Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Miller T, Cudkowicz M, Shaw PJ, et al. Phase 1–2 trial of antisense oligonucleotide tofersen for *SOD1* ALS. N Engl J Med 2020;383:109-19. DOI: 10.1056/NEJMoa2003715

Supplement to: Miller T, Cudkowicz M, Shaw PJ, et al. Phase 1–2 Trial of Antisense Oligonucleotide Tofersen for *SOD1* ALS. N Engl J Med. DOI: 10.1056/NEJMoa2003715.

SUPPLEMENTARY APPENDIX

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SECTION S1: STUDY INVESTIGATORS

Belgium: Philip Van Damme. **Canada:** Angela Genge, Lorne Zinman. **France:** François Salachas. **Germany:** Albert Ludolph. **United Kingdom:** Chris McDermott. **United States:** Nazem Atassi, Robert Bucelli, Jonathan Glass, Ira Goodman, Jonathan Katz, Shafeeq Ladha, Nicholas Maragakis, Alan Pestronk, John Ravits, Randall Trudell.

SECTION S2: EXPLORATORY OUTCOME DETAILS

The Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised (ALSFRS-R) is a 12-question instrument for evaluation of the functional status of patients with ALS across four domains: respiratory function, bulbar function, gross motor skills, and fine motor skills. Each item is scored from 0 (no function) to 4 (full function), with a total possible score of 48 points.[1]

Slow vital capacity (SVC) is a relatively less demanding (compared with forced vital capacity testing), noninvasive test of respiratory function frequently used in patients with ALS to monitor disease progression.[2] The maximum of the percent predicted upright SVC value at each visit was used for the analysis.

Handheld dynamometry (HHD) is a reliable and reproducible quantitative measure of muscle strength decline in ALS.[3] For this analysis, 16 muscle groups (left and right shoulder flexion, left and right elbow flexion, left and right wrist extension, left and right abduction index finger, left and right abduction thumb, left and right abduction fifth digit, left and right knee extension, and left and right ankle dorsiflexion) were examined in both upper and lower extremities to derive the overall HHD megascore.

Muscle strength values are normalized to Z-scores as (postbaseline measurements – mean)/SD and averaged to provide the HHD overall megascore. The mean and SD are based on the baseline values across all participants regardless of dose/treatment group. The megascore is created by averaging the eight bilateral measurement Z-scores, if no more than

10 of 16 muscle measures are missing. If >10 measures are missing, then the HHD megascore is considered as missing.

SECTION S3: STATISTICAL ANALYSIS DETAILS

The mixed model for repeated measures (MMRM) was used as the primary analysis method for inference. Summary statistics and least squares mean estimates with 95% CIs for the MMRM model were presented for changes from baseline in each of SOD1, ALSFRS-R, SVC, and neurofilament concentrations. Other imputation methods were also applied for sensitivity analysis purposes and analyzed using MMRM. The MMRM model included dose group, visit, treatment-by-visit interaction, baseline score, and baseline score by visit interaction terms, and adjusted for the covariate of disease progression type (fast-progressing [FP] vs. other). Only visits to Day 85 (and Day 92 for ALSFRS-R) were included in the model. An unstructured covariance matrix was used to model the within-participant variability. In case the model failed to converge, the Fisher scoring algorithm was used to provide initial values of the covariance parameters, instead of the default Newton-Raphson algorithm. In the event that none of these methods yielded convergence, the heterogeneous first-order autoregressive structure was used. For SOD1 and neurofilament concentrations, modeling was performed on a log scale due to the distribution of these data, and so the model for these outcomes was for the log ratio to baseline; geometric mean ratios and 95% CIs were presented.

An MMRM was not used to analyze HHD megascore, due to the high level of missing data in such a small sample size and the collection of this outcome at fewer time points than other key outcomes (Days 22, 92, and 169). In particular, there is a high level of missing data in the placebo group as participants progressing in this group could not attend all clinic visits, in addition to the dropouts and death in this group. Furthermore, this assessment was only collected at Day 22 under a protocol amendment, by which time participants in Cohort 5 had already completed this visit, which reduces the amount of data collected for both the placebo

group and tofersen 20-mg group. Therefore, because the MMRM may result in unreliable results in a small, sparse dataset, the HHD megascore was consistently summarized using descriptive statistics for the overall population and by disease progression, using last observation carried forward for imputation of missing data to Day 92.

The results for HHD and SVC are not presented for completers through to Day 169, as the data are sparse and have limitations in sample size. All participants receiving 100 mg tofersen completed all assessments for HHD and SVC; however, of the 12 placebo participants, only six and five completed all SVC and HHD assessments, respectively. A number of placebo participants either discontinued the study early or had disease progression, which resulted in an inability to attend clinic visits. ALSFRS-R was more complete, because this could be collected over the telephone. Excluding these participants leaves a small subset of completers in the placebo group for HHD and SVC, and comparing this group of participants with the active treatment group is misleading, as the true change in participants with disease progression is not reflected in the placebo group.

SECTION S4: DEFINITION OF *SOD1* FAST-PROGRESSING MUTATIONS

Blinded to genetic results obtained from multiple ascending dose (MAD) participants, we conducted a literature review of *SOD1* variants associated with ALS. We particularly focused on variants that had been reported as associated with an average disease course of <3 years from first symptom to death. We defined such variants as *SOD1* fast-progressing mutations. Participants not meeting this fast-progressing definition were considered “other”. Ten *SOD1* variants fulfilled our criteria of (1) being described as fast-progressing mutations with sufficient detail in at least two independent cohorts (p.Ala5Val, p.Ala5Thr, p.Gly42Ser, p.His44Arg, p.Gly94Ala, p.Leu107Val, p.Leu39Val, p.Val149Gly), or (2) enriched and associated with a little variant rapid course of disease in a distinct ethnicity (p.Leu85Val, p.Arg116Gly).

Upon unblinding of the 100-mg subgroup, an ALSFRS-R slope of 0.0 (at baseline and Day 85) in a participant carrying the *SOD1* mutation p.Arg116Gly triggered a revision to the fast progressor definition to include a criterion for a prerandomization ALSFRS-R of ≥0.2 points per month in an effort to ensure the participants were in fact progressing at the time of enrollment.

Forty-seven MAD participants had *SOD1* gene variants that could be assigned to previously described mutations, one participant had a novel *SOD1* mutation, and two had variants that could not be assigned to known *SOD1* alleles. In total, 22 *SOD1* mutations were identified; of those, the fast-progressing mutation p.Ala5Val was most prevalent (N = 10).

SECTION S5: PHARMACOKINETICS

Measured plasma concentrations peaked between 2 and 6 hours after intrathecal bolus administration and were dose proportional (Supplemental Fig. S4A). Trough CSF concentrations were less than dose proportional and were highest in the 100-mg group, lowest in the 20-mg group, and similar in the 40- and 60-mg groups (Supplemental Fig. S4B). Examination of trough CSF concentrations from baseline to Day 169 suggested that steady-state concentrations were achieved following the third loading dose on Day 29. Repeat pharmacokinetic assessments during the study demonstrated marginal or no apparent accumulation after the third loading dose in the plasma or in the CSF. There was moderate to high inter- and intraparticipant variability in CSF concentration profiles (most coefficients of variation were ≥50%).

SECTION S6: SUPPLEMENTARY FIGURES

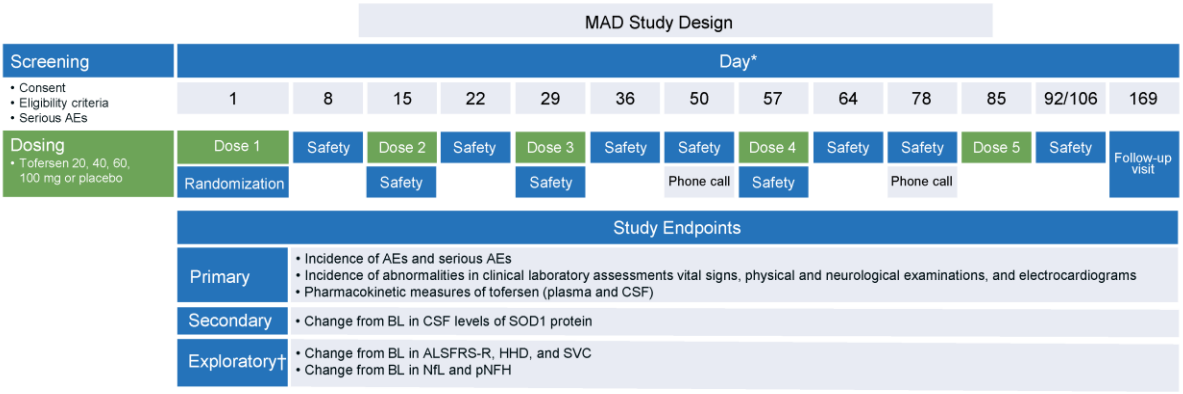


Figure S1. MAD Study Design.

*Single ascending dose study was performed first. †Exploratory outcomes shown were analyzed in this study. Additional exploratory outcomes include changes from baseline (BL) in electrical impedance myography, motor unit number index, ALS Assessment Questionnaire scores, Fatigue Severity Scale scores, EuroQol Five-Dimension Three-Level Questionnaire scores, 36-Item Short Form Health Survey, and Zarit Burden Interview scores, and possible relationships between tofersen pharmacokinetics, CSF SOD1 protein concentrations, and potential biomarker measures including misfolded or mutant *SOD1*, phosphorylated neurofilament heavy chains (pNfH), and neurofilament light chains (NfL). Analyses of these exploratory outcomes are ongoing. Two participants in MAD received an initial dose in the single ascending dose study and enrolled in MAD after a washout period of approximately 20 weeks.

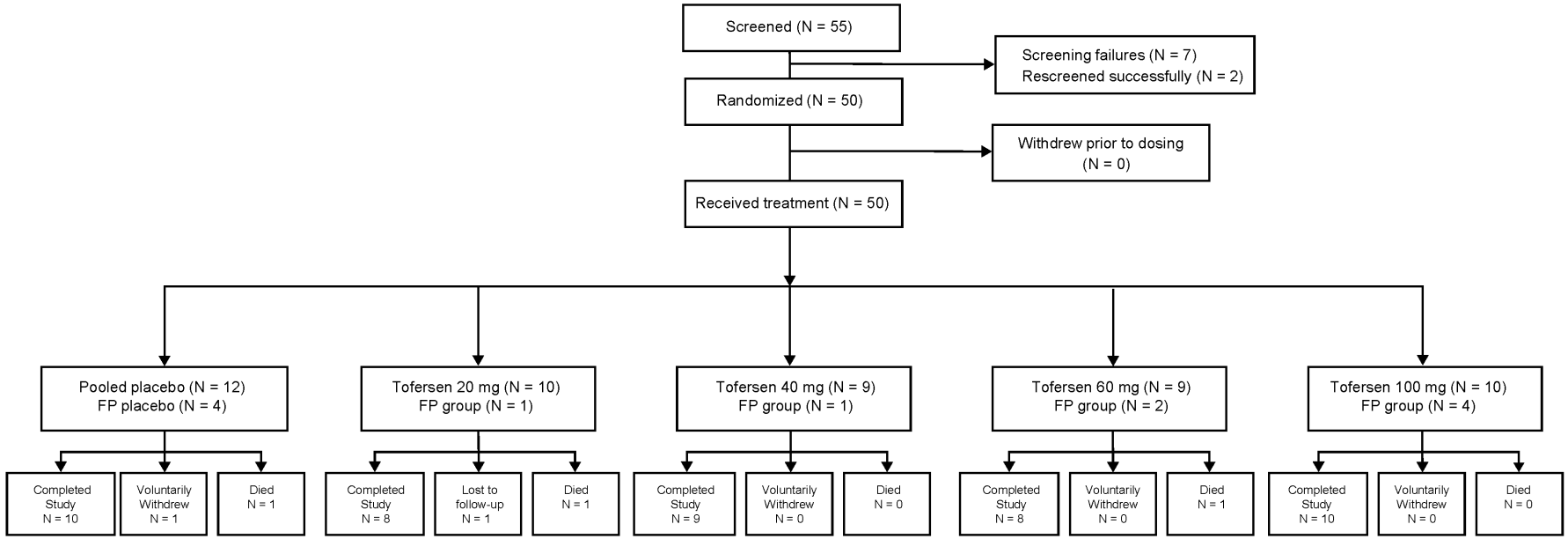
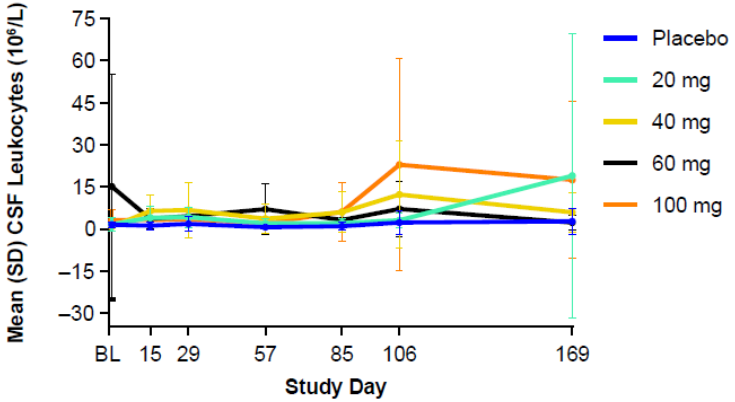


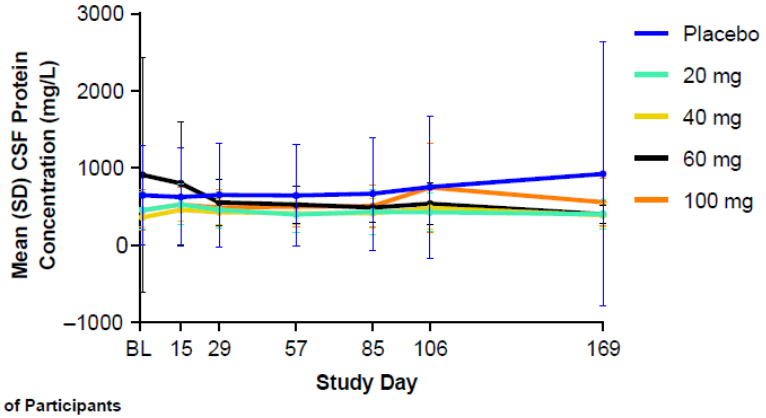
Figure S2. CONSORT Flow Diagram.

A



No. of Participants							
Placebo	12	12	12	11	11	10	8
Tofersen 20 mg	10	10	9	9	9	9	8
Tofersen 40 mg	9	9	9	9	9	9	6
Tofersen 60 mg	9	9	9	9	9	8	7
Tofersen 100 mg	10	10	10	10	10	10	8

B

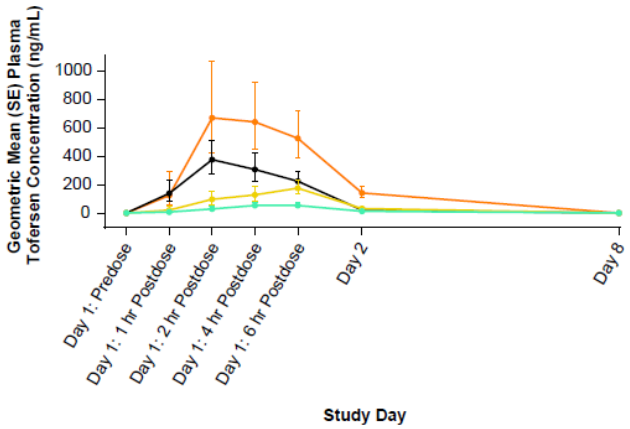


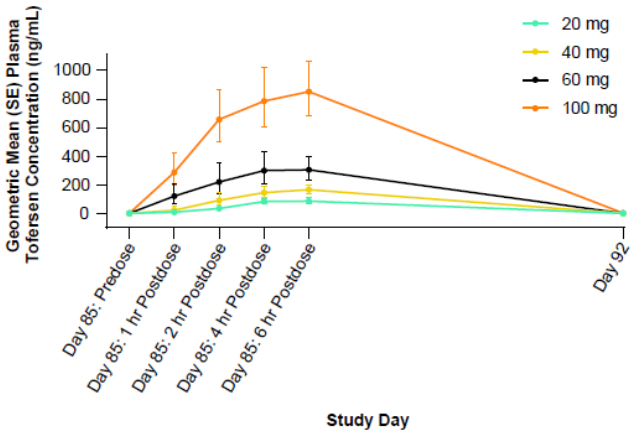
No. of Participants							
Placebo	12	12	12	11	11	11	8
Tofersen 20 mg	10	10	9	9	9	9	8
Tofersen 40 mg	9	8	9	9	9	9	6
Tofersen 60 mg	9	9	9	9	9	8	7
Tofersen 100 mg	10	10	10	10	10	10	8

Figure S3. CSF Laboratory Values.

Panel A, leukocytes. Panel B, protein. Erythrocyte results >10,000 are excluded.

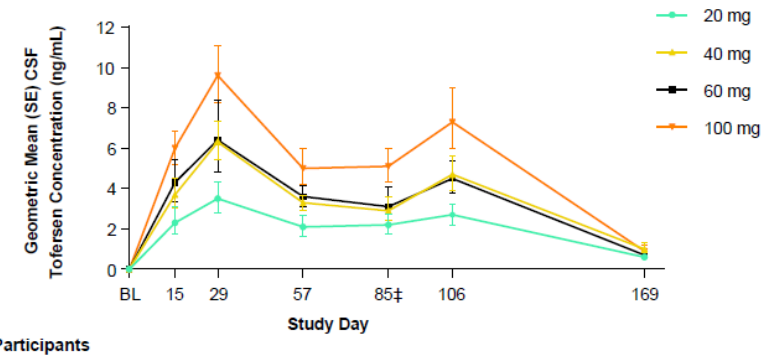
A





No. of Participants					
Tofersen 20 mg	10*	10	10	9	9
Tofersen 40 mg	9	9	9	8†	9
Tofersen 60 mg	9	8	8	9	7
Tofersen 100 mg	10	10	10	10	10

B



No. of Participants							
Tofersen 20 mg	10	10	9	9	9	9	8
Tofersen 40 mg	9	9	9	9	9	9	6
Tofersen 60 mg	8	8	9	9	9	8	7
Tofersen 100 mg	10	10	10	10	10	10	8

Figure S4. Tofersen Exposure.

Panel A shows the geometric mean (standard error [SE]) concentration of tofersen in plasma, according to dose group, over the 24-hour periods after the administration of the first dose (Day 1) and fifth dose (Day 85). Panel B shows the maximum predose (i.e., 28-day trough) geometric mean (SE) concentration of tofersen in CSF according to dose group. Tofersen values below limit of quantitation are set to half of lower limit of quantitation (1 ng/mL) in calculations. *N = 9 for Day 1: 6 hours postdose, 20 mg. †N = 9 for Day 85: predose, 40 mg. ‡Final dosing day.

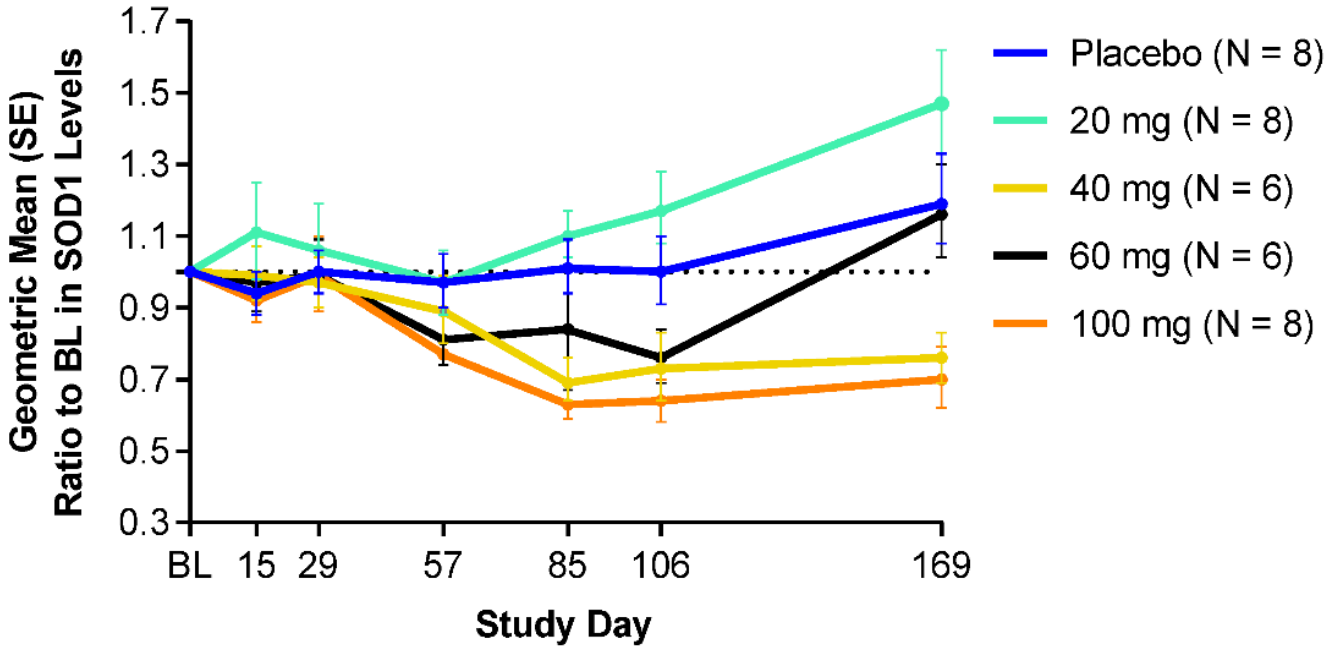


Figure S5. CSF SOD1 in Observed Completers to Day 169.

Values below the lower limit of quantitation (15.6 ng/mL) and data points where N = 1 are not presented. Completers are defined as participants who completed the study through to Day 169 (i.e., all expected visits).

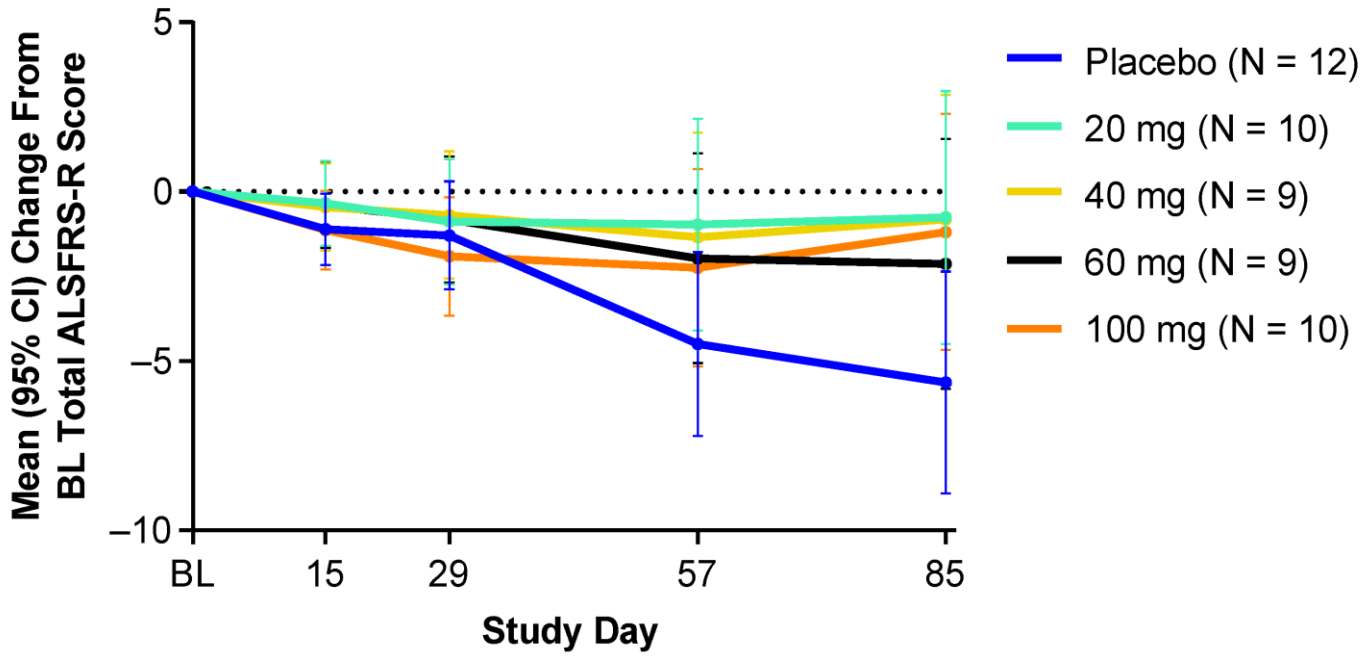


Figure S6. Change from Baseline in ALSFRS-R Score for All Cohorts.

Postbaseline missing values were imputed using an MMRM model. Means were calculated using the least squares method.

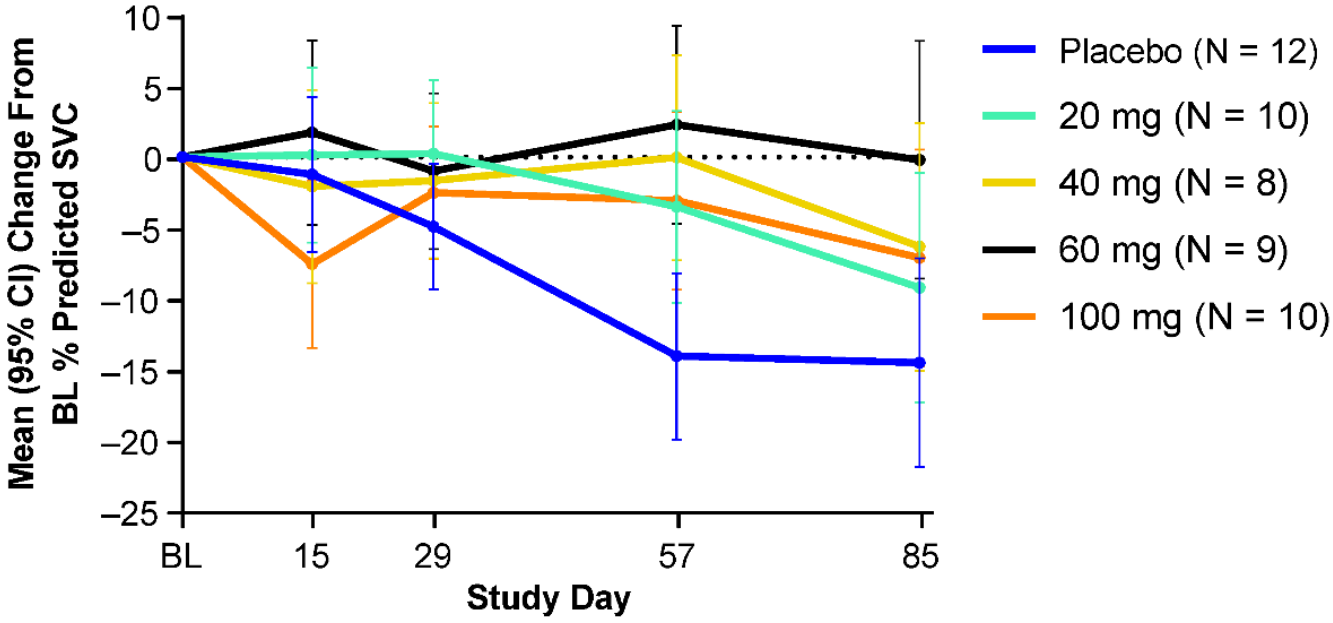
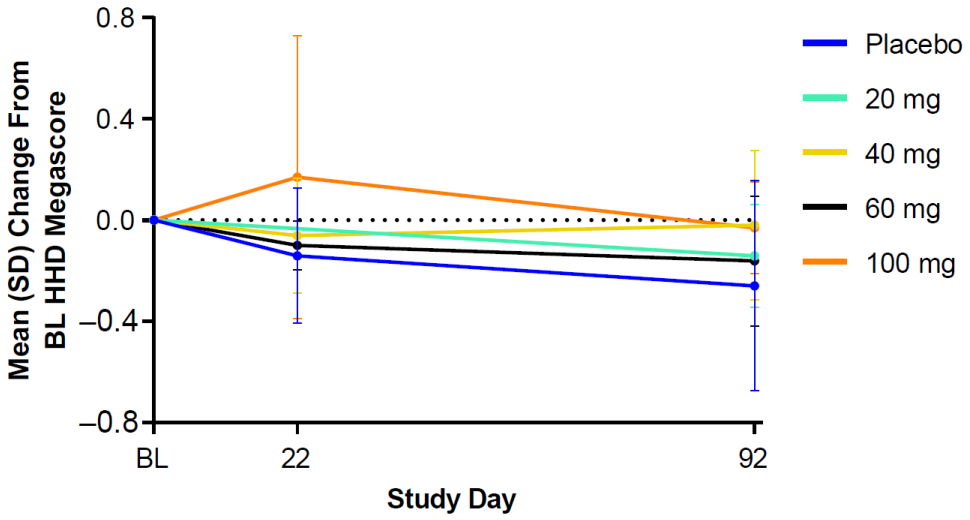


Figure S7. Change from Baseline in Percent Predicted SVC for All Cohorts.

Postbaseline missing values were imputed using an MMRM model. Means were calculated using the least squares method.



No. of Participants			
Placebo	12	9	12
Tofersen 20 mg	10	0	9
Tofersen 40 mg	9	8	9
Tofersen 60 mg	9	9	9
Tofersen 100 mg	10	10	10

Figure S8. Change from Baseline in HHD Megascore for All Cohorts.

Postbaseline missing values were imputed using last observation carried forward. Due to the timing of the protocol amendment to collect HHD at Day 22, no participants in Cohort 5 (placebo and 20 mg) have data for HHD at this visit.

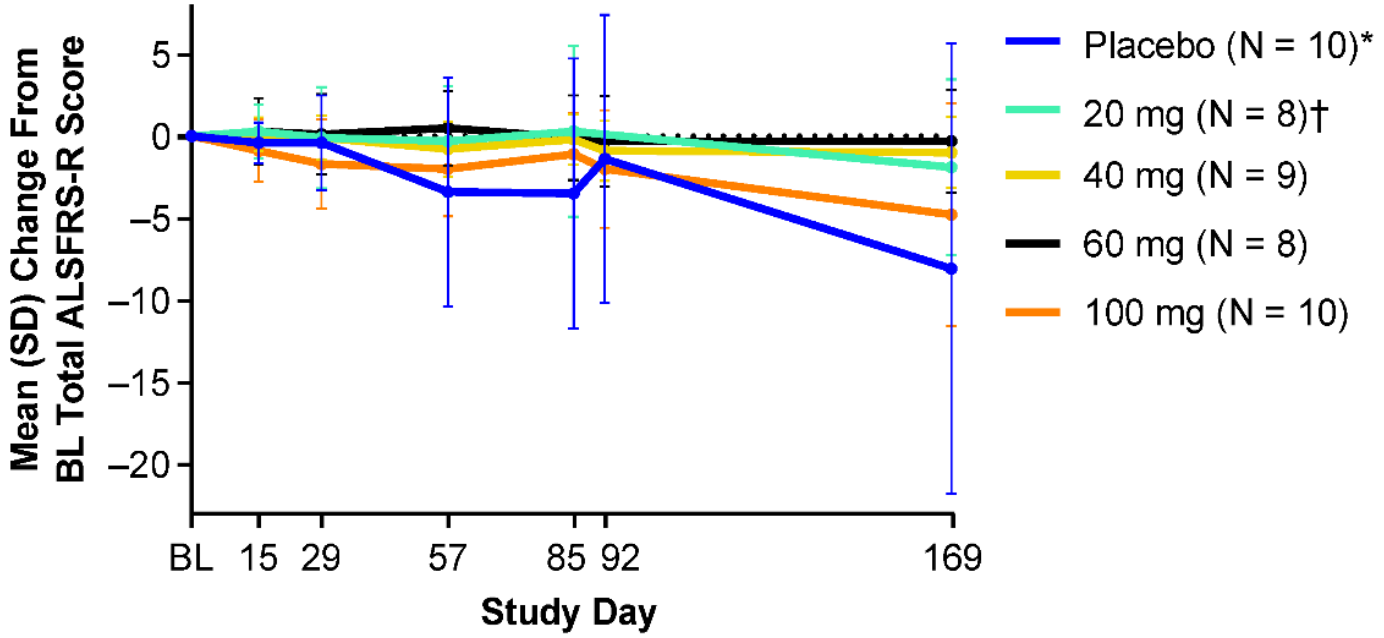


Figure S9. Total ALSFRS-R Score in Observed Completers to Day 169.

Completers are defined as participants who completed the study through to Day 169 (i.e., all expected visits). Some assessments were not performed at certain visits for participants in Cohort 5 based on the timing of protocol amendment affecting both those on placebo and 20 mg in this cohort. *N = 7 for Day 92. †Due to the timing of the protocol amendment to collect ALSFRS-R at Day 92, no participants were included for analysis on Day 92 for this cohort.

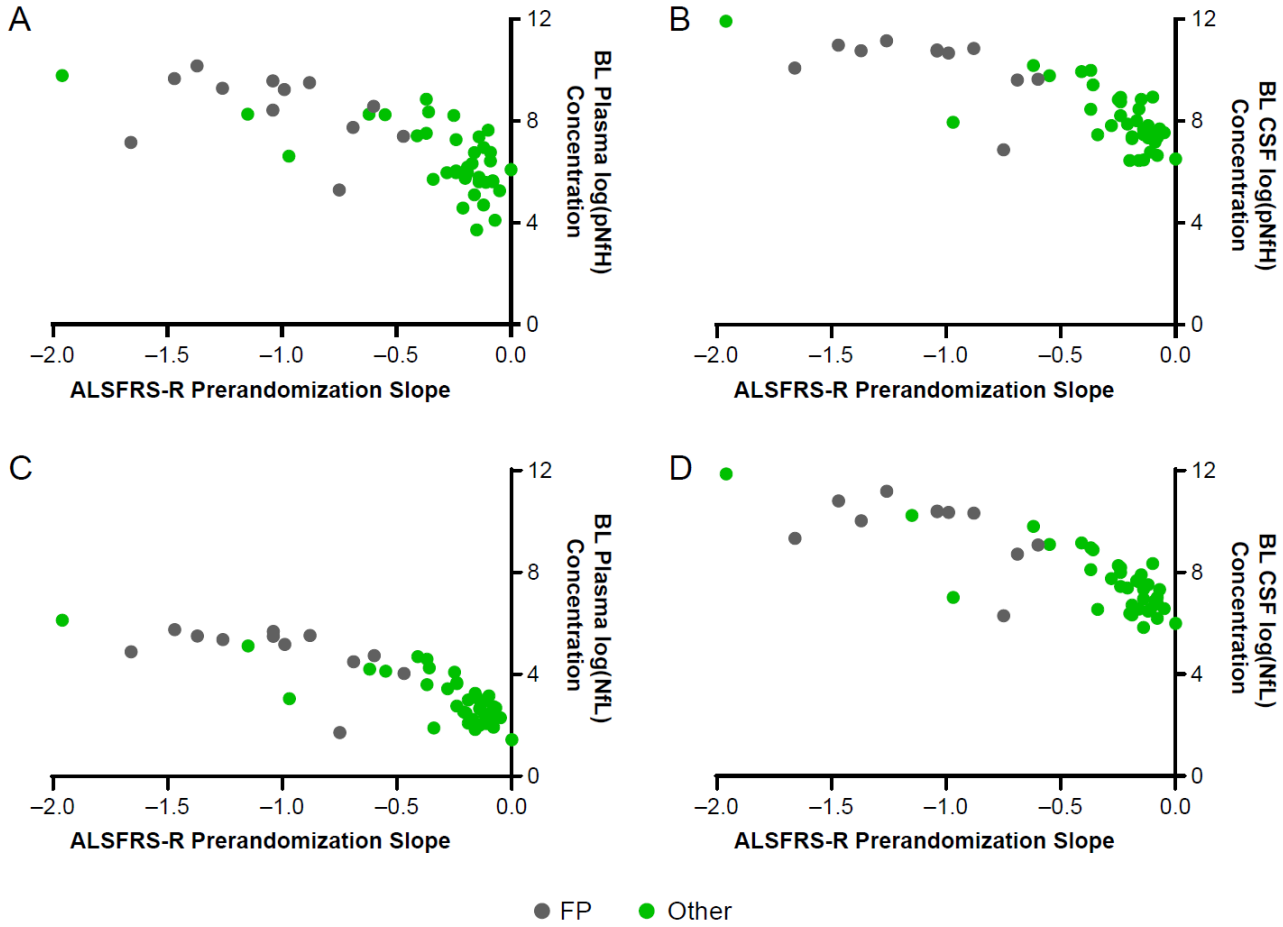
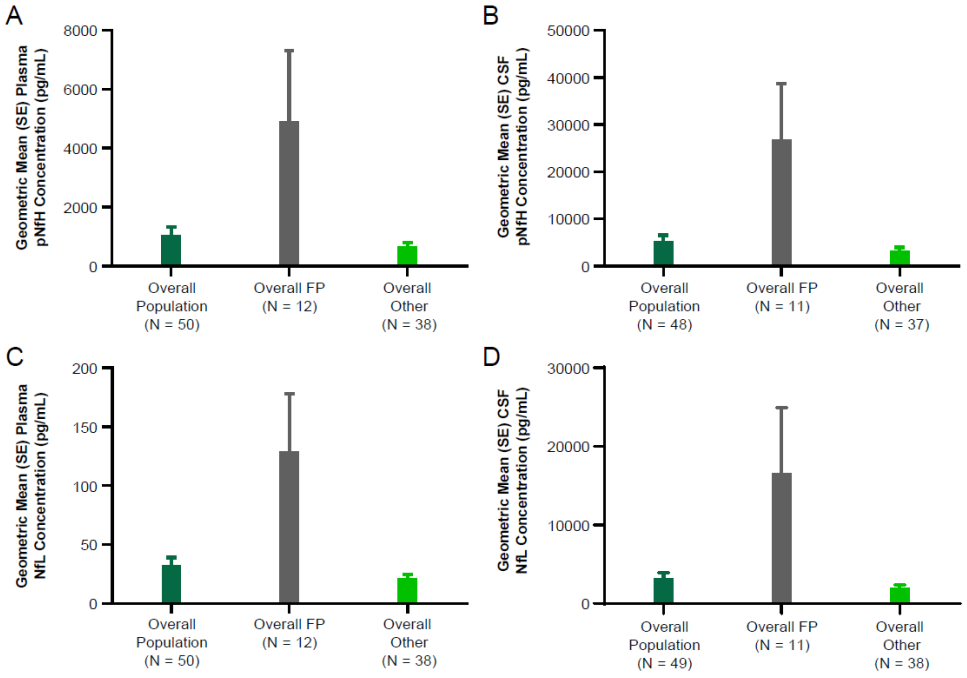


Figure S10. Baseline Neurofilament Concentrations Were Associated with Disease Activity as Measured by Prerandomization ALSFRS-R Slope.

pNfH in plasma (Panel A) and CSF (Panel B); NfL in plasma (Panel C) and CSF (Panel D).



Mean (±SE) Concentration (pg/mL)	Plasma pNfH	CSF pNfH	Plasma NfL	CSF NfL
Overall population	1049.4 (835.9, 1317.5)	5242.6 (4219.2, 6514.3)	32.6 (27.1, 39.1)	3175.1 (2539.0, 3970.6)
Overall FP	4896.9 (3274.0, 7324.2)	26764.1 (18526.5, 38664.3)	128.8 (93.2, 178.1)	16562.4 (11002.6, 24931.7)
Overall other	645.2 (517.9, 803.8)	3229.0 (2642.1, 3946.2)	21.1 (17.9, 24.9)	1968.3 (1599.7, 2421.9)

Figure S11. Baseline Neurofilament Concentrations Were Highest in Fast-Progressing Participants.

pNfH in plasma (Panel A) and CSF (Panel B); pNfL in plasma (Panel C) and CSF (Panel D).

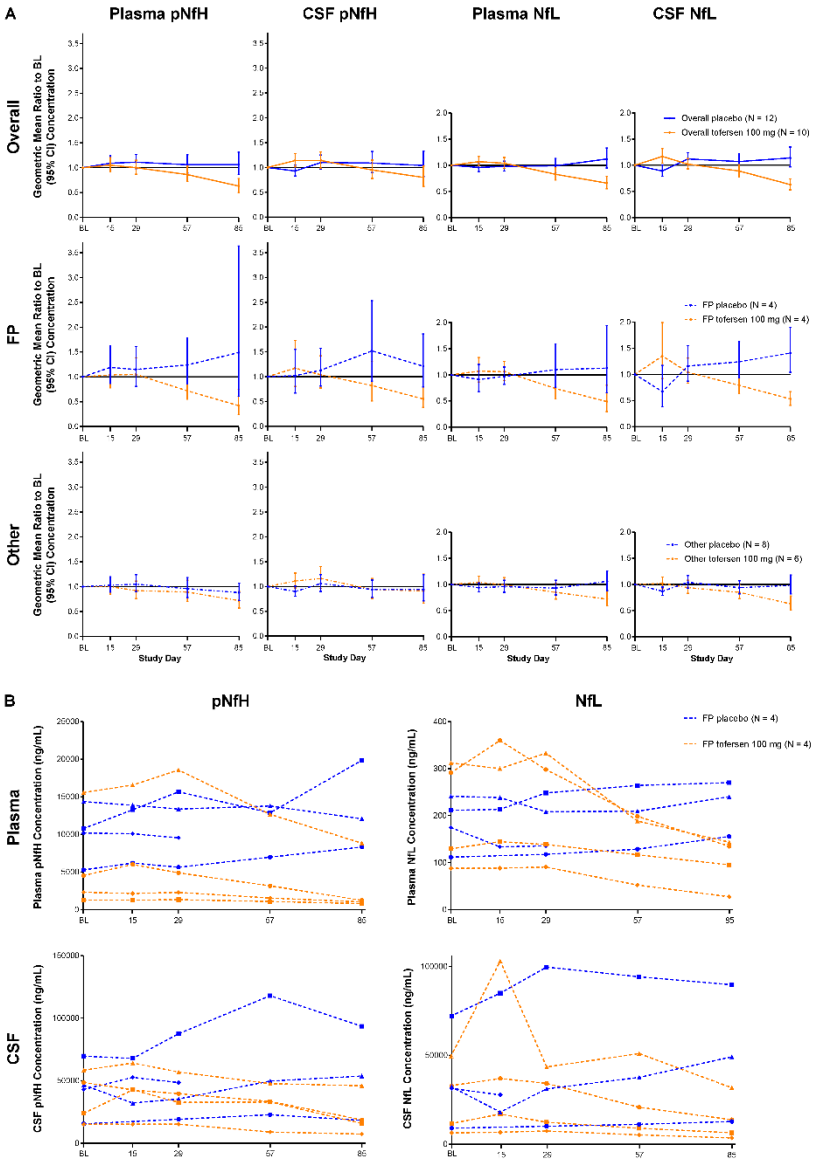
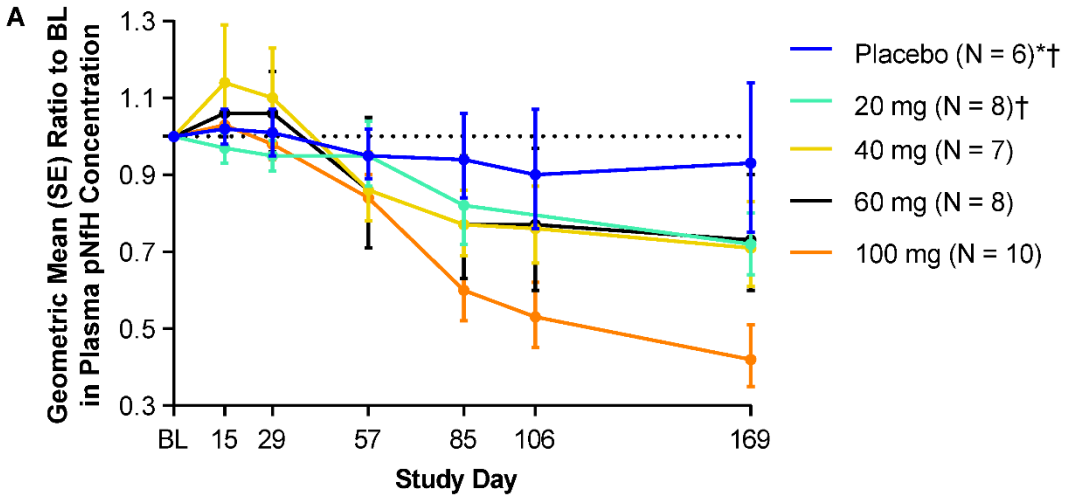

A
Plasma pNfH
CSF pNfH
Plasma NfL
CSF NfL
Overall
FP
Other
Geometric Mean Ratio to BL (95% CI) Concentration
Overall placebo (N = 12)
Overall tofersen 100 mg (N = 10)
FP placebo (N = 4)
FP tofersen 100 mg (N = 4)
Other placebo (N = 8)
Other tofersen 100 mg (N = 6)
Study Day
B
pNfH
NfL
Plasma
CSF
Plasma pNfH Concentration (ng/mL)
Plasma NfL Concentration (ng/mL)
CSF pNfH Concentration (ng/mL)
CSF NfL Concentration (ng/mL)
FP placebo (N = 4)
FP tofersen 100 mg (N = 4)

Figure S12. Effect of Tofersen on Plasma and CSF Neurofilament Concentrations.

Panel A shows geometric mean (95% CI) ratios to baseline for plasma and CSF pNfH and NfL for overall, fast-progressing, and other participants. Postbaseline missing values were imputed using an MMRM model. Panel B shows individual neurofilament traces for fast-progressing participants. Geometric mean ratios were calculated using the least squares method.


A
Geometric Mean (SE) Ratio to BL in Plasma pNfH Concentration
1.3
1.1
0.9
0.7
0.5
0.3
BL
15
29
57
85
106
169
Study Day
Placebo (N = 6)*†
20 mg (N = 8)†
40 mg (N = 7)
60 mg (N = 8)
100 mg (N = 10)

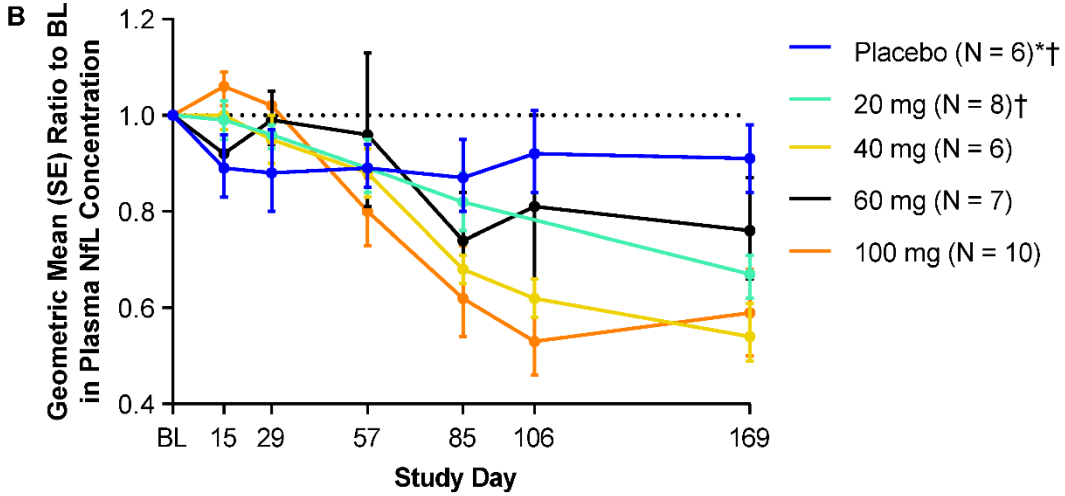
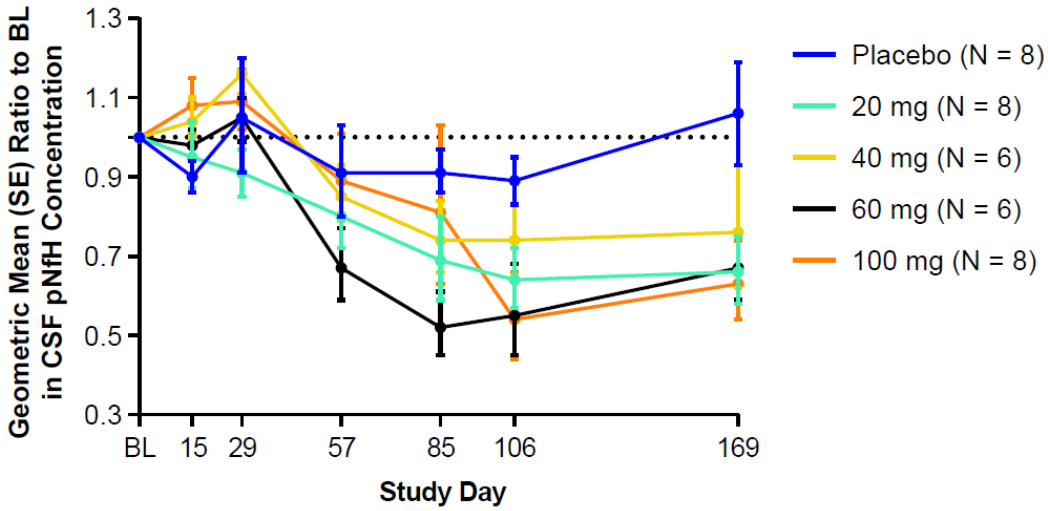

B
Geometric Mean (SE) Ratio to BL in Plasma NfL Concentration
1.2
1.0
0.8
0.6
0.4
BL
15
29
57
85
106
169
Study Day
Placebo (N = 6)*†
20 mg (N = 8)†
40 mg (N = 6)
60 mg (N = 7)
100 mg (N = 10)

Figure S13. Ratio to Baseline Plasma pNfH (Panel A) and NfL (Panel B) Concentration in Observed Completers to Day 169.

Completers are defined as participants who completed the study through to Day 169 (i.e., all expected visits). *N = 4 at Day 106. †Due to the timing of the protocol amendment to collect plasma samples for biomarkers at Day 106, no participant in the placebo and 20-mg dose group had data for plasma pNfH and NfL at this visit.

A


Geometric Mean (SE) Ratio to BL in CSF pNfH Concentration
1.3
1.1
0.9
0.7
0.5
0.3
BL
15
29
57
85
106
169
Study Day
Placebo (N = 8)
20 mg (N = 8)
40 mg (N = 6)
60 mg (N = 6)
100 mg (N = 8)

B

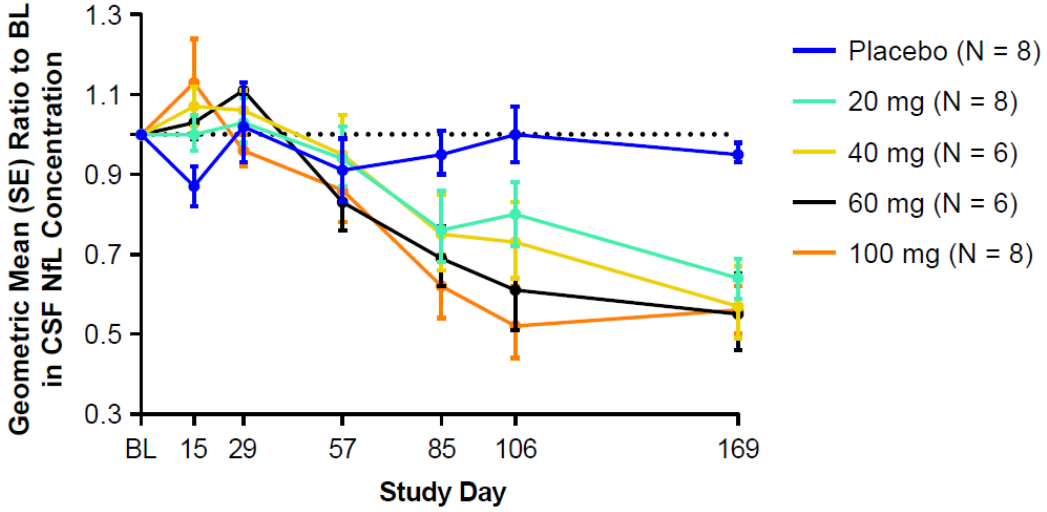

Geometric Mean (SE) Ratio to BL in CSF NfL Concentration
1.3
1.1
0.9
0.7
0.5
0.3
BL
15
29
57
85
106
169
Study Day
Placebo (N = 8)
20 mg (N = 8)
40 mg (N = 6)
60 mg (N = 6)
100 mg (N = 8)

Figure S14. Ratio to Baseline CSF pNfH (Panel A) and NfL (Panel B) Concentration in Observed Completers to Day 169.

Completers are defined as participants who completed the study through to Day 169 (i.e., all expected visits).

SECTION S7: SUPPLEMENTARY TABLES

Table S1. *SOD1* Mutations Associated with Fast-Progressing ALS, Reported as Showing an Average Time from First Symptom to Death Within 3 Years.

SOD1 FP Mutation	Alternative Nomenclature	Position (Chr21; hg19)	rsID	Transcript Consequence	Annotation	ALS Disease Progression	N Patients Described	Disease Duration/Progression Rate – Mean (SD)	Country	Reference
p.Ala5Val	A4V	33032096	rs121912442	c.14C>T	Missense	Fast	87	yr: 1.4 (0.9); median, 1.0; range: 0.5–4.0	USA	Cudkowicz et al, 1997[4]
							63	yr: 1.4 (0.7); median, 1.2	USA	Bali et al, 2017[5]
							4	yr: 0.9	Sweden/ Finland	Andersen et al, 1997[6]
							75	yr: 1.0 (0.4)	USA	Juneja et al, 1997[7]
p.Ala5Thr	A4T	33032095	rs121912444	c.13G>A	Missense	Fast	7	yr: 1.5 (0.4)	USA	Juneja et al, 1997[7]
							2	yr: 0.8 (0.05)	USA	Bali et al, 2017[5]
p.Gly42Ser	G41S	33036154	rs121912433	c.124G>A	Missense	Fast	8	mo: 11.6 (1.7); range, 9–13	Italy	Rainero et al, 1994[8]
							4	mo: range, <12–15	Italy	Battistini et al, 2005[9]
							8	yr: 0.9 (0.3); range, 2–15	Italy	Battistini et al, 2010[10]
							4	yr: 0.9 (0.5); median, 1.0	USA	Cudkowicz et al, 1997[4]
							1	yr: 0.4	USA	Bali et al, 2017[5]

p.His44Arg	H43R	33036161	rs121912435	c.131A>G	Missense	Fast	4	yr: 2.8 (1.5); median, 2.5	USA	Cudkowicz et al, 1997[4]
							7	yr: 1.4 (0.8)	USA	Juneja et al, 1997[7]
							1	yr: 0.3	USA	Bali et al, 2017[5]
p.Leu85Val	L84V	33039584	rs121912452	c.253T>G	Missense	Fast	5	yr: 1.6 (0.5)	Japan	Abe et al, 1996[11]
p.Gly94Ala	G93A	33039612	–	c.281G>C	Missense	Fast	9	yr: 2.2 (1.5); median, 1.7	USA	Cudkowicz et al, 1997[4]
							2	yr: 2.2 (0.6)	USA	Bali et al, 2017[5]
							6	yr: 2.4 (1.4)	USA	Juneja et al, 1997[7]
p.Arg116Gly	R115G	33039677	–	c.346C>G	Missense	Fast	8	yr: mean, 2–3	Germany	Rabe et al, 2010[12]
p.Leu107Val	L106V	33039650	rs121912440	c.319C>G	Missense	Fast	2	yr: 1.2 (0.1)	USA	Juneja et al, 1997[7]
							4	yr: 2.3 (1.3); median, 1.9	USA	Cudkowicz et al, 1997[4]
p.Leu39Val	L38V	33036145	rs121912432	c.115C>G	Missense	Fast	12	yr: 2.8 (1.9); median, 2.0; range, 0.9–7.0	USA	Cudkowicz et al, 1997[4]
p.Val149Gly	V148G	33040872	–	c.446T>G	Missense	Fast	7	yr: 2.0 (0.9)	USA	Juneja et al, 1997[7]
							4	yr: 2.3 (2.2); median, 1.3	USA	Cudkowicz et al, 1997[4]
							2	yr: mean, 2.5	Germany	Rabe et al, 2010[12]

Table S2. Demography and Baseline Characteristics.

		Tofersen			
	Placebo* (N = 12)	20 mg (N = 10)	40 mg (N = 9)	60 mg (N = 9)	100 mg (N = 10)
Mean (SD) age — yr	49.2 (11.0)	41.5 (10.7)	58.0 (11.1)	45.6 (10.7)	48.9 (10.8)
Male — n (%)	7 (58.3)	7 (70.0)	4 (44.4)	6 (66.7)	4 (40.0)
Riluzole use — n (%)	5 (41.7)	8 (80.0)	5 (55.6)	8 (88.9)	7 (70.0)
Mean (SD) time since symptom onset — mo	49.4 (49.0)	61.4 (44.1)	64.2 (58.3)	72.3 (83.4)	41.4 (41.4)
Mean (SD) baseline ALSFRS-R score	36.0 (4.8)	34.4 (7.4)	36.7 (6.9)	38.3 (6.5)	38.2 (2.4)
Mean (SD) prerandomization ALSFRS-R slope — score change/month	–0.65 (0.60)	–0.41 (0.37)	–0.27 (0.20)	–0.34 (0.42)	–0.61 (0.59)
Mean (SD) baseline % predicted SVC	77.4 (21.8)	79.8 (17.7)	88.3 (15.6)†	72.8 (17.3)	85.5 (10.3)
Mean (SD) baseline HHD megascore	0.02 (1.06)	–0.11 (0.36)	0.09 (1.16)	0.08 (0.67)	–0.05 (0.67)
Geometric mean (SE) baseline CSF SOD1 — ng/mL	84.6 (75.4–95.0)	79.9 (71.5–89.4)	140.9 (120.3–165.1)	102.5 (90.5–116.0)	139.8 (122.7–159.2)
SOD1 mutation, n (%)	12 (100.0)	10 (100.0)	9 (100.0)	9 (100.0)	10 (100.0)
A4V‡	4 (33.3)	1 (10.0)	1 (11.1)	2 (22.2)	2 (20.0)
D90A	0	1 (10.0)	2 (22.2)	0	0
I113T	0	1 (10.0)	1 (11.1)	1 (11.1)	2 (20.0)
L106V‡	0	0	0	0	1 (10.0)

R115G‡	0	0	0	0	1 (10.0)
Unknown	0	1 (10.0)	0	0	0
Other	8 (66.7)	6 (60.0)	5 (55.6)	6 (66.7)	4 (40.0)

*Combined placebo from all cohorts.

†N = 8.

‡Fast-progressing mutations.

Table S3. Day 85 CSF SOD1 Reduction in Treatment Groups.

	Tofersen			
	20 mg (N = 10)	40 mg (N = 9)	60 mg (N = 9)	100 mg (N = 10)
Mean difference: Ratio to baseline in CSF SOD1 (95% CI) percentage points (tofersen dose minus placebo)	2 (–18, 27)	–25 (–40, –5)	–19 (–35, 2)	–33 (–47, –16)

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