Evaluating Efficacy and Safety of Tofersen in Adults with *SOD1*-ALS: Results from the Phase 3 VALOR Trial and Open-Label Extension

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Plain language summary

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Disclosures

- TMM: advisory board and clinical research support for Biogen; licensing agreement with, and consulting for, Ionis Pharmaceuticals, Inc.; consultant for Cytokinetics; licensing agreements with C2N; advisory board for Disarm Therapeutics; and advisory board for UCB Pharma
- MEC: compensation from an advisory board for Biogen; compensation from QurAlis, RRD, Sunovian, Cytokinetics, Takeda, Regeneron, Transposon, and Locust Walk; member of Praxis Board of Directors
- AG: ad hoc consultant for genetic testing for Biogen; consultant on ALS trial design for Alexion, AL-S Pharma, Calico, Cytokinetics, and Sanofi; and CMO at QurAlis
- PJS: advisory board member for Biogen, Aclipse Therapeutics, Quell Therapeutics, BenevolentAI, and QurAlis and receives research support from Quell Therapeutics, Aclipse Therapeutics, Pfizer, and SwanBio. Support for clinical trials participation has been received from Biogen, Alexion, the EU Horizon programme and UK NIHR.
- GS: compensation from Mitsubishi Tanabe Pharma, Takeda, and Sumitomo Dainippon Pharma
- TC, IN, DG, PS, MM, LF, TAF, and SF: employees of and hold stock/stock options in Biogen

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Tofersen is an investigational antisense oligonucleotide (ASO) designed to reduce synthesis of SOD1 protein through degradation of *SOD1* mRNA[1,2]

mRNA = messenger ribonucleic acid; SOD1 = superoxide dismutase 1

1. Miller T, et al. *N Engl J Med.* 2020;383(2):109-119. 2. Miller T, Cudkowicz M. ANA 2021.

VALOR and its Open-Label Extension

VALOR[1]
28 weeks
Tofersen 100 mg vs. placebo

Data were integrated to evaluate early- vs. delayed-start tofersen initiation

OLE[2]
~3–7 years
Tofersen 100 mg

Data presented October 2021[3]

- Data cut date: July 2021
  - VALOR completion + first interim of the OLE
  - All participants had the opportunity for at least **6 months** of follow-up
- **Prespecified subgroups** based on:
  - Mutation/ALSFRS-R slope OR
  - Baseline neurofilament

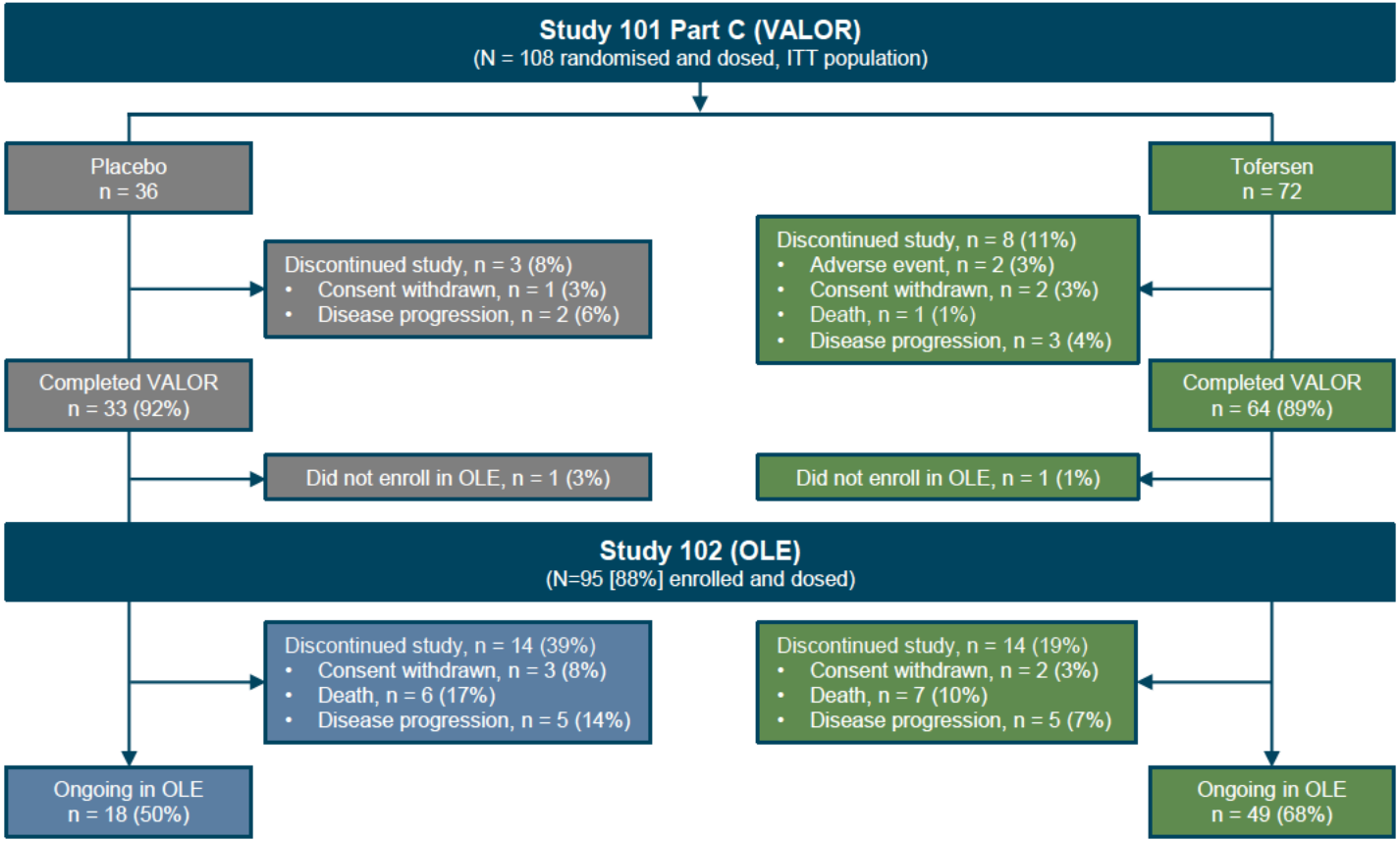
Data in this presentation

- Data cut date: January 2022
  - New interim cut of the OLE
  - All participants had the opportunity for at least **12 months** of follow-up
- Prior to database lock, baseline plasma NfL was incorporated as a covariate, thus **controlling for heterogeneity of disease progression in the overall (ITT) population**

ALS = amyotrophic lateral sclerosis; ALSFRS-R = ALS Functional Rating Scale–Revised; ITT = intention-to-treat. OLE = open-label extension; NfL = neurofilament light chain

1. https://clinicaltrials.gov/ct2/show/NCT02623699. 2. https://clinicaltrials.gov/ct2/show/NCT03070119. 3. Miller T, Cudkowicz M. ANA 2021.

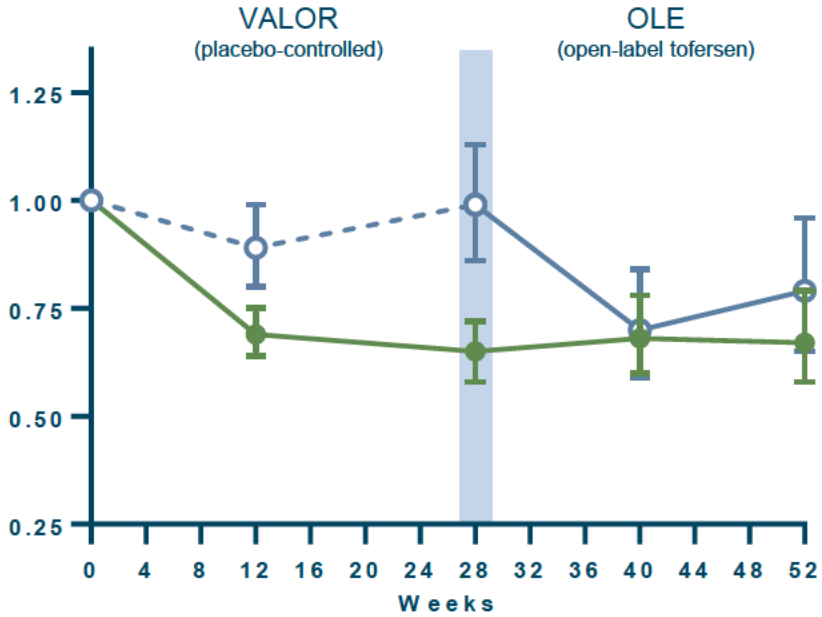
Participant Disposition



ITT = intention-to-treat; OLE = open-label extension

Target Engagement

Adjusted geometric mean ratio (95% CI) to baseline of total CSF SOD1 protein



Placebo → Delayed-start tofersen, n =	36	36	30	27	25
Early-start tofersen, n =	71	64	57	52	53

Week 52 percent reduction (GMR) from baseline:

21% (95% CI, 4–35%)

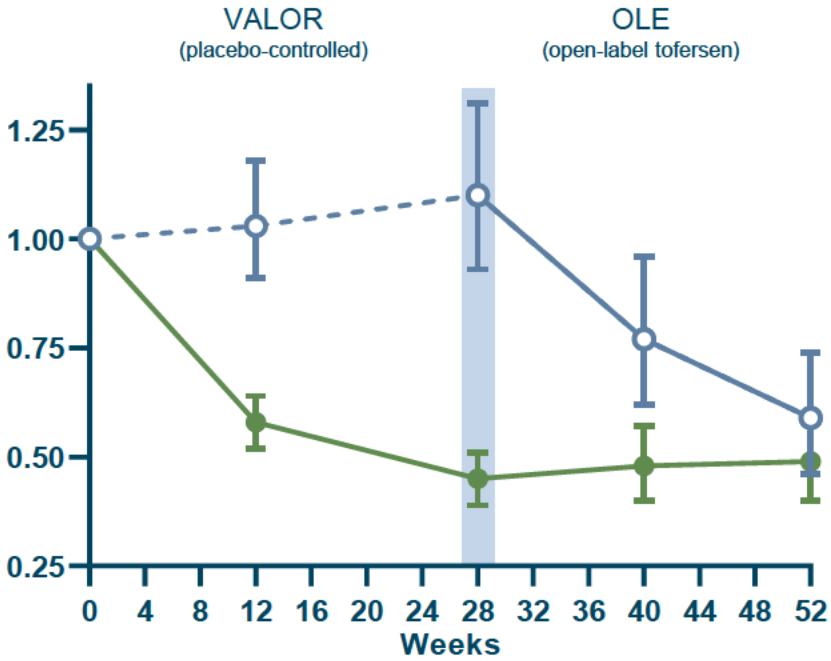
33% (95% CI, 21–42%)

CSF = cerebrospinal fluid; OLE = open-label extension; SOD1 = superoxide dismutase 1

Analysis is based on ANCOVA model in conjunction with multiple imputation for missing data; based on natural log transformed data. The model includes covariates for the corresponding baseline value i.e. log value, and use of riluzole or edaravone.

Effect on Neurofilament

Adjusted geometric mean ratio (95% CI) to baseline of plasma NfL



Placebo → Delayed-start tofersen, n =	36	35	31	28	23
Early-start tofersen, n =	71	62	53	50	50

Week 52 percent reduction (GMR) from baseline:

41% (95% CI, 26–54%)

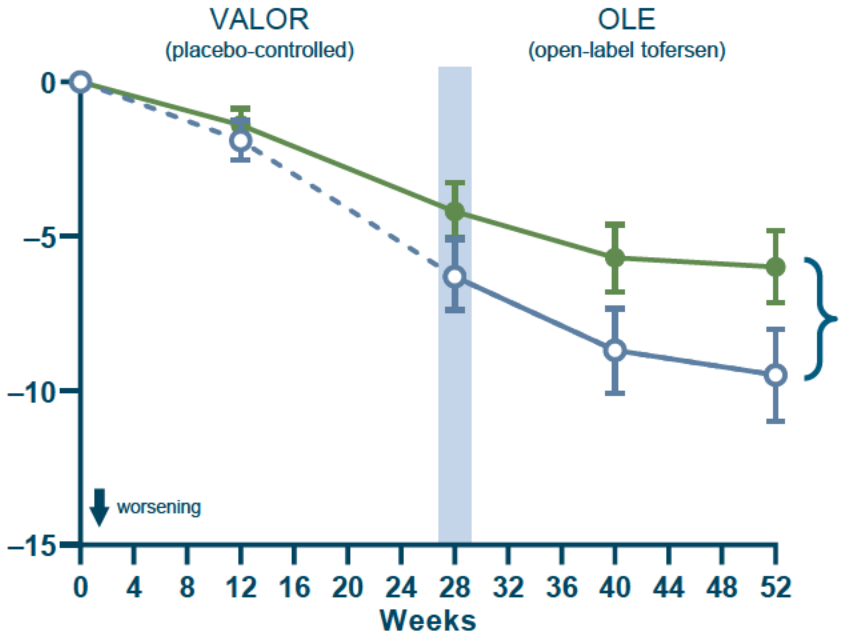
51% (95% CI, 42–60%)

NfL = neurofilament light chain; OLE = open-label extension

Analysis is based on ANCOVA model in conjunction with multiple imputation for missing data; based on natural log transformed data. The model includes covariates for the corresponding baseline value i.e. log value, and use of riluzole or edaravone.

Effect on Clinical Function

Adjusted mean (±SE) change from baseline in ALSFRS-R total score



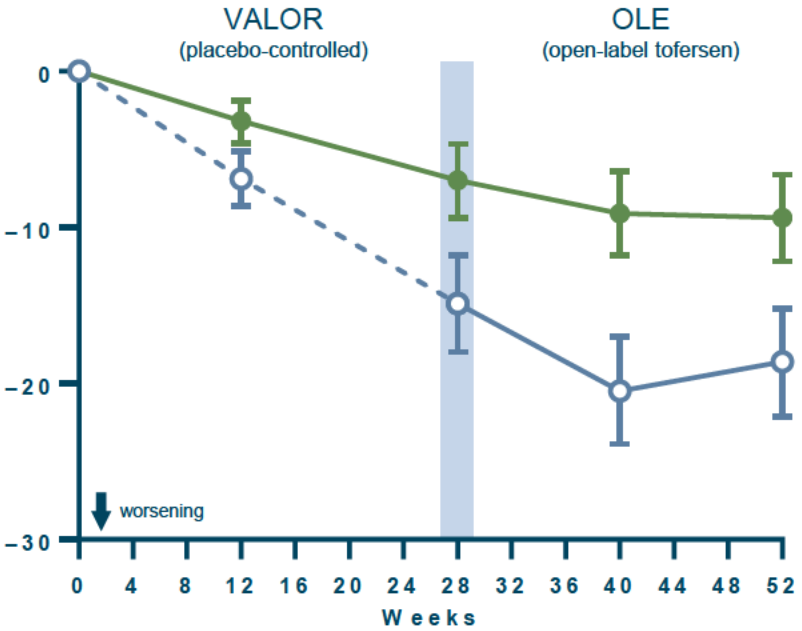
ALSFRS-R total score
Adjusted mean difference at Week 52:
3.5 (95% CI, 0.4–6.7)
p = 0.0272

Placebo → Delayed-start tofersen, n =	36	36	33	29	28
Early-start tofersen, n =	72	66	63	58	57

ALS = amyotrophic lateral sclerosis; ALSFRS-R = ALS Functional Rating Scale–Revised; OLE = open-label extension
Analysis is based on ANCOVA model in conjunction with multiple imputation for missing data. The model includes covariates for the corresponding baseline value, baseline plasma NfL, and use of riluzole or edaravone.

Effect on Respiratory Function

Adjusted mean (±SE) change from baseline in percent-predicted SVC



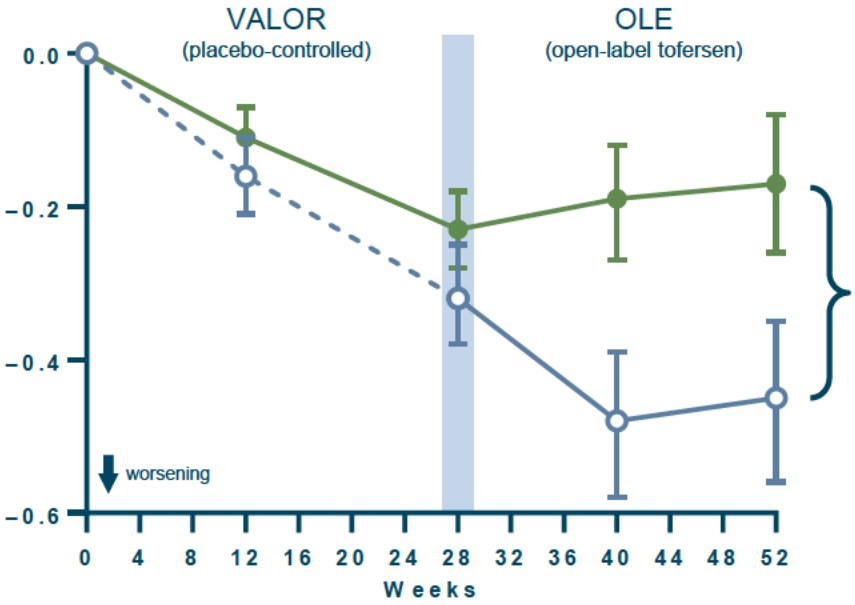
Percent-predicted SVC
Adjusted mean difference at Week 52:
9.2 (95% CI, 1.7–16.6)
p = 0.0159

Placebo → Delayed-start tofersen, n =	36	34	25	20	20
Early-start tofersen, n =	72	59	52	39	38

OLE = open-label extension; SVC = slow vital capacity
Analysis is based on ANCOVA model in conjunction with multiple imputation for missing data. The model includes covariates for the corresponding baseline value, baseline plasma NfL, and use of riluzole or edaravone.

Effect on Muscle Strength

Adjusted mean (±SE) change from baseline in HHD megascore



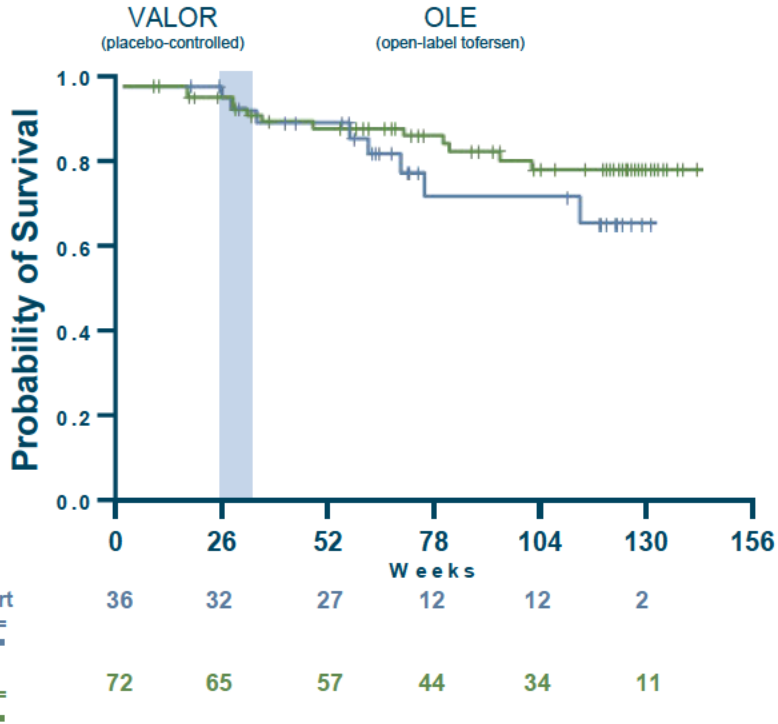
HHD megascore
Adjusted mean difference at Week 52:
0.28 (95% CI, 0.05–0.52)
p = 0.0186

Placebo → Delayed-start tofersen, n =	36	35	27	24	25
Early-start tofersen, n =	72	64	58	47	42

HHD = handheld dynamometry; OLE = open-label extension
Analysis is based on ANCOVA model in conjunction with multiple imputation for missing data. The model includes covariates for the corresponding baseline value, baseline plasma NfL, and use of riluzole or edaravone.

Time-to-Event Analyses

Kaplan-Meier plot of time to death or PV



Events	Early-start tofersen	Placebo → delayed-start tofersen	Hazard ratio
Death or Permanent Ventilation	12/72 (16.7%)	8/36 (22.2%)	**0.36** 95% CI, 0.137–0.941
Death	8/72 (11.1%)	6/36 (16.7%)	**0.27** 95% CI, 0.084–0.890
Death with additional post-withdrawal vital status data	12/72 (16.7%)	11/36 (30.6%)	**0.24** 95% CI: 0.096, 0.602
Death, PV, or withdrawal due to disease progression	18/72 (25.0%)	13/36 (36.1%)	**0.38** 95% CI: 0.180, 0.821

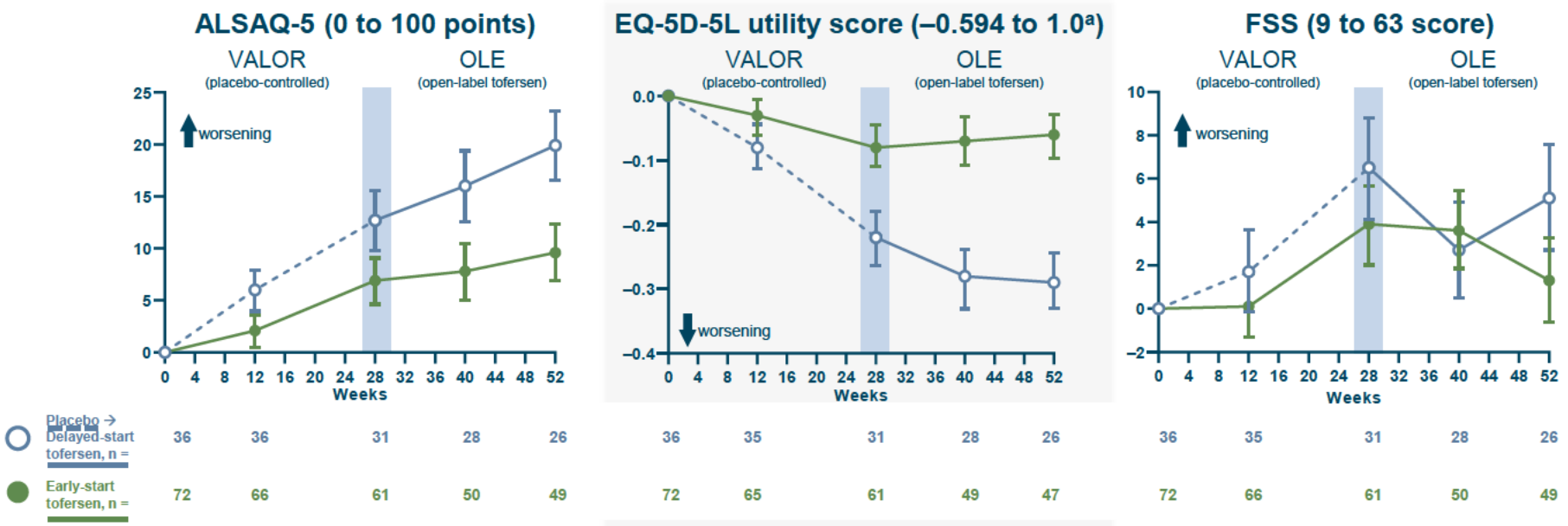
Median time to death and time to death or PV were non-estimable due to the number of events

OLE = open-label extension; PV = permanent ventilation

Time to death or permanent ventilation is defined as he time from first dose to death or PV (≥22 hours of mechanical ventilation per day for ≥21 consecutive days), whichever comes first. Participants who do not meet the endpoint definition are censored a participant's last known alive date. Events are based on adjudicated events by an independent committee. Plots are Kaplan-Meier curves. Hazard ratios and confidence intervals are based on a Cox regression model adjusted for baseline plasma NfL, and riluzole or edaravone use.

Effect on ALS PROs

Adjusted mean (±SE) change from baseline



Placebo → Delayed-start tofersen, n =	36	36	31	28	26	36	35	31	28	26	36	35	31	28	26
Early-start tofersen, n =	72	66	61	50	49	72	65	61	49	47	72	66	61	50	49

Adjusted mean difference, Week 52:
–10.3
(95% CI: –17.3 to –3.2), p=0.0044

Adjusted mean difference, Week 52:
0.2
(95% CI: 0.13 to 0.32), p<0.0001

Adjusted mean difference, Week 52:
–3.8
(95% CI: –9.0 to 1.38), p=0.1493

ALS = amyotrophic lateral sclerosis; ALSAQ-5 = 5 Item ALS Assessment Questionnaire; EQ-5D = EuroQOL-5 Dimension 5-Level Questionnaire; FSS = Fatigue Severity Scale; OLE = open-label extension; PRO = patient-reported outcome

Analysis is based on ANCOVA model in conjunction with multiple imputation for missing data. The model includes covariates for the corresponding baseline value, baseline plasma NfL, and use of riluzole or edaravone.

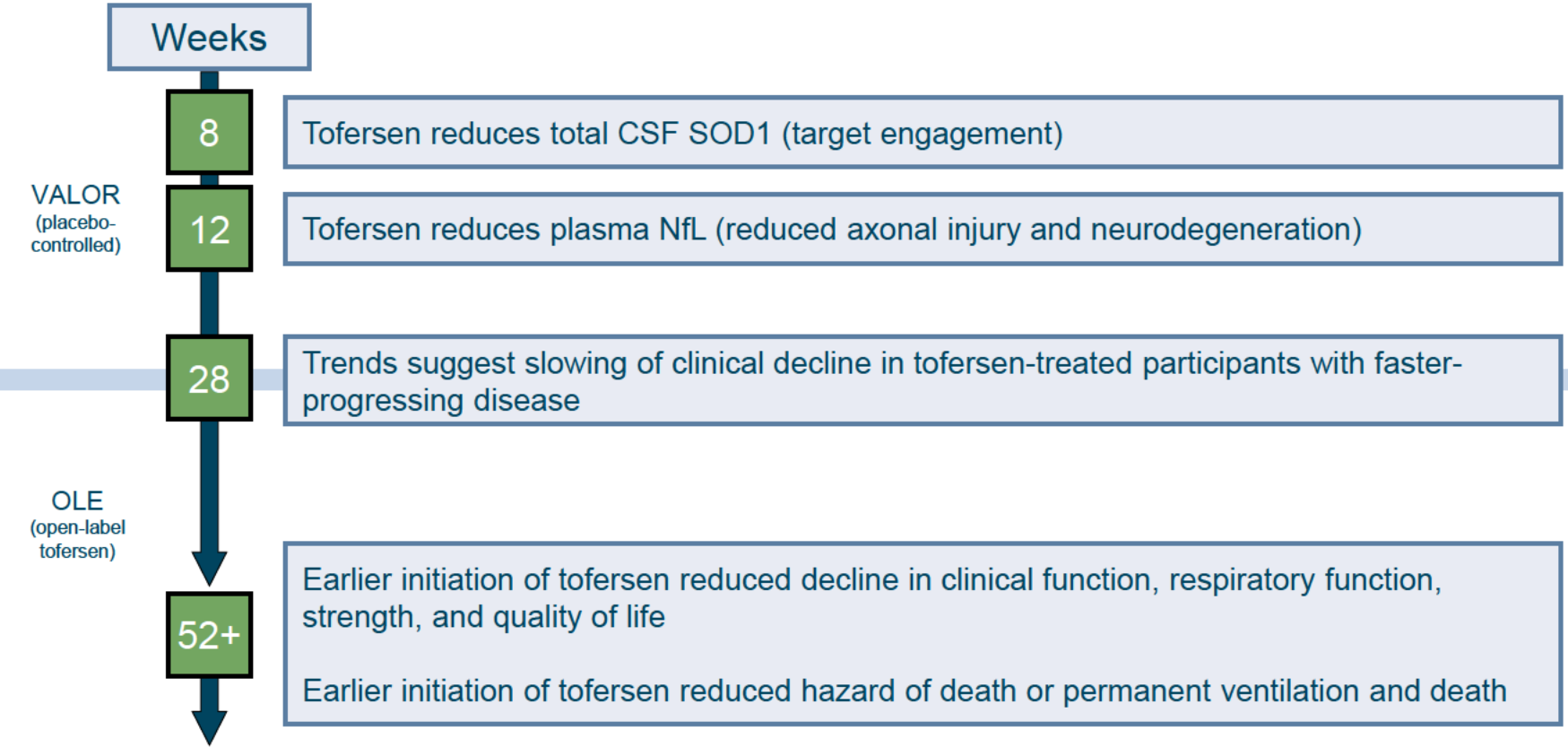
[a]Using UK valuation weights.

Summary of Adverse Events

	VALOR		VALOR and OLE Integrated[d]
	Placebo (N = 36) n (%)	Tofersen 100 mg (N = 72) n (%)	Tofersen 100 mg (N = 104) n (%)
No. of participants with treatment-emergent event[a]			
Any event	34 (94.4)	69 (95.8)	102 (98.1)
Related event[b]	2 (5.6)	28 (38.9)	63 (60.6)
Events related to lumbar puncture[b]	29 (80.6)	58 (80.6)	84 (80.8)
Events with fatal outcome	0	1 (1.4)	14 (13.5)
Events leading to drug discontinuation	0	4 (5.6)	18 (17.3)
Serious event	5 (13.9)	13 (18.1)	38 (36.5)
No. of participants with SAEs of note[c]	0	4 (5.6)	7 (6.7)
Intracranial pressure increased	0	0	1 (1.0)
Myelitis/myelitis transverse	0	2 (2.8)	2 (2.0)
Lumbar radiculopathy	0	1 (1.4)	1 (1.0)
Meningitis aseptic/chemical	0	1 (1.4)	2 (2.0)
Nervous system disorder	0	0	1 (1.0)
Papilloedema	0	0	1 (1.0)

OLE = open-label extension; SAE = serious adverse event.
[a]A Participant can appear in more than one category; [b]Related as assessed by the investigator; [c]A participant is counted only once in each preferred term (MedDRA version 24.0); [d]an event in a placebo participant during VALOR is only counted once; an event in a tofersen participant during VALOR is counted in bo h the "VALOR/tofersen 100 mg" column, and again in the "VALOR and OLE Integrated" column.

Evidence of Biologic Effect Precedes Evidence of Clinical Benefit



CSF = cerebrospinal fluid; OLE = open-label extension; NfL = neurofilament light chain; SOD1 = superoxide dismutase.

Many thanks!

VALOR

Thank you to the **study participants** and their **caregivers and families**, the VALOR and OLE Steering Committee, investigators and site staff, and the entire community, without whom these important studies could not have been conducted.

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Principal Investigators

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