L., 2024. Updates on disease mechanisms and therapeutics for amyotrophic lateral sclerosis. Cells 13 (11), 888. https://doi.org/10.3390/cells13110888.

NINDS (National Institute of Neurological Disorders and Stroke), 2024. Amyotrophic lateral sclerosis (ALS): how is ALS diagnosed and treated? (cited 2026/03/17). Available at the web address https://www.ninds.nih.gov/health-information/disorders/amyotrophic-lateral-sclerosis-als#toc-how-is-amyotrophic-lateral-sclerosis-als-diagnosed-and-treated.

NLMa (National Library of Medicine, ClinicalTrials.gov), 2025 (cited 2026/03/17). Available at the web address https://www.clinicaltrials.gov/study/NCT04856982.

NLMb (National Library of Medicine, ClinicalTrials.gov), 2025. A study of BIIB067 (tofersen) initiated in clinically presymptomatic adults with a confirmed superoxide dismutase 1 mutation (ATLAS) (cited 2026/03/17). Available at the web address https://www.clinicaltrials.gov/study/NCT04856982.

Oliveira-Santos, M., de Carvalho, M., 2024. Profiling tofersen as a treatment of superoxide dismutase 1 amyotrophic lateral sclerosis. Expert. Rev. NeurOther 24 (6), 549–553. https://doi.org/10.1080/14737175.2024.2355983, 2024 Jun.

Qalsody, 2025. Tofersen: safety and adverse events. Warnings Precaut. (cited 2026/03/17). Available at the web address https://www.qalsodyhcp.com/en-us/home/safety-and-adverse-events.html.

Simonini, C., Zucchi, E., Martinelli, I., Gianferrari, G., Lunetta, C., Sorarù, G., Trojsi, F., Pepe, R., Piras, R., Giacchino, M., Banchelli, F., Mandrioli, J., 2025. Neurodegenerative and neuroinflammatory changes in SOD1-ALS patients receiving tofersen. Sci. Rep. 15 (1), 11034. https://doi.org/10.1038/s41598-025-94984-1.

SMH (Spanish Ministry of Health), 2025. The Ministry of Health approves the financing of 'tofersen', the first treatment aimed at a genetic cause of ALS (in Spanish) (cited 2026/03/17). Available at the web address: https://www.sanidad.gob.es/gabinete/notasPrensa.do?id=6675.

Smith, H.L., Chaytow, H., Gillingwater, T.H., 2024. Excitotoxicity and ALS: new therapy targets an old mechanism. Cell Rep. Med. 5 (2), 101423. https://doi.org/10.1016/j.xcrm.2024.101423.

Smith, S.E., McCoy-Gross, K., Malcolm, A., Oranski, J., Markway, J.W., Miller, T.M., Bucelli, R.C., 2025. Tofersen treatment leads to sustained stabilization of disease in SOD1 ALS in a "real-world" setting. Ann. Clin. Transl. Neurol. 12 (2), 311–319. https://doi.org/10.1002/acn3.52264.

Tafuri, F., Ronchi, D., Magri, F., Comi, G.P., Corti, S., 2015. SOD1 misplacing and mitochondrial dysfunction in amyotrophic lateral sclerosis pathogenesis. Front. Cell Neurosci. 9, 336. https://doi.org/10.3389/fncel.2015.00336.

Tsekrekou, M., Giannakou, M., Papanikolopoulou, K., Skretas, G., 2024. Protein aggregation and therapeutic strategies in SOD1- and TDP-43- linked ALS. Front. Mol. Biosci. 11, 1383453. https://doi.org/10.3389/fmolb.2024.1383453.

Vázquez-Costa, J.F., Borrego-Hernández, D., Paradas, C., Gómez-Caravaca, M.T., Rojas-Garcia, R., Varona, L., Povedano, M., García-Sobrino, T., Jericó Pascual, I., Gutiérrez, A., Riancho, J., Turon-Sans, J., Assialioui, A., Pérez-Tur, J., Sevilla, T., Esteban Pérez, J., García-Redondo, A., ALSGESCO, 2023. Characterizing SOD1 mutations in Spain. the impact of genotype, age, and sex in the natural history of the disease. Eur. J. Neurol. 30 (9), 861–871. https://doi.org/10.1111/ene.15661.

Vidal Notari, S., Bertran Recasens, B., Hernández Guillamet, G., Jiménez-Balado, J., Rubio Pérez, M., 2024. Epidemiología de la ELA en Cataluña (2015-2020). Neurol. Perspect. 4, 64. https://doi.org/10.1016/S2667-0496(24)00234-5.

Wiesenfarth, M., Dorst, J., Brenner, D., Elmas, Z., Parlak, Ö., Uzelac, Z., Kandler, K., Mayer, K., Weiland, U., Herrmann, C., Schuster, J., Freischmidt, A., Müller, K., Siebert, R., Bachhuber, F., Simak, T., Günther, K., Fröhlich, E., Knehr, A., Regensburger, M., German, A., Petri, S., Grosskreutz, J., Klopstock, T., Reilich, P., Schöberl, F., Hagenackerm, T., Weyen, U., Günther, R., Vidovic, M., Jentsch, M., Haarmeier, T., Weydt, P., Valkadinov, I., Hesebeck-Brinckmann, J., Conrad, J., Weishaupt, J.H., Schumann, P., Körtvélyessy, P., Meyer, T., Ruf, W.P., Witzel, S., Senel, M., Tumani, H., Ludolph, A.C., 2024. 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 69, 102495. https://doi.org/10.1016/j.eclinm.2024.102495.

Woo, T.G., Yoon, M.H., Kang, S.M., Park, S., Cho, J.H., Hwang, Y.J., Ahn, J., Jang, H., Shin, Y.J., Jung, E.M., Ha, N.C., Kim, B.H., Kwon, Y., Park, B.J., 2021. Novel chemical inhibitor against SOD1 misfolding and aggregation protects neuron-loss and ameliorates disease symptoms in ALS mouse model. Commun. Biol. 4 (1), 1397. https://doi.org/10.1038/s42003-021-02862-z.

Zufiría, M., Gil-Bea, F.J., Fernández-Torrón, R., Poza, J.J., Muñoz-Blanco, J.L., Rojas-García, R., Riancho, J., López de Munain, A., 2016. ALS: a bucket of genes, environment, metabolism and unknown ingredients. Prog. Neurobiol. 142, 104–129. https://doi.org/10.1016/j.pneurobio.2016.05.004.