JAMA Neurology | Original Investigation

Long-Term Tofersen in *SOD1* Amyotrophic Lateral Sclerosis

Timothy M. Miller, MD; Merit E. Cudkowicz, MD; Pamela J. Shaw, MD; Angela Genge, MD; Gen Sobue, MD; Robert C. Bucelli, MD; Adriano Chiò, MD; Philip Van Damme, MD; Albert C. Ludolph, MD; Jonathan D. Glass, MD; Jinsy A. Andrews, MD; Suma Babu, MBBS; Michael Benatar, PhD; Christopher J. McDermott, MD; François Salachas, MD; Gaëlle Bruneteau, MD; Ammar Al-Chalabi, PhD; Matthew Amorin, PharmD; Ivan Nestorov, PhD; Danielle Graham, PhD; Luan Lin, PhD; Peng Sun, PhD; Manjit McNeill, MSc; Sohail Malek, MD; Jennifer Inra, MD; Steve Garafalo, PhD; Stephanie Fradette, PharmD; for the VALOR and OLE Working Group

IMPORTANCE Approximately 2% of amyotrophic lateral sclerosis (ALS) cases are attributable to a pathogenic variant in the superoxide dismutase 1 (*SOD1*) gene. Tofersen, an intrathecal antisense oligonucleotide designed to reduce SOD1 protein synthesis, is the first and only approved therapy for the treatment of ALS in adults who have a variant in the *SOD1* gene.

OBJECTIVE To evaluate the long-term effects of tofersen in adults with *SOD1*-ALS.

DESIGN, SETTING, AND PARTICIPANTS The phase 3, randomized, double-blind, placebo-controlled VALOR trial (A Study to Evaluate Efficacy, Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Tofersen in *SOD1*-ALS; conducted from March 2019 to July 2021) evaluated tofersen use over 28 weeks in adults (18 years and older) with weaknesses attributable to ALS and a confirmed *SOD1* pathogenic variant at 32 sites in 10 countries; participants could then enroll in an open-label extension (OLE; completed August 2024).

INTERVENTION AND EXPOSURE Adults with *SOD1*-ALS were randomly assigned 2:1 to receive tofersen (100 mg) or placebo over a 24-week period in the VALOR study. All participants in the OLE were treated with tofersen.

MAIN OUTCOMES AND MEASURES Integrated analysis of VALOR and the OLE study aimed to compare early start vs placebo/delayed start (approximately 6 months later) treatment with tofersen. Key efficacy end points included measures of axonal injury and neurodegeneration (neurofilament), function and strength, quality of life, and survival.

RESULTS VALOR enrolled 108 participants with 42 unique *SOD1* pathogenic variants (mean [SD] age: placebo/delayed-start group 51.2 [11.6] [n = 36]; early-start group: 48.1 [12.6] [n = 72]) with 19 (53%) and 43 (60%) of participants being male in the placebo/delayed- and early-start groups, respectively. Overall, 95/108 participants (88%) enrolled in the OLE, and 46 participants completed the OLE (early-start group, 34 [47%]; placebo/delayed-start group, 12 [33%]). At OLE completion, participants could have accumulated 3.5 years or more (range, 192-276 weeks) of follow-up from the start of VALOR. Over 148 weeks, earlier initiation of tofersen (compared to later initiation) was associated with numerically less decline in measures of clinical function (Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised score, −9.9 vs −13.5 points), respiratory function (slow vital capacity, −13.8% vs −18.1%), muscle strength (handheld dynamometry megascore, −0.38 vs −0.43 points), and quality of life (Amyotrophic Lateral Sclerosis Assessment Questionnaire 5 score, 17.0 vs 22.5 points; EuroQol 5 Dimension, 5 Level Questionnaire score, −0.1 vs −0.2 points). Tofersen prolonged survival relative to the expected natural history of *SOD1*-ALS. Most adverse events were consistent with ALS progression or known procedural adverse effects. All serious neurological adverse events were reversible; few led to tofersen discontinuation.

CONCLUSIONS AND RELEVANCE Final data from VALOR and the OLE demonstrated the benefit of tofersen in *SOD1*-ALS and provide clear rationale for its use in this population.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: VALOR NCT02623699; OLE NCT03070119

Editorial

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The VALOR and OLE Working Group members appear in Supplement 2.

Corresponding Authors: Timothy M. Miller, MD, Department of Neurology, Neuromuscular Medicine, Washington University School of Medicine in St Louis, 660 S Euclid Ave, Box 8111, St Louis, MO 63110 (millert@neuro.wustl.edu); Stephanie Fradette, PharmD, Biogen, 225 Binney St, Cambridge, MA 02142 (stephanie.fradette@biogen.com).

JAMA Neurol. doi:10.1001/jamaneurol.2025.4946
Published online December 22, 2025. Corrected on January 26, 2026.

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that results in motor neuron loss leading to progressive loss of bulbar, respiratory, and limb muscle function.[1,2] Approximately 2% of ALS cases are associated with pathogenic variants in the superoxide dismutase 1 (*SOD1*) gene, leading to a toxic form of the SOD1 protein.[2-4] Over 200 ALS-associated *SOD1* variants induce varying disease progression rates; aggressive ALS has an associated survival of less than 15 months from symptom onset.[2,5]

Tofersen is an intrathecally administered antisense oligonucleotide designed to reduce SOD1 protein synthesis by inducing RNase H-mediated degradation of *SOD1* messenger RNA.[6] The efficacy, safety, tolerability, pharmacokinetics, and pharmacodynamics of tofersen were previously investigated in a 3-part study; part C was the pivotal phase 3 trial investigating efficacy and safety of tofersen in adults with *SOD1*-ALS (A Study to Evaluate Efficacy, Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Tofersen in *SOD1*-ALS [VALOR]: ClinicalTrials.gov NCT02623699).[7,8] At the end of VALOR, participants could enroll in an open-label extension (OLE; ClinicalTrials.gov NCT03070119).[8] VALOR and OLE data were prospectively integrated to evaluate the impact of earlier vs delayed tofersen initiation; 1-year findings have been reported.[8] Here, we report final integrated results from VALOR/OLE informing the long-term effects of tofersen.

Key Points

Question What are the long-term effects of early-start and placebo/delayed-start tofersen treatment in adults with *SOD1* amyotrophic lateral sclerosis (ALS)?

Findings This integrated analysis of the phase 3, randomized, double-blind, placebo-controlled VALOR study and its open-label extension (OLE) found that participants with earlier initiation of tofersen exhibited numerically less decline in function, strength, and risk of death-equivalent events than participants in the placebo/delayed-start group (tofersen initiated approximately 6 months later), consistent with a slowing of disease progression. No new safety concerns were identified with long-term exposure to tofersen.

Meaning Final data from VALOR and its OLE demonstrated the benefit of tofersen treatment for adults with *SOD1*-ALS and provide a clear rationale for starting therapy in this population.

Methods

Trial Oversight

Studies were conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation and the ethical principles outlined in the Declaration of Helsinki. Study protocols were approved by relevant ethics committees. An independent data monitoring committee reviewed safety data. Written informed consent was provided by participants or their legal representatives.

Trial Design

The VALOR/OLE study design has been reported.[8] Briefly, following the 28-week, phase 3, randomized, double-blind, placebo-controlled study that included individuals with confirmed pathogenic or likely pathogenic ALS-associated *SOD1* variants, participants could enroll in the OLE. The OLE study personnel, participants, and caregivers remained blinded to the VALOR randomized assignment. The OLE was completed in August 2024 when the last enrolled participant had the opportunity for their week 192 post-VALOR visit. VALOR/OLE integrated analyses evaluated early-start (tofersen initiated during VALOR) and placebo/delayed-start (tofersen initiated during the OLE, approximately 6 months later) groups.

End Points

End points assessed in the VALOR/OLE integrated analysis included changes from baseline in key biomarkers of target engagement (total SOD1 protein) and neurodegeneration (plasma neurofilament light chain [NfL] levels); clinical function (Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised [ALSFRS-R] score); respiratory strength (percentage of predicted slow vital capacity [SVC]); muscle strength (handheld dynamometry [HHD]); and survival. Survival measures included time to death; time to death or permanent ventilation (PV; ≥22 hours of mechanical ventilation per day for ≥21 consecutive days); and time to death, PV, or study withdrawal due to disease progression (as determined by the principal investigator).

Health-related quality of life (QoL) was assessed using the Amyotrophic Lateral Sclerosis Assessment Questionnaire 5 (ALSAQ-5), Fatigue Severity Scale (FSS) total scores, and the EuroQol 5 Dimension, 5 Level Questionnaire (EQ-5D-5L) utility score. Responder analyses for ALSFRS-R, SVC, and HHD assessed the proportion of participants with stabilization (and/or improvement) (eMethods in Supplement 1).

Statistical Analysis

Integrated analyses of data from VALOR/OLE followed the integrated statistical analysis plan to inform the effects of tofersen over time. At OLE completion, participants had the opportunity for 3.5 years or more of follow-up from VALOR start. To minimize risk of bias and preserve original randomization in VALOR, integrated analyses were based on the intention-to-treat (ITT) principle.

Participants were divided into cohorts according to baseline NfL level, a strong prognostic biomarker of disease progression and survival (eMethods in Supplement 1). Slower- and faster-progressing groups were defined as those below and above the median baseline plasma NfL level, respectively. This approach better accounted for disease heterogeneity than that used in VALOR (subgroups by *SOD1* variant type and ALFSRS-R prerandomization slope). An overview of the proportion of participants from the original modified ITT (mITT) and non-mITT populations included in the faster and slower-progressing subgroups defined by NfL level is presented in eTable 3 in Supplement 1. Statistical procedures have been described previously.[8]

Analysis of covariance (ANCOVA) was conducted on changes from VALOR baseline to week 148 in measures of function, strength, and QoL. SVC and HHD were assessed every

Table 1. Baseline Demographic Characteristics at VALOR Enrollment

Characteristic	ITT (n = 108)		Subgroup (NfL based)[a]			
			Faster progressing (n = 54)		Slower progressing (n = 54)	
	Placebo/delayed start (n = 36)	Early start (n = 72)	Placebo/delayed start (n = 16)	Early start (n = 38)	Placebo/delayed start (n = 20)	Early start (n = 34)
Age, mean (SD), y	51.2 (11.6)	48.1 (12.6)	50.4 (11.9)	47.3 (13.2)	51.8 (11.5)	48.9 (12.1)
Sex, No. (%)						
Male	19 (53)	43 (60)	7 (44)	21 (55)	12 (60)	22 (65)
Female	17 (47)	29 (40)	9 (56)	17 (45)	8 (40)	12 (45)
BMI, mean (SD)	27.4 (6.5)	26.4 (5.6)	25.7 (6.0)	26.2 (6.3)	28.8 (6.7)	26.4 (4.8)
Riluzole use, No. (%)	22 (61)	45 (62)	11 (69)	21 (55)	11 (55)	24 (71)
Edaravone use, No. (%)	3 (8)	6 (8)	1 (6)	2 (5)	2 (10)	4 (12)
Time from symptom onset, median (range), mo	14.6 (2.4-103.2)	11.4 (1.7-145.7)	10.3 (2.4-30.3)	8.9 (2.3-59.9)	31.7 (3.0-103.2)	28.9 (1.7-145.7)
Concentration of NfL in plasma, pg/mL						
Mean (SD)	89.7 (86.5)	100.4 (82.8)	160.3 (85.5)	159.4 (73.7)	33.1 (20.9)	36.2 (21.9)
Geometric mean	56.6	66.6	145.3	143.5	26.9	28.5
Range	7.9-370.4	5.2-328.8	78.2-370.4	77.5-328.8	7.9-70.4	5.2-73.7
ALSFRS-R total score, mean (SD; range)	37.3 (5.8; 24.0-47.0)	36.9 (5.9; 15.0-48.0)	34.5 (5.8; 24.0-42.0)	36.4 (6.6; 15.0-46.0)	39.6 (4.9; 32.0-47.0)	37.5 (5.1; 25-48)
Percentage of predicted SVC, mean (SD; range)	85.1 (16.5; 54.8-120.4)	82.1 (16.6; 46.7-134.7)	81.8 (19.6; 54.8-120.4)	82.6 (17.2; 46.7-134.7)	87.8 (13.5; 67.4-114.4)	81.5 (16.2; 55.4-108.9)

Abbreviations: ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ITT, intention-to-treat; NA, not available; NfL, neurofilament light chain; SVC, slow vital capacity.

[a] NfL-based subgroups are based on median baseline NfL (slower-progressing subgroup, <75.6 pg/mL; faster-progressing subgroup, ≥75.6 pg/mL).

3 months (vs monthly) to reduce participant burden. Consequently, week 148 was selected for the main analysis as it was the last time point with sufficient data across all clinical end points. Event-free survival analyses included all follow-up data through last contact for the last participant (week 276). Missing data were handled using multiple imputation. Comparisons of clinical function, strength, and QoL between the early-start and placebo/delayed-start groups were reported as the least squares (LS) mean difference with corresponding 95% CIs and nominal *P* values. The treatment effect of tofersen on the ALSFRS-R total score (change from baseline) was analyzed using the joint rank test for further statistical inference. Participants who died were assigned progressively lower ranks based on their time of death. Responder analyses assessed the proportion of participants with stabilization or improvement (baseline to week 148 change ≥0) in function or improvement (baseline to week 148 change ≥0) in function, strength, and QoL. Deaths or withdrawals before week 148 were considered nonresponders. All other missing data were handled using multiple imputation.

Time-to-event analyses were performed in the ITT population comparing the treatment difference of early-start to placebo/delayed-start groups on survival end points. Despite long-term follow-up, median time to death or death-equivalent event (ie, PV or withdrawal due to disease progression) was not estimable in the full ITT population due to few events. Event-free survival extension estimation was analyzed in the NfL faster-progressing subgroup where median time to death or PV and median time to death were reached in both treatment arms.

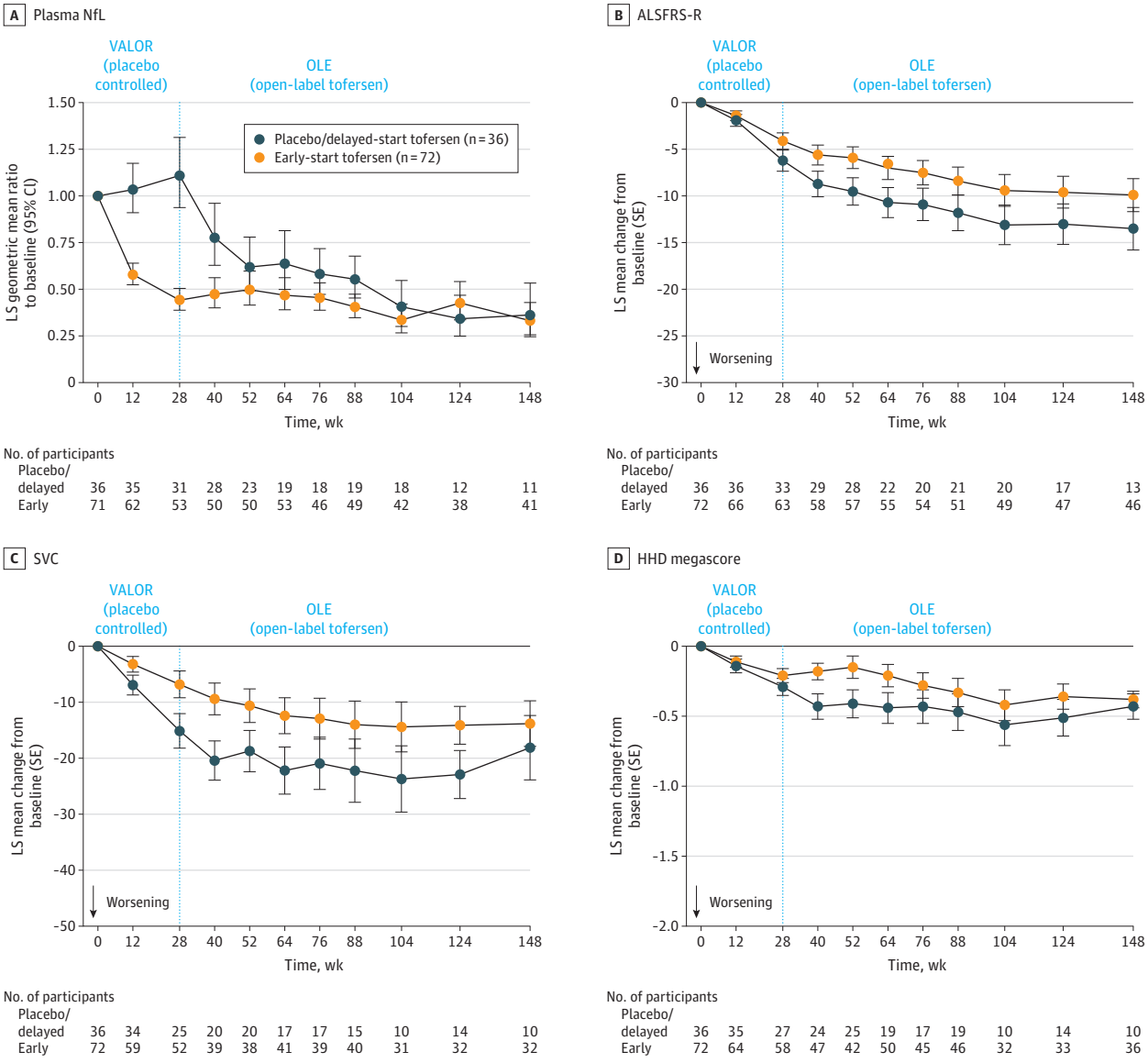
Results

Participants

VALOR enrolled 108 participants across 32 sites in 10 countries (tofersen, 100 mg: n = 72; placebo: n = 36) (mean [SD] age: placebo/delayed-start group 51.2 [11.6] [n = 36]; early-start group: 48.1 [12.6] [n = 72]). In the placebo/delayed-start group, 19 participants (53%) were male and 17 (47%) were female; in the early-start group, 43 (60%) were male and 29 (40%) were female. Overall, 97 of 108 (90%) participants completed VALOR, and 95 of 108 (88%) enrolled in the OLE. At OLE completion, the median opportunity for follow-up (time from VALOR baseline to OLE completion per participant) was 4.9 years (range, 3.6-5.4 years), and 46 participants completed the study (early start: 34 [47%]; placebo/delayed start 12 [33%]) (eFigure 1 in Supplement 1). Participants who completed the study had a variable length of clinical follow-up from VALOR baseline (range, 3.5-5.4 years). Most premature discontinuations from the OLE study were due to death, disease progression, and withdrawn consent (eTable 1 in Supplement 1).

As previously reported,[8] baseline clinical characteristics were similar across groups for use of riluzole, edaravone, or both; time from symptom onset of disease weakness; ALSFRS-R score; and percentage of predicted SVC (**Table 1**). However, baseline NfL concentrations were approximately 12% numerically higher for participants in the early-start group. In multiple ALS studies,[9-11] increased baseline NfL has been found to be associated with faster progression.

Figure 1. Change in Outcomes From Baseline to Week 148



Error bars represent 95% CIs (A) or standard errors (B, C and D). Missing data were handled using multiple imputation. ALSFRS-R indicates Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised; HHD, handheld dynamometry; LS, least squares; NfL, neurofilament light chain; OLE, open-label extension; SVC, slow vital capacity.

Cerebrospinal Fluid SOD1 Protein

Reductions in total cerebrospinal fluid (CSF) SOD1 protein became apparent by approximately 8 weeks of treatment, consistent with the estimated time to steady-state concentrations of tofersen in CSF and estimated half-life of SOD1 protein (each approximately 1 month). Early reductions in CSF SOD1 concentrations were sustained at week 148, with a reduction of 21% and 25% in the early-start and placebo/delayed-start groups, respectively (eFigures 2 and 3 in Supplement 1).

Plasma NfL

Maximal reductions in plasma NfL were observed approximately 16 weeks after treatment initiation and sustained over time. Specifically, reductions in plasma NfL from baseline to week 148 were 67% in the early-start and 64% in the placebo/delayed-start groups (**Figure 1**A). These data suggest that tofersen slowed neurodegeneration, without evidence of effect attenuation over time.

Clinical Function and Strength

Given the small number of participants in the trial, and all participants having the opportunity to receive tofersen for 2.5 or more years, the studies were not powered to detect statistically significant differences between the early-start (≥3 years taking the drug) and placebo/delayed-start (0.5 years placebo and ≥2.5 or more years taking the drug) groups. Over 148 weeks,

earlier initiation of tofersen (compared to later initiation) was associated with numerically less decline in measures of clinical function (ALSFRS-R score, −9.9 vs −13.5 points), respiratory function (SVC, −13.8% vs −18.1%), muscle strength (HHD megascore, −0.38 vs −0.43 points), and QoL (ALSAQ-5 score, 17.0 vs 22.5 points; EQ-5D-5L score, −0.1 vs −0.2 points) (Figure 1B-D; **Table 2**). Numerical favoring of the early-start group was observed across populations (ITT; faster-progressing [NfL > median] and slower- progressing [NfL < median] subgroups) regardless of the covariates incorporated into the analyses (eFigures 4-6 in Supplement 1).

Many participants experienced improvement on measures of clinical function, breathing, and strength ranging from 10.7% to 17.3% and 21.0% to 27.3% in the placebo/delayed- and early-start group, respectively (Table 2; eTable 4 in Supplement 1). The slower progressing subgroup generally showed greater improvement. To contextualize strength improvements, in the early-start group, a prior investigation fit model using clinical outcome data (accounting for dropout) from the dexpramipexole A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study of the Safety and Efficacy of Dexpramipexole in Subjects With Amyotrophic Lateral Sclerosis (EMPOWER) study was analyzed.[12] Based on the model parameters, 1 million hypothetical trials with 72 participants each were simulated. The probability of 27.3% of untreated individuals with ALS experiencing an improvement in HHD over 1 year was calculated to be 0% ($P < .001$). HHD data were only collected through 1 year in EMPOWER, thus precluding an assessment at approximately 3 years in line with the VALOR/OLE follow-up period, but the probability would likely be even lower at approximately 3 years given the progressive nature of the disease.

QoL

ALS substantially worsens QoL across multiple domains, and studies generally link better QoL with less severe disease and worse QoL with later stages of ALS (eMethods in Supplement 1).[13,14] At week 148, mean differences between groups on ALSAQ-5 (−5.5) and EQ-5D-5L (0.1) favored the early-start group, and on FSS (4.3) favored the placebo/delayed-start group (eFigure 7 in Supplement 1).

Event-Free Survival

Limited death-equivalent events precluded estimation of median time to death or PV (or time to death) in both groups of the ITT population (**Figure 2**). However, median time to death, PV, or withdrawal due to disease progression was reached in the early-start group, estimated at 260.7 weeks.

Notably, comparisons of early-start and placebo/delayed-start tofersen treatment were associated with a hazard ratio (HR) of 0.64 (95% CI, 0.28-1.46) for risk of death or PV and 0.52 (95% CI, 0.20-1.36) for risk of death (Table 2). In the faster-progressing subgroup, median time to event (death or PV; death; death, PV, or withdrawal due to disease progression) was longer in the early-start group (253.6 weeks, 253.6 weeks, and 103.6 weeks, respectively) than the placebo/delayed-start group (76.0 weeks, 115.4 weeks, and 57.3 weeks, respectively), representing extended event-free survival (by approximately 3.4 years, by approximately 2.65 years, and by approximately 0.89 years, respectively). In the slower-progressing subgroup, median time to event was not reached in either treatment group.

Safety

At study completion, 104 of 108 participants from VALOR received 1 or more dose of tofersen, 100 mg, and were exposed to tofersen over approximately 305.35 participant-years (median exposure, approximately 181.71 weeks). Most adverse events (AEs) were consistent with ALS disease progression, conditions in the general population, or known adverse effects of lumbar puncture (**Table 3**). The most common AEs included headache, procedural pain, fall, back pain, and pain in the extremities.

Overall, 9 participants (8.7%) reported 10 serious neurological AEs, including myelitis or radiculitis, papilledema and/or increased intracranial pressure, and chemical or aseptic meningitis. These events were manageable with local standard of care and resolved. One myelitis event and 1 chemical meningitis event led to treatment discontinuation. These findings are consistent with VALOR/OLE safety findings previously reported.[15]

Eighty-three of the 104 participants (79.8%) who received tofersen, 100 mg, in VALOR/OLE had 1 or more instance of postbaseline elevation of CSF leukocytes greater than 10×10^6/L, and 93 (89.4%) had 1 or more postbaseline value greater than 5×10^6/L. Sixty of 68 participants (88.2%) who received tofersen, 100 mg, with a normal or low CSF protein value at baseline had a shift to high protein (based on local laboratory reference ranges).

Discussion

ALS is well characterized by loss of function, breathing, and strength in nearly all patients. To date, no studies have reported a sustained or meaningful improvement in clinical outcomes over approximately 3 years. This report demonstrates that both the early- and placebo/delayed-start groups experienced numerically less decline than would be expected in a natural history (NH) cohort, consistent with a slowing of disease progression and prolonged survival in both groups.

Elevated neurofilament levels have been described in several neurological conditions characterized by neuroaxonal damage.[16,17] In ALS, neurofilament levels are prognostic for disease progression and survival.[9,18-20] One NH study found that a 1-SD increase in NfL was associated with 0.41-point per month decline in ALSFRS-R scores.[11] Another showed via a Cox proportional hazards model that plasma NfL levels were associated with survival (HR for 1 SD increase in log10 plasma NfL, 2.99; 95% CI, 1.65-5.41; $P = .02$) and rate of disability progression, independent of other prognostic factors.[9] Insights from these and other NH studies suggest that the more than 60% sustained NfL reduction in VALOR/OLE likely represents a substantial slowing of neurodegeneration in *SOD1*-ALS; NfL reductions preceded and predicted clinical benefit over time.

Table 2. Integrated Efficacy Results[a]

Measure/analysis	ITT (n = 108)		Subgroup (based on baseline NfL)			
			Faster progressing (NfL ≥ 75.6 pg/mL; n = 54)		Slower progressing (NfL < 75.6 pg/mL; n = 54)	
	Placebo/delayed start (n = 36)	Early start (n = 72)	Placebo/delayed start (n = 16)	Early start (n = 38)	Placebo/delayed start (n = 20)	Early start (n = 34)
Reductions in plasma NfL, %[b]	64.0	67.0	76.0	79.0	43.0	45.0
Reductions in total SOD1 protein, %[b]	25.0	21.0	31.0	22.0	21.0	19.0
Function and strength						
ALSFRS-R						
Change from baseline to 148 wk	−13.5	−9.9	−24.8	−18.1	−4.5	−3.2
LSM difference (95% CI)	3.6 (−1.2 to 8.4)		6.6 (−1.8 to 15.0)		1.3 (−3.2 to 5.7)	
ANCOVA + MI *P* value	.14 (alternative JRT: .05)		.12		.57	
Proportion of participants that improved from baseline to 148 wk, % (95% CI)	17.3 (4.7 to 29.8)	21.0 (11.6 to 30.5)	12.5 (−3.7 to 28.7)	16.2 (4.3 to 28.0)	21.0 (2.8 to 39.3)	26.5 (11.6 to 41.3)
SVC						
Change from baseline to 148 wk	−18.1	−13.8	−30.2	−25.2	−7.7	−3.5
LSM difference (95% CI)	4.3 (−6.6 to 15.2)		5.1 (−11.9 to 22.0)		4.2 (−7.4 to 15.8)	
ANCOVA + MI *P* value	.44		.56		.48	
Proportion of participants that improved from baseline to 148 wk, % (95% CI)	15.8 (2.5 to 29.0)	23.1 (12.5 to 33.7)	18.8 (−0.4 to 37.9)	12.1 (1.0 to 23.1)	13.4 (−4.8 to 31.5)	35.5 (17.8 to 53.2)
Change in HHD megascore	−0.43	−0.38	−0.60	−0.48	−0.31	−0.28
Change from baseline to 148 wk	−0.43	−0.38	−0.60	−0.48	−0.31	−0.28
LSM difference (95% CI)	0.06 (−0.124 to 0.234)		0.12 (−0.163 to 0.393)		0.02 (−0.181 to 0.228)	
ANCOVA + MI *P* value	.55		.42		.82	
Proportion of participants that improved from baseline to 148 wk, % (95% CI)	10.7 (−0.5 to 21.8)	27.3 (16.3 to 38.3)	7.7 (−6.3 to 21.7)	6.9 (−2.0 to 15.8)	13.1 (−3.3 to 29.4)	50.0 (31.9 to 68.1)
Survival, time-to-event analyses (early start vs placebo/delayed start tofersen)[c]						
Time to death from first dose received in VALOR or PV, whichever came first						
Median time (95% CI), wk	NE	NE	76.0 (33.9 to NE)	253.6 (95.1 to NE)	NE	NE
HR (95% CI)	0.64 (0.28 to 1.46)		0.47 (0.19 to 1.18)		2.03 (0.22 to 18.66)	
P value from Cox	.29		.11		.53	
P value from log rank	.42		.22		.56	
Time to death from first dose received in VALOR						
Median time (95% CI), wk	NE	NE	115.4 (57.1 to NE)	253.6 (125.3 to NE)	NE	NE
HR (95% CI)	0.52 (0.20 to 1.36)		0.41 (0.13 to 1.24)		1.22 (0.11 to −3.04)	
P value from Cox	.18		.12		.87	
P value from log rank	.31		.17		.73	
Time to death, PV, or withdrawal due to disease progression						
Median time (95% CI), wk	NE	260.7 (171.0 to NE)	57.3 (27.4 to 135.6)	103.6 (70.9 to 253.6)	NE	NE
HR (95% CI)	0.61 (0.31 to 1.18)		0.49 (0.23 to 1.02)		0.95 (0.17 to 5.34)	
P value from Cox	.14		.06		.95	
P value from log rank	.23		.18		>.99	

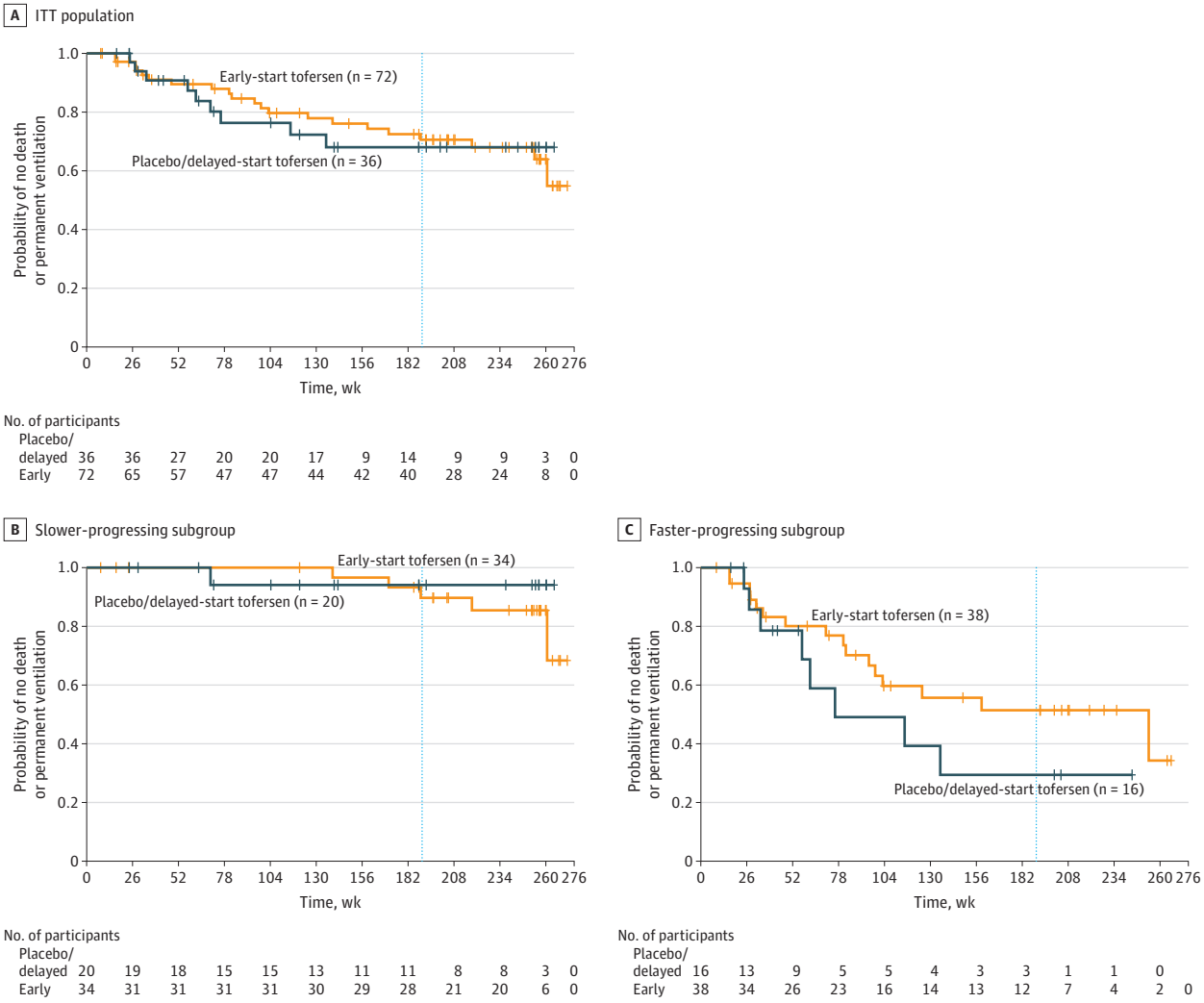
Abbreviations: ALS, amyotrophic lateral sclerosis; ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised; ANCOVA, analysis of covariance; HR, hazard ratio; ITT, intention-to-treat; JRT, joint rank test; LSM, least-squares mean; MI, multiple imputation; NE, not estimable; NfL, neurofilament light chain; PV, permanent ventilation; SOD1, superoxide dismutase 1; SVC, slow vital capacity.

[a] Adjusted 95% CI values were based on the distribution of the log hazard ratio retaining the Cox regression P value from the ITT analysis back-transformed to the original scale. Cox proportional hazards model adjusted for baseline plasma NfL and riluzole or edaravone use. Log rank test stratified by median baseline plasma NfL. For ALSFRS-R total score (change from baseline), when implementing JRT, MI was used to handle withdrawals for reasons other than death.

[b] 1 Minus geometric mean ratio to baseline at week 148.

[c] PV was defined as ≥22 hours of mechanical ventilation (invasive or noninvasive) per day for ≥21 consecutive days. Time to death, PV, or withdrawal due to disease progression was defined as the time from first dose to death, PV, or withdrawal from the study due to disease progression, whichever came first.

Figure 2. Time to Death or Permanent Ventilation



Baseline plasma neurofilament light chain (NfL) was <75.6 pg/mL in the slower-progressing subgroup and ≥75.6 pg/mL in the faster-progressing subgroup. Time to death or permanent ventilation was defined as the time from first dose to death or permanent ventilation (≥22 hours of mechanical ventilation [invasive or noninvasive] per day for ≥21 consecutive days), whichever came first. Participants who did not meet the end point definition were censored at the last known date they were alive. Only events that were adjudicated by the end point adjudication committee were included. Cross marks indicate censored observations. The dotted line corresponds to week 192, the time point when the last participant enrolled reached the end of the study. ITT indicates intention-to-treat.

Although analyses were not powered to detect statistically significant differences between groups over the longer term (given the small number of participants and that all had the opportunity to receive tofersen from week 28 onward), both groups demonstrated numerically less decline across measures than expected based on the NH of ALS. On a population basis, people with ALS would be estimated to decline by an average of 0.6 to 1.0 points per month on the ALSFRS-R scale,[21-23] equating to approximately 22 to 34 points over the 148-week follow-up period. In contrast, the early-start group declined by 9.9 points, and the placebo/delayed-start group by 13.5 points.

In addition, improvements in strength and function were observed over approximately 3 years in approximately 21% to 27% of early-start participants, unlike the progressive decline expected based on NH of ALS. Fewer than 70 reports of sustained ALS symptom improvement have been documented in the history of the disease, with no known documented reversals in individuals with *SOD1*-ALS.[24,25] To further validate that these observations in participants treated with tofersen are not due to chance, we fitted a model using clinical outcome data from the dexpramipexole EMPOWER study. Comparison with 1-year HHD data from EMPOWER is a conservative approach, given that the probability of improvement would be expected to decrease over the longer, 3-year period assessed in VALOR/OLE. Even with this conservative approach, the probability of observing a more than 20% response with increased strength at 1 year was cal-

Table 3. Summary of Adverse Events[a]

Treatment-emergent adverse event	VALOR and OLE Tofersen, 100 mg (N = 104), No. (%)[b]
Any event	103 (99.0)
Event related to trial agent[c]	66 (63.5)
Event related to lumbar puncture[c]	87 (83.7)
Serious event	58 (55.8)
Serious event related to trial agent[c]	10 (9.6)
Event with fatal outcomes	22 (21.2)
Event leading to drug discontinuation	28 (26.9)
Event occurring in ≥25% of participants[d]	
Headache	63 (60.6)
Procedural pain	62 (59.6)
Fall	49 (47.1)
Back pain	49 (47.1)
Pain in extremity	41 (39.4)
Arthralgia	38 (36.5)
COVID-19	36 (34.6)
Fatigue	32 (30.8)
CSF protein increased	28 (26.9)
Post lumbar puncture syndrome	26 (25.0)
Nausea	26 (25.0)
Constipation	26 (25.0)
Serious event occurring in ≥3% of participants[d]	
Respiratory failure	13 (12.5)
Pneumonia aspiration	12 (11.5)
Acute respiratory failure	8 (7.7)
Dysphagia	8 (7.7)
Pulmonary embolism	6 (5.8)
Pneumonia	4 (3.8)
Serious neurologic events[e]	9 (8.7)
Myelitis	4 (3.9)
Papilledema	3 (2.9)
Aseptic meningitis	2 (1.9)
Radiculitis	1 (1.0)

Abbreviations: CSF, cerebrospinal fluid; OLE, open-label extension.

[a] Within the VALOR study, the following adverse events occurred in at least 5% of patients treated with tofersen and at >5% higher frequency than patients treated with placebo: pain, back pain, pain in extremity, fatigue, arthralgia, csf white blood cell increased, pleocytosis, myalgia, CSF protein increased, musculoskeletal stiffness, and neuralgia. Of note, 1 participant reported aseptic meningitis and later reported papilledema.

[b] A participant could appear in more than 1 category.

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

[d] A participant is counted only once for each preferred term (*Medical Dictionary for Regulatory Activities*, version 25.1).

[e] Myelitis includes the preferred term myelitis transverse; papilledema includes the preferred term intracranial pressure increased; aseptic meningitis includes the preferred terms meningitis chemical and meningitis aseptic.

culated to be 0% ($P < .001$), reinforcing the remarkable impact of tofersen on slowing ALS disease course in this study, in which 27.3% of participants gained strength. Given the disease heterogeneity, it is worth noting that what constitutes a clinically relevant response varies by patient. Across the dataset, outcomes (eg, slowing of decline vs stabilization vs improvement) were most heavily influenced by the intersection between phenotype (*SOD1* variant and baseline plasma NfL) and disease duration (from symptom onset to the start of therapy). Evidence from the traditional clinical outcome measures of strength and function are further supported by key QoL measures, including ALSAQ-5 and EQ-5D-5L.

The median disease duration reported in the NH of *SOD1*-ALS is estimated to be approximately 2.3 years from symptom onset.[5] As participants in the placebo/delayed-start group initiated tofersen at approximately 28 weeks in the OLE, it was not possible to precisely estimate survival outcomes without tofersen treatment. However, our data suggest that tofersen substantially impacted survival. Despite a median opportunity for follow-up of 4.9 years (range, 3.6-5.4 years), median time to death or PV and median time to death were not reached in either group in the ITT population. Nonetheless, earlier-start tofersen was associated with a 36% reduction in risk of death or PV and a 48% reduction in risk of death 6 months later, relative to placebo/delayed-start tofersen. In the faster-progressing subgroup, median time to death or PV was met in both treatment groups, enabling straightforward and precise survival estimates: participants on early-start tofersen experienced a 3.4-year extension of event-free survival compared with those in the placebo/delayed-start tofersen group. In carriers of a p.Ala5Val (A5V) variant, the most prevalent *SOD1* variant in North America and most common variant in the faster-progressing subgroup, disease duration has been estimated at approximately 1 to 1.2 years.[4,5] Median (range) disease duration (time from symptom onset to death, withdrawal [reasons for withdrawal are presented in eTable 2 in Supplement 1], or the end of the study) in A5V carriers in our study was 15.4 (8.6-34.4) months in the placebo/delayed-start group (n = 6) and 23.2 (10.5-73.9) months in the early-start group (n = 11).

Greater treatment benefits with early-start tofersen are consistent with observations in other neurodegenerative diseases such as SMA.[26,27] These data support the hypothesis that tofersen initiation in the early symptomatic or presymptomatic (upon neurofilament elevation; a disease biomarker) stage of ALS may further delay ALS onset or slow functional decline after symptoms emerge. Importantly, the ongoing phase 3, randomized, double-blind, placebo-controlled A Phase 3 Randomized, Placebo-Controlled Trial With a Longitudinal Natural History Run-In and Open-Label Extension to Evaluate BIIB067 Initiated in Clinically Presymptomatic Adults With a Confirmed Superoxide Dismutase 1 Mutation (ATLAS) study (NCT04856982) is testing this hypothesis.[28] Conducting asymptomatic trials for *SOD1*-ALS and other genetic subsets will require focused studies in asymptomatic gene carriers, which are ongoing (Pre-symptomatic Familial Amyotrophic Lateral Sclerosis [Pre-fALS; NCT00317616] and Longitudinal Biomarker Study for Participants Who Are Genetically at Risk for Amyotrophic Lateral Sclerosis [ALS] [PREVENT ALL ALS; NCT06581861]). Beyond earlier treatment, there may be adjunctive therapies that will further increase response in patients treated with tofersen.

The benefits of tofersen must be weighed against potential risks. Most AEs reported during treatment were consistent with the types and severities of AEs seen in patients with *SOD1*-ALS, common comorbidities, or events observed in the context of lumbar puncture. Some participants experienced serious neurological events, which were manageable with standard of care; most participants continued treatment. The type and rate of events were similar to those previously reported from this dataset and will continue to be monitored and characterized in the postmarketing setting.[8]

Limitations

This study had several limitations, including variable disease heterogeneity in the study population, relatively small sample size, crossover to active treatment at 6 months for the placebo group, and limited statistical power. Notably, while the primary analysis population of the VALOR study was enriched for faster disease progression according to *SOD1* variant type and prerandomization ALSFRS-R slope, it became apparent that variability within and across *SOD1* variant types, as well as nonlinear progression of the ALSFRS-R with periods of stable disease preceded or followed by periods of rapid decline,[29,30] could confound and limit the prognostic value of these measures. Importantly, evolving research in ALS continued to demonstrate that NfL is a strong prognostic biomarker of disease progression and survival, with higher levels associated with worse outcomes.[3,9,18,19,31-36] Recognizing the importance of NfL to control for disease heterogeneity, the statistical analysis plan for the VALOR/OLE analyses defined disease progression subgroups by baseline plasma NfL level and also adjusted for baseline NfL as a continuous covariate to estimate treatment differences in the population with greater precision. Importantly, despite the limited sample size, crossover to active treatment at 6 months for the placebo group, and efficacy analyses not powered to detect a statistically significant difference, earlier initiation of tofersen was associated with reduced decline in function, strength, and the risk of death-equivalent events compared to initiation of tofersen approximately 6 months later, while both groups demonstrated numerically less decline across clinical measures than would be expected based on the natural history of ALS.

Conclusion

VALOR/OLE data are consistent with global trial and expanded access programs indicating that tofersen is slowing neurodegeneration and clinical disease progression in patients.[37-41] These tofersen-driven effects are impacting care expectations in *SOD1*-ALS, from diagnosis and monitoring to management. Additionally, findings further promote the growing literature supporting NfL as a prognostic biomarker of ALS disease progression and survival, and a response biomarker with utility for quantifying therapeutic effect. Specifically, these data have supported US Food and Drug Administration acceptance of NfL as a surrogate biomarker reasonably likely to predict clinical benefit in *SOD1*-ALS. They have also supported the use of NfL as a key decision-making end point in smaller and shorter-duration phase 1 and 2 studies to prioritize investigational therapies for later stages of development more conclusively.[42,43] As of October 2025, tofersen has received regulatory approval in the US, Europe, China, Japan, and several other countries around the world. Furthermore, European Academy of Neurology guidelines recommend offering tofersen as first-line treatment in patients with progressive *SOD1*-ALS.[44]

The substantial benefits of tofersen in *SOD1*-ALS have resparked enthusiasm for ALS drug development, as these data suggest that, with the right drug treating an upstream cause of disease, large meaningful effects are possible. We expect insights from this experience to empower therapeutic advances in other forms of ALS.

ARTICLE INFORMATION

Accepted for Publication: October 24, 2025.

Published Online: December 22, 2025. doi:10.1001/jamaneurol.2025.4946

Correction: This article was corrected on January 26, 2026, to fix the database linking of the nonauthor collaborators.

Author Affiliations: Department of Neurology, Neuromuscular Medicine, Washington University School of Medicine in St Louis, St Louis, Missouri (Miller, Bucelli); Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston (Cudkowicz, Babu); Sheffield Institute for Translational Neuroscience, University of Sheffield, Sheffield, United Kingdom (Shaw); National Institute for Health and Care Research Sheffield Biomedical Research Centre and Clinical Research Facility, University of Sheffield and Sheffield Teaching Hospitals National Health Service Foundation Trust, Sheffield, United Kingdom (Shaw); Department of Neurology and Neurosurgery, Faculty of Medicine and Health Sciences, McGill University, Montreal, Quebec, Canada (Genge); Department of Neurology, Nagoya University Graduate School of Medicine, Nagoya, Japan (Sobue); Rita Levi Montalcini Department of Neurosciences, University of Turin, Turin, Italy (Chiò); University Hospitals Leuven, Leuven, Belgium (Van Damme); Neuroscience Department, Leuven Brain Institute, KU Leuven, Leuven, Belgium (Van Damme); Department of Neurology, University of Ulm, Ulm, Germany (Ludolph); Emory University School of Medicine, Atlanta, Georgia (Glass); Department of Neurology, NYU Langone, New York, New York (Andrews); Department of Neurology, University of Miami Miller School of Medicine, Miami, Florida (Benatar); Division of Neuroscience, School of Medicine and Population Health, University of Sheffield, Sheffield, United Kingdom (McDermott); Paris Amyotrophic Lateral Sclerosis Center, Department of Neurology, Pitié-Salpêtrière Hospital, Assistance Publique Hôpitaux de Paris, Paris, France (Salachas, Bruneteau); Maurice Wohl Clinical Neuroscience Institute, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom (Al-Chalabi); Department of Neurology, King's College Hospital, London, United Kingdom (Al-Chalabi); Biogen, Cambridge, Massachusetts (Amorin, Nestorov, Graham, Lin, Sun, Malek, Inra, Garafalo, Fradette); Biogen, Maidenhead, United Kingdom (McNeill); Aichi Medical University, Aichi, Japan (Sobue); Amyotrophic Lateral Sclerosis Center, University of Miami Miller School of Medicine, Miami, Florida (Benatar).

Author Contributions: Dr Fradette had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Miller, Cudkowicz, Sobue, Chio, Van Damme, Ludolph, Benatar, Amorin, Graham, Lin, Sun, McNeill, Garafalo, Fradette.
Acquisition, analysis, or interpretation of data: Miller, Shaw, Genge, Sobue, Bucelli, Chio, Ludolph, Glass, Andrews, Babu, Benatar, McDermott, Salachas, Bruneteau, Al-Chalabi, Amorin, Nestorov, Graham, Lin, Sun, McNeill, Malek, Inra, Garafalo, Fradette.

Drafting of the manuscript: Miller, Ludolph, Amorin, McNeill, Malek, Inra, Garafalo, Fradette.
Critical review of the manuscript for important intellectual content: Miller, Cudkowicz, Shaw, Genge, Sobue, Bucelli, Chio, Van Damme, Ludolph, Glass, Andrews, Babu, Benatar, McDermott, Salachas, Bruneteau, Al-Chalabi, Nestorov, Graham, Lin, Sun, McNeill, Malek, Inra, Garafalo, Fradette.
Statistical analysis: Nestorov, Lin, Sun, McNeill, Malek, Fradette.
Obtained funding: Shaw.
Administrative, technical, or material support: Cudkowicz, Shaw, Sobue, Ludolph, Andrews, McDermott, Amorin, Graham, Garafalo, Fradette.
Supervision: Miller, Cudkowicz, Shaw, Genge, Sobue, Ludolph, Andrews, Graham, Inra, Fradette.

Conflict of Interest Disclosures: Dr Miller reported that resources to complete the study were provided by Biogen during the conduct of the study and reported personal fees from Ionis Pharmaceuticals, Biogen, Arbor Bio, and Biomarin outside the submitted work; in addition, Dr Miller had a patent for Ionis licensed and a patent for C2N licensed. Dr Cudkowicz reported board member service for Praxis Precision Medicines and consulting for Novartis, Quralis, Immunity Pharma, Regeneron, Otsuka, and Ono outside the submitted work. Dr Shaw reported grants from Biogen outside the submitted work. Dr Sobue reported personal fees from Biogen during the conduct of the study. Dr Bucelli reported personal fees from Biogen (consultant and advisory board fees) and grants from Biogen (site principal investigator [PI] for multiple Biogen-sponsored trials, including the trials covered in this article) during the conduct of the study as well as personal fees from Regeneron for advisory board service outside the submitted work and serving as site PI for an Ionis-sponsored FUSION trial (NCT04768972) but received no direct personal compensation related to this role and is no longer the PI for this trial. Dr Van Damme reported advisory board fees (paid to institution) from Biogen, Amylyx, Zambon, Ferrer, QurAlis, Argenx, UCB, Augustine Therapeutics, VectorY, Sapreme Technologies, and Novartis as well as grants from CSL Behring (paid to institution) outside the submitted work. Dr Ludolph reported grants from Biogen during the conduct of the study. Dr Andrews reported grants (paid to institution) from Amylyx, Biogen, Cytokinetics, Corcept, Ra Pharma, Biohaven, Clene, Prilenia, and Calico and personal fees for data safety monitoring board service and/or advisory board service from AL-S Pharma, Quralis, Sanofi, Novartis, Apellis, Bristol Myers Squibb, Neurosense, and Akava outside the submitted work. Dr Babu reported grants from Biogen, Ionis, and Denali and consulting fees (paid to institution) from Uniqure and Takeda outside the submitted work. Dr Benatar reported other from Biogen (per patient costs for trial participants) during the conduct of the study as well as personal fees for scientific advisory board service from Biogen, Trace Neuroscience, Evox, Novartis, Woolsey, Eli Lilly, Prilenia, Alector, Alaunos, Arrowhead, Coya, and VectorY outside the submitted work; in addition, Dr Benatar had a patent for Determining the Onset of ALS pending and serves as a nonpaid member of the Board of Trustees of the ALS Association. Dr McDermott reported other from Biogen (funds to support the clinical trial) and grants from Amlyx (consultancy), Verge (data monitoring committee member), the National Institute for Health and Care Research, Motor Neurone Disease Association, My Name'5 Doddie Foundation, and LifeArc outside the submitted work. Dr Bruneteau reported other from Biogen (serving as a site investigator) during the conduct of the study. Dr Al-Chalabi reported grants from the National Institute for Health and Care Research, EU Horizon 2020, Motor Neurone Disease Association, My Name'5 Doddie Foundation, Motor Neurone Disease Scotland, and the Alan Davidson Foundation outside the submitted work; in addition, Dr Al-Chalabi had a patent for use of CSF-neurofilament determinations and CSF-neurofilament thresholds of prognostic and stratification value with regards to response to therapy in neuromuscular and neurodegenerative diseases pending and reports consultancies or advisory board service for Amylyx, Apellis, Biogen, Clene Therapeutics, Cytokinetics, GenieUs, GSK, Lilly, Mitsubishi Tanabe Pharma, Novartis, OrionPharma, Quralis, Sano, Sanofi, Voyager Therapeutics, and Wave Pharmaceuticals. Dr Graham reported employment at and stock and/or stock option ownership in Biogen. Dr McNeill reported employment at Biogen during the conduct of the study. Dr Malek reported employment at Biogen during the conduct of the study. Dr Inra reported employment at Biogen during the conduct of the study. Dr Garafalo employment at and stock and/or stock option ownership in Biogen during the conduct of the study. Dr Fradette reported employment at and shareholdership in Biogen during the conduct of the study. No other disclosures were reported.

Funding/Support: This study was funded by Biogen.

Role of the Funder/Sponsor: The study funder was involved in study design and monitoring, data collection and management, statistical analysis, data interpretation, and drafting the report of this study. The sponsor and authors designed the studies. The sponsor provided tofersen and placebo and oversaw the studies. Data were collected by the investigators and analyzed by the sponsor.

Group Information: The VALOR and OLE Working Group members are listed in Supplement 2.

Data Sharing Statement: See Supplement 3.

Additional Contributions: Biogen provided funding for medical writing support in the development of this article, with both Vanessa Ducas, PhD, Excel Scientific Solutions and Jo Gordon, PhD, Oxford PharmaGenesis, providing writing assistance with earlier and later drafts of the article, respectively, based on input from the authors. We thank the study participants and their caregivers and families, the study steering committee, investigators and site staff, and the entire ALS community, without whom these important studies could not have been conducted. No named individuals were compensated for their contributions (outside of regular wages or salary).

REFERENCES

1. Zou ZY, Zhou ZR, Che CH, Liu CY, He RL, Huang HP. Genetic epidemiology of amyotrophic lateral sclerosis: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry*. 2017;88(7):540-549. doi:10.1136/jnnp-2016-315018

2. Benatar M, Robertson J, Andersen PM. Amyotrophic lateral sclerosis caused by *SOD1* variants: from genetic discovery to disease prevention. *Lancet Neurol*. 2025;24(1):77-86. doi:10.1016/S1474-4422(24)00479-4

3. Abu-Rumeileh S, Vacchiano V, Zenesini C, et al; BoReALS. Diagnostic-prognostic value and electrophysiological correlates of CSF biomarkers of neurodegeneration and neuroinflammation in amyotrophic lateral sclerosis. *J Neurol*. 2020;267(6):1699-1708. doi:10.1007/s00415-020-09761-z

4. Bali T, Self W, Liu J, et al. Defining *SOD1* ALS natural history to guide therapeutic clinical trial design. *J Neurol Neurosurg Psychiatry*. 2017;88(2):99-105. doi:10.1136/jnnp-2016-313521

5. Opie-Martin S, Iacoangeli A, Topp SD, et al. The *SOD1*-mediated ALS phenotype shows a decoupling between age of symptom onset and disease duration. *Nat Commun*. 2022;13(1):6901. doi:10.1038/s41467-022-34620-y

6. QALSODY. Tofersen. highlights of prescribing information. Accessed November 13, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/215887s000lbl.pdf

7. Miller T, Cudkowicz M, Shaw PJ, et al. Phase 1-2 trial of antisense oligonucleotide tofersen for *SOD1* ALS. *N Engl J Med*. 2020;383(2):109-119. doi:10.1056/NEJMoa2003715

8. Miller TM, Cudkowicz ME, Genge A, et al; VALOR and OLE Working Group. Trial of antisense oligonucleotide tofersen for *SOD1* ALS. *N Engl J Med*. 2022;387(12):1099-1110. doi:10.1056/NEJMoa2204705

9. Thompson AG, Gray E, Verber N, et al. Multicentre appraisal of amyotrophic lateral sclerosis biofluid biomarkers shows primacy of blood neurofilament light chain. *Brain Commun*. 2022;4(1):fcac029. doi:10.1093/braincomms/fcac029

10. Benatar M, Zhang L, Wang L, et al; CReATe Consortium. Validation of serum neurofilaments as prognostic and potential pharmacodynamic biomarkers for ALS. *Neurology*. 2020;95(1):e59-e69. doi:10.1212/WNL.0000000000009559

11. Benatar M, Macklin EA, Malaspina A, et al; CReATe Consortium PGB1 Study Investigators. Prognostic clinical and biological markers for amyotrophic lateral sclerosis disease progression: validation and implications for clinical trial design and analysis. *EBioMedicine*. 2024;108:105323. doi:10.1016/j.ebiom.2024.105323

12. Cudkowicz ME, van den Berg LH, Shefner JM, et al; EMPOWER investigators. Dexpramipexole versus placebo for patients with amyotrophic lateral sclerosis (EMPOWER): a randomised, double-blind, phase 3 trial. *Lancet Neurol*. 2013;12(11):1059-1067. doi:10.1016/S1474-4422(13)70221-7

13. Peseschkian T, Cordts I, Günther R, et al. A nation-wide, multi-center study on the quality of life of ALS patients in Germany. *Brain Sci*. 2021;11(3):372. doi:10.3390/brainsci11030372

14. Stenson K, Fecteau TE, O'Callaghan L, et al. Health-related quality of life across disease stages in patients with amyotrophic lateral sclerosis: results from a real-world survey. *J Neurol*. 2024;271(5):2390-2404. doi:10.1007/s00415-023-12141-y

15. Lovett A, Chary S, Babu S, et al. Serious neurologic adverse events in tofersen clinical trials for amyotrophic lateral sclerosis. *Muscle Nerve*. 2025;71(6):1006-1015. doi:10.1002/mus.28372

16. Gaetani L, Blennow K, Calabresi P, Di Filippo M, Parnetti L, Zetterberg H. Neurofilament light chain as a biomarker in neurological disorders. *J Neurol*

Neurosurg Psychiatry. 2019;90(8):870-881. doi:10.1136/jnnp-2018-320106

17. Khalil M, Teunissen CE, Otto M, et al. Neurofilaments as biomarkers in neurological disorders. *Nat Rev Neurol*. 2018;14(10):577-589. doi:10.1038/s41582-018-0058-z

18. Thouvenot E, Demattei C, Lehmann S, et al. Serum neurofilament light chain at time of diagnosis is an independent prognostic factor of survival in amyotrophic lateral sclerosis. *Eur J Neurol*. 2020;27(2):251-257. doi:10.1111/ene.14063

19. Vacchiano V, Mastrangelo A, Zenesini C, et al. Plasma and CSF neurofilament light chain in amyotrophic lateral sclerosis: a cross-sectional and longitudinal study. *Front Aging Neurosci*. 2021;13:753242. doi:10.3389/fnagi.2021.753242

20. Thompson AG, Gray E, Verber N, et al. Multicentre appraisal of amyotrophic lateral sclerosis biofluid biomarkers shows primacy of blood neurofilament light chain. *Brain Commun*. 2022;4(1):fcac029. doi:10.1093/braincomms/fcac029

21. Westeneng HJ, Debray TPA, Visser AE, et al. Prognosis for patients with amyotrophic lateral sclerosis: development and validation of a personalised prediction model. *Lancet Neurol*. 2018;17(5):423-433. doi:10.1016/S1474-4422(18)30089-9

22. van Eijk RPA, Weemering DN, Opie-Martin S, et al. Natural history of the revised ALS functional rating scale and its association with survival: the PRECISION-ALS Extant study. *Amyotroph Lateral Scler Frontotemporal Degener*. 2025;26(sup1):30-40. doi:10.1080/21678421.2024.2443985

23. Atassi N, Berry J, Shui A, et al. The PRO-ACT database: design, initial analyses, and predictive features. *Neurology*. 2014;83(19):1719-1725. doi:10.1212/WNL.0000000000000951

24. Crayle J, Lutz M, Raymond J, Mehta P, Bedlack R. Study of "ALS reversals": LifeTime environmental exposures (StARLiTE). *Amyotroph Lateral Scler Frontotemporal Degener*. 2023;24(1-2):54-62. doi:10.1080/21678421.2022.2090846

25. Crayle JI, Rampersaud E, Myers JR, et al. Genetic associations with an amyotrophic lateral sclerosis reversal phenotype. *Neurology*. 2024;103(4):e209696. doi:10.1212/WNL.0000000000209696

26. De Vivo DC, Bertini E, Swoboda KJ, et al; NURTURE Study Group. Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the phase 2 NURTURE study. *Neuromuscul Disord*. 2019;29(11):842-856. doi:10.1016/j.nmd.2019.09.007

27. Crawford TO, Swoboda KJ, De Vivo DC, et al; NURTURE Study Group. 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. doi:10.1002/mus.27853

28. Benatar M, Wuu J, Andersen PM, 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. doi:10.1007/s13311-022-01237-4

29. Proudfoot M, Jones A, Talbot K, Al-Chalabi A, Turner MR. The ALSFRS as an outcome measure in therapeutic trials and its relationship to symptom onset. *Amyotroph Lateral Scler Frontotemporal Degener*. 2016;17(5-6):414-425. doi:10.3109/21678421.2016.1140786

30. Ramamoorthy D, Severson K, Ghosh S, et al; Answer ALS; Pooled Resource Open-Access ALS Clinical Trials Consortium; ALS/MND Natural History Consortium. Identifying patterns in amyotrophic lateral sclerosis progression from sparse longitudinal data. *Nat Comput Sci*. 2022;2(9):605-616. doi:10.1038/s43588-022-00299-w

31. Brettschneider J, Petzold A, Süssmuth SD, Ludolph AC, Tumani H. Axonal damage markers in cerebrospinal fluid are increased in ALS. *Neurology*. 2006;66(6):852-856. doi:10.1212/01.wnl.0000203120.85850.54

32. De Schaepdryver M, Lunetta C, Tarlarini C, et al. Neurofilament light chain and C reactive protein explored as predictors of survival in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry*. 2020;91(4):436-437. doi:10.1136/jnnp-2019-322309

33. Falzone YM, Domi T, Mandelli A, et al. Integrated evaluation of a panel of neurochemical biomarkers to optimize diagnosis and prognosis in amyotrophic lateral sclerosis. *Eur J Neurol*. 2022;29(7):1930-1939. doi:10.1111/ene.15321

34. Lu CH, Macdonald-Wallis C, Gray E, et al. Neurofilament light chain: a prognostic biomarker in amyotrophic lateral sclerosis. *Neurology*. 2015;84(22):2247-2257. doi:10.1212/WNL.0000000000001642

35. Rossi D, Volanti P, Brambilla L, Colletti T, Spataro R, La Bella V. CSF neurofilament proteins as diagnostic and prognostic biomarkers for amyotrophic lateral sclerosis. *J Neurol*. 2018;265(3):510-521. doi:10.1007/s00415-017-8730-6

36. Zetterberg H, Jacobsson J, Rosengren L, Blennow K, Andersen PM. Cerebrospinal fluid neurofilament light levels in amyotrophic lateral sclerosis: impact of *SOD1* genotype. *Eur J Neurol*. 2007;14(12):1329-1333. doi:10.1111/j.1468-1331.2007.01972.x

37. Meyer T, Schumann P, Weydt P, 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(6):515-521. doi:10.1002/mus.27818

38. Wiesenfarth M, Dorst J, Brenner D, 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;69:102495. doi:10.1016/j.eclinm.2024.102495

39. Sabatelli M, Cerri F, Zuccarino R, et al. Long-term treatment of *SOD1* ALS with tofersen: a multicentre experience in 17 patients. *J Neurol*. 2024;271(8):5177-5186. doi:10.1007/s00415-024-12437-7

40. Meyer T, Schumann P, Weydt P, 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. doi:10.1002/mus.28182

41. Smith SE, McCoy-Gross K, Malcolm A, et al. Tofersen treatment leads to sustained stabilization of disease in *SOD1* ALS in a "real-world" setting. *Ann Clin Transl Neurol*. 2025;12(2):311-319. doi:10.1002/acn3.52264

42. van den Berg LH, Rothstein JD, Shaw PJ, et al. Safety, tolerability, and pharmacokinetics of antisense oligonucleotide BIIB078 in adults with *C9orf72*-associated amyotrophic lateral sclerosis: a phase 1, randomised, double blinded, placebo-controlled, multiple ascending dose study. *Lancet Neurol*. 2024;23(9):901-912. doi:10.1016/S1474-4422(24)00216-3

43. Ravits J, Day JW, Chiò A, et al; ALSpire Working Group. Results from the ALSpire study phase 1/2 trial with open-label extension of BIIB105 in adults with ALS. Presented at the 2024 Annual Meeting of the European Network to Cure ALS (ENCALS); June 17-20, 2024; Stockholm, Sweden.

44. Van Damme P, Al-Chalabi A, Andersen PM, et al. European Academy of Neurology (EAN) guideline on the management of amyotrophic lateral sclerosis in collaboration with European Reference Network for Neuromuscular Diseases (ERN EURO-NMD). *Eur J Neurol*. 2024;31(6):e16264. doi:10.1111/ene.16264