Results from the Phase 3 VALOR study and its open-label extension: evaluating the clinical efficacy and safety of tofersen in adults with ALS and confirmed *SOD1* mutation

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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; licensing agreement with, and reagents for, Ionis Pharmaceuticals, Inc.; Principal Investigator for Amylyx and Orion

MC

- Compensation from an advisory board for Biogen
- Compensation from QurALiS, RRD, Transposon, Sunovian, Cytokinetics, and Takeda; Member Praxis Board of Directors

This study was sponsored by Biogen (Cambridge, MA, USA); tofersen was discovered by Ionis Pharmaceuticals

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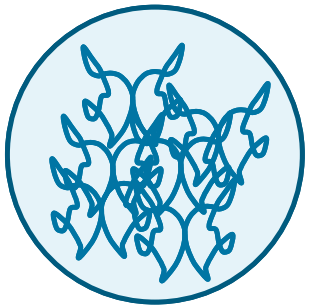
Mutations in the *SOD1* gene were the first-identified genetic cause of ALS

Dominantly inherited *SOD1* mutations implicated in ~ 2% of all ALS cases [1]



Mutant SOD1 protein is prone to misfolding and may interfere with multiple cellular processes[2]

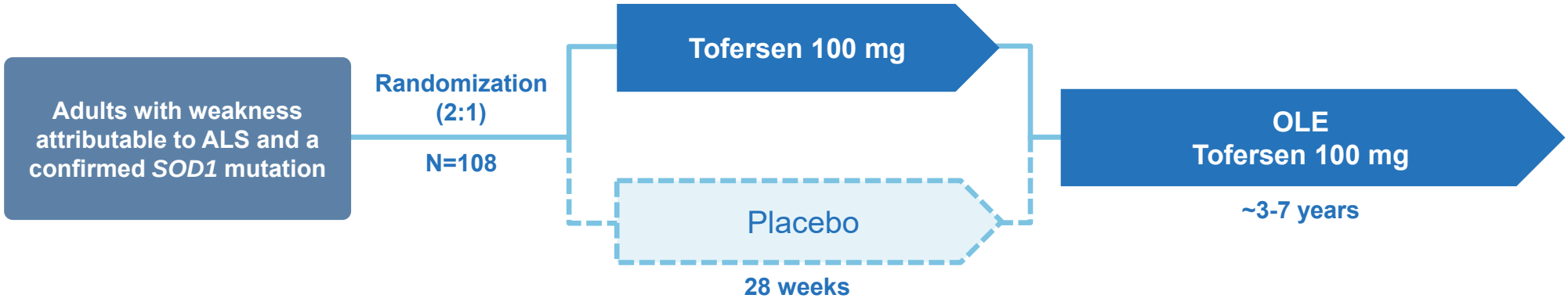
Evidence indicates that the toxicity of mutant SOD1 is derived from a toxic gain-of-function mechanism[1]

Tofersen is an intrathecally-administered ASO designed to reduce SOD1 protein levels and potentially slow disease progression [2,3]

ASO = antisense oligonucleotide

1. Bunton-Stasyshyn RKA, et al. *Neuroscientist.* 2015;21:519-529. 2. Rinaldi C, Wood MJ. *Nat Rev Neurol.* 2018;14:9-21. 3. Bennett FC, et al. *Annu Rev Neurosci.* 2019;42:385-406.

VALOR study design[1,2]



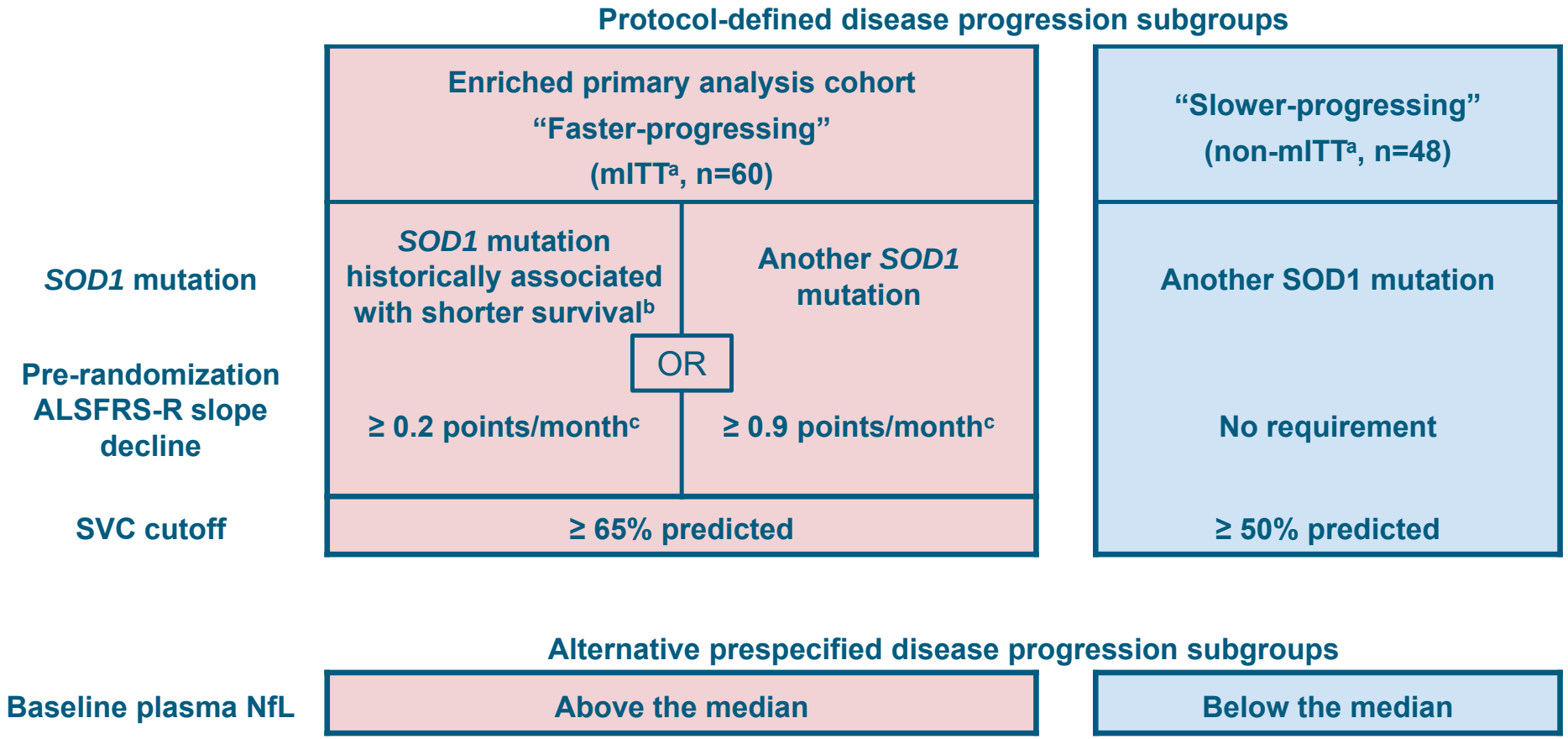
ENDPOINTS

	Primary	Key Secondary	Key Exploratory
Clinical	ALSFRS-R total score	% predicted SVC HHD megascore Time to death or PV Time to death	
Fluid Biomarker		Total CSF SOD1 Plasma NfL	
Quality-of-life			ALSAQ-5

ALSAQ-5 = ALS Assessment Questionnaire; ALSFRS-R = ALS Functional Rating Scale–Revised; CSF = cerebrospinal fluid; HHD = handheld dynamometry; OLE = open-label extension; NfL = neurofilament light chain; PV = permanent ventilation; SVC = slow vital capacity

1. Biogen. Data on file. 2. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02623699. Accessed August 1, 2021. 3. PV defined as ≥ 22 hours of mechanical ventilation (invasive or noninvasive) per day for ≥ 21 consecutive days.

Study enrichment



a. The study-defined modified intention to treat (mITT) population was the subset of this cohort that was randomized and received at least one dose of study treatment; all other participants comprise the non-mITT population; formal statistical testing of primary endpoint and key secondary endpoints (plasma NfL, SVC, HHD, time to death, time to death or permanent ventilation) performed in enriched primary analysis population (mITT) only
b. p.Ala5Val, p.Ala5Thr, p.Gly42Ser, p.His44Arg, p.Gly94Ala, p.Leu107Val, p.Leu39Val, p.Val149Gly, p.Leu85Val
c. Pre-randomization ALSFRS-R slope was calculated as [(48 – baseline score) / (time since symptom onset)].

VALOR baseline characteristics

	Faster-progressing (mITT; N=60)		Slower-progressing (non-mITT; N=48)		Overall (ITT; N=108)	
	placebo (n=21)	tofersen 100 mg (n=39)	placebo (n=15)	tofersen 100 mg (n=33)	placebo (n=36)	tofersen 100 mg (n=72)
Riluzole Use n (%)	13 (62)	25 (64)	9 (60)	20 (61)	22 (61)	45 (63)
Edaravone Use* n (%)	1 (5)	2 (5)	2 (13)	4 (12)	3 (8)	6 (8)
Time from symptom onset (m) median (Q1, Q3) Range: min, max	8.3 (5.1, 12.1) 2.4, 21.3	8.3 (6.0, 10.4) 1.7, 18.5	39.6 (30.3, 53.6) 11.8, 103.2	35.5 (19.5, 60.9) 3.9, 145.7	14.6 (6.6, 32.0) 2.4, 103.2	11.4 (7.2, 28.9) 1.7, 145.7
Plasma NfL mean (SD) Range: min, max	127.3 (94.4) 9, 370	146.2 (82.6) 12, 329	37 (29.5) 8, 99	47.6 (41.8) 5, 211	89.7 (86.5) 8, 370	100.4 (82.8) 5, 329
ALSFRS-R pre-randomization slope mean (SD) Range: min, max	-1.81 (1.2) -4.91, -0.42	-1.74 (1.6) -8.30, -0.39	-0.26 (0.3) -0.84, -0.02	-0.30 (0.2) -0.77, 0.00	-1.16 (1.2) -4.91, -0.02	-1.08 (1.4) -8.30, 0.00
ALSFRS-R baseline total score mean (SD) Range: min, max	35.4 (5.7) 24, 45	36.0 (6.4) 15, 44	39.9 (5.1) 32, 47	38.1 (5.1) 26, 48	37.3 (5.8) 24, 47	36.9 (5.9) 15, 48
% predicted SVC at baseline mean (SD) Range: min, max	83.7 (17.9) 57.4, 120.4	80.3 (14.2) 46.7, 114.8	87.1 (14.8) 54.8, 114.4	84.2 (19.0) 55.4, 134.7	85.1 (16.5) 54.8, 120.4	82.1 (16.6) 46.7, 134.7

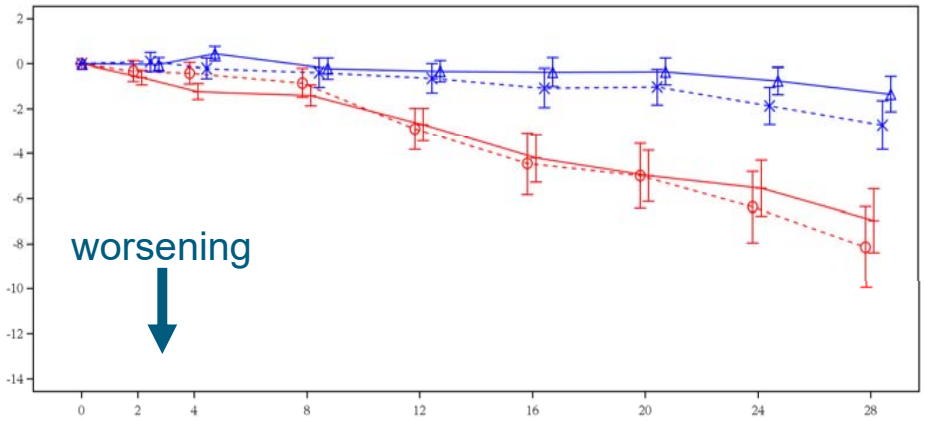
Effect on clinical function

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

Faster-progressing (mITT), tofersen (n=39)
Faster-progressing (mITT), placebo → tofersen (n=21)
Slower-progressing (non-mITT), tofersen (n=33)
Slower-progressing (non-mITT), placebo → tofersen (n=15)

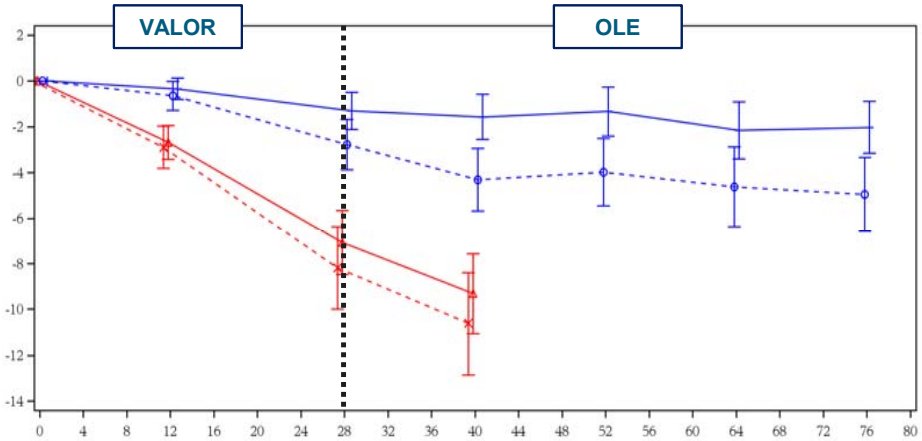
VALOR

(Primary endpoint)



Weeks from VALOR baseline

VALOR + OLE



Weeks from VALOR baseline

	Placebo	Tofersen	Difference Tofersen vs Placebo (p-value)
Faster-progressing (mITT); Week 28	**-8.14**	**-6.98**	**1.2 (p=0.97 joint rank)**
Slower-progressing (non-mITT); Week 28	**-2.73**	**-1.33**	**1.4**

	Placebo → tofersen	Early-start tofersen	Difference Tofersen vs Placebo (95% CI)
Faster-progressing (mITT); Week 40	**-10.6**	**-9.3**	**1.3 (-4.1, 6.7)**
Slower-progressing (non-mITT); Week 76	**-4.9**	**-2.0**	**2.9 (-0.7, 6.6)**

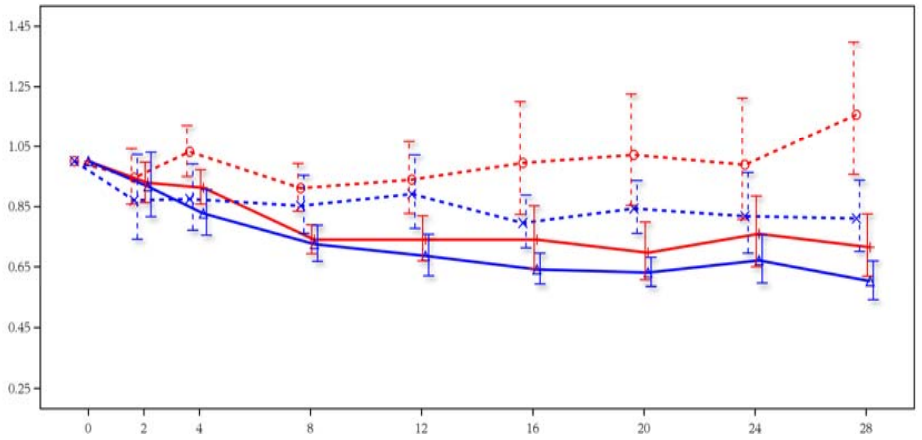
Target engagement

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

Faster-progressing (mITT), tofersen (n=39)
Faster-progressing (mITT), placebo → tofersen (n=21)
Slower-progressing (non-mITT), tofersen (n=33)
Slower-progressing (non-mITT), placebo → tofersen (n=15)

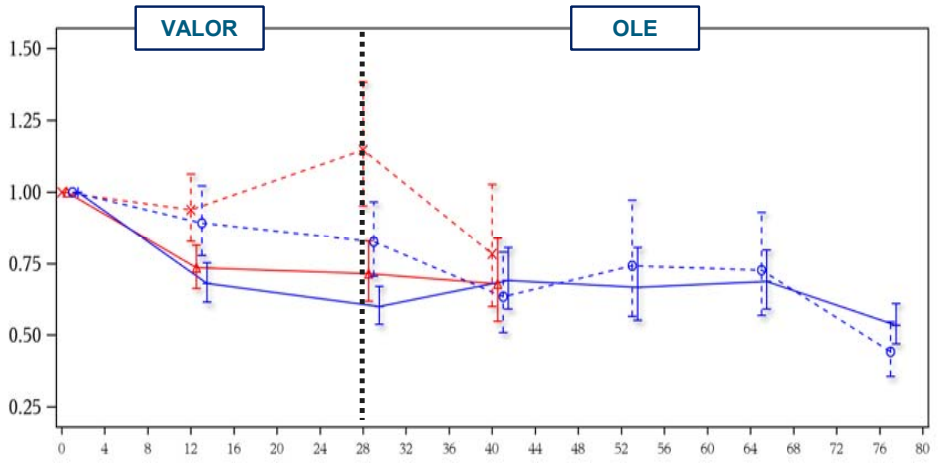
VALOR

(Key secondary endpoint)



Weeks from VALOR baseline

VALOR + OLE



Weeks from VALOR baseline

	Placebo	Tofersen	Geo mean ratio Tofersen:Placebo (p-value)
Faster-progressing (mITT); Week 28	**1.16 (16% incr)**	**0.71 (29% decr)**	**0.62 (p<0.0001)**
Slower-progressing (non-mITT); Week 28	**0.81 (19% decr)**	**0.60 (40% decr)**	**0.74 (p=0.0007)**

	Placebo → tofersen	Early-start tofersen	Geo mean ratio Tofersen:Placebo (95% CI)
Faster-progressing (mITT); Week 40	**0.78 (22% decr)**	**0.68 (32% decr)**	**0.87 (0.63, 1.18)**
Slower-progressing (non-mITT); Week 76	**0.44 (56% decr)**	**0.54 (46% decr)**	**1.21 (0.94, 1.56)**

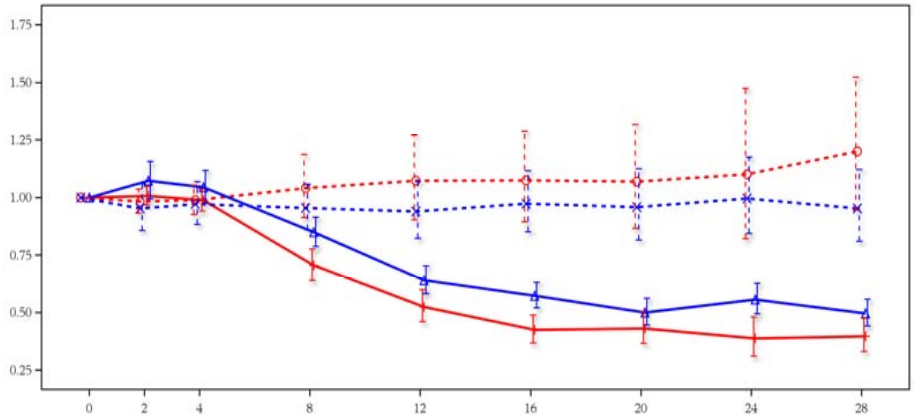
Effect on neurofilament

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

Faster-progressing (mITT), tofersen (n=39)
Faster-progressing (mITT), placebo → tofersen (n=21)
Slower-progressing (non-mITT), tofersen (n=33)
Slower-progressing (non-mITT), placebo → tofersen (n=15)

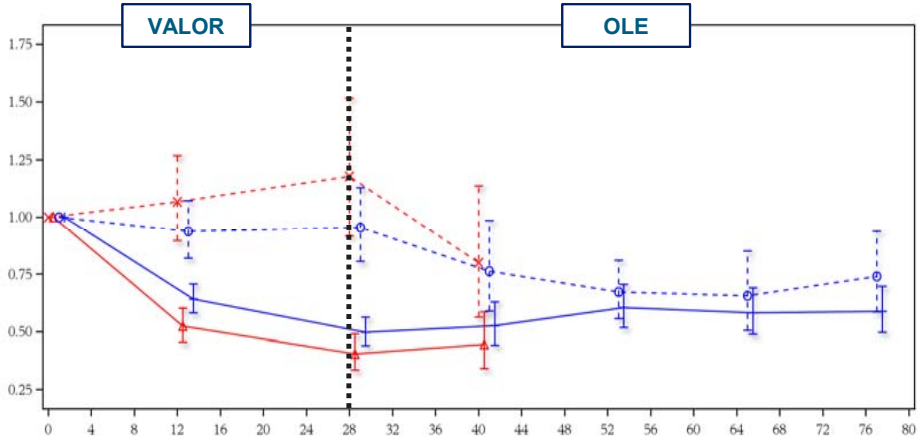
VALOR

(Key secondary endpoint)



Weeks from VALOR baseline

VALOR + OLE



Weeks from VALOR baseline

	Placebo	Tofersen	Geo mean ratio Tofersen:Placebo (p-value)
Faster-progressing (mITT); Week 28	**1.20 (20% incr)**	**0.40 (60% decr)**	**0.33 (p<0.0001)**
Slower-progressing (non-mITT); Week 28	**0.95 (5% decr)**	**0.50 (50% decr)**	**0.52**

	Placebo → tofersen	Early-start tofersen	Geo mean ratio Tofersen:Placebo (95% CI)
Faster-progressing (mITT); Week 40	**0.80 (20% decr)**	**0.45 (55% decr)**	**0.56 (0.36, 0.86)**
Slower-progressing (non-mITT); Week 76	**0.74 (26% decr)**	**0.59 (41% decr)**	**0.79 (0.60, 1.05)**

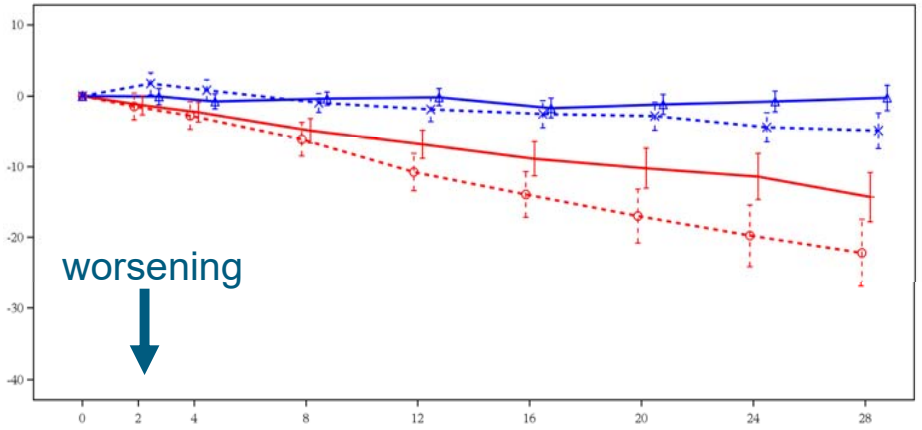
Effect on respiratory function

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

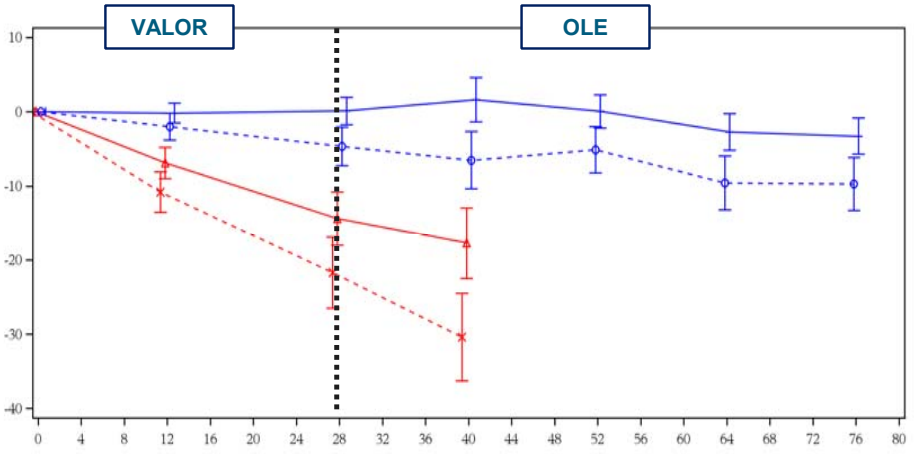
- Faster-progressing (mITT), tofersen (n=39)
- Faster-progressing (mITT), placebo → tofersen (n=21)
- Slower-progressing (non-mITT), tofersen (n=33)
- Slower-progressing (non-mITT), placebo → tofersen (n=15)

VALOR

(Key secondary endpoint)



VALOR + OLE



	Placebo	Tofersen	Difference Tofersen vs Placebo (p-value)
Faster-progressing (mITT); Week 28	-22.2%	-14.3%	7.9% (p=0.32 joint rank)
Slower-progressing (non-mITT); Week 28	-4.90%	-0.26%	4.6%

	Placebo → tofersen	Early-start tofersen	Difference Tofersen vs Placebo (95% CI)
Faster-progressing (mITT); Week 40	-30.4%	-17.7%	12.7% (-1.1, 26.5)
Slower-progressing (non-mITT); Week 76	-9.7%	-3.3%	6.5% (-1.6, 14.5)

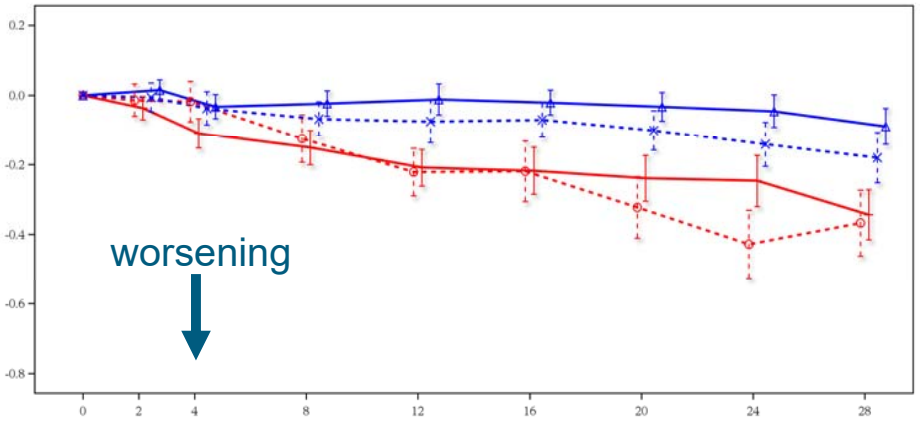
Effect on muscle strength

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

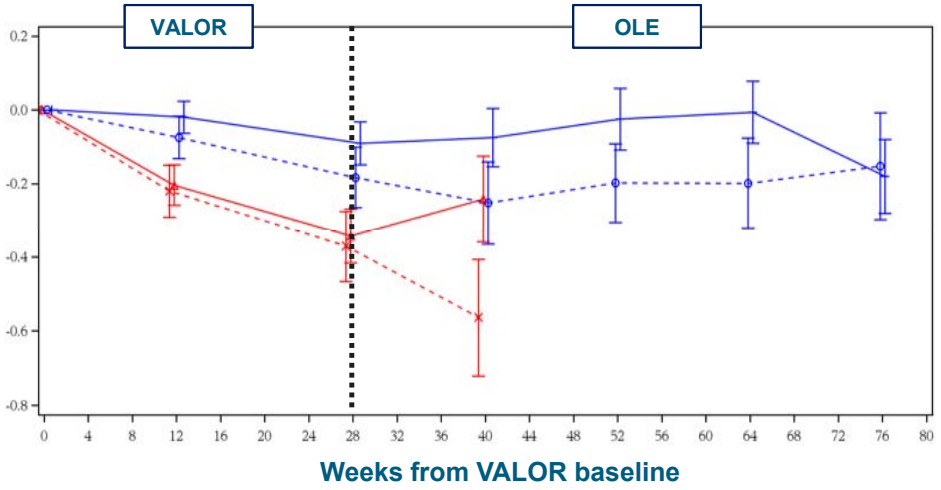
Faster-progressing (mITT), tofersen (n=39)
Faster-progressing (mITT), placebo → tofersen (n=21)
Slower-progressing (non-mITT), tofersen (n=33)
Slower-progressing (non-mITT), placebo → tofersen (n=15)

VALOR

(Key secondary endpoint)



VALOR + OLE



	Placebo	Tofersen	Difference Tofersen vs Placebo (p-value)
Faster-progressing (mITT); Week 28	**-0.37**	**-0.34**	**0.02 (p=0.84 ANCOVA)**
Slower-progressing (non-mITT); Week 28	**-0.18**	**-0.09**	**0.09**

	Placebo → tofersen	Early-start tofersen	Difference Tofersen vs Placebo (95% CI)
Faster-progressing (mITT); Week 40	**-0.56**	**-0.24**	**0.32 (-0.06, 0.70)**
Slower-progressing (non-mITT); Week 76	**-0.15**	**-0.18**	**-0.03 (-0.36, 0.30)**

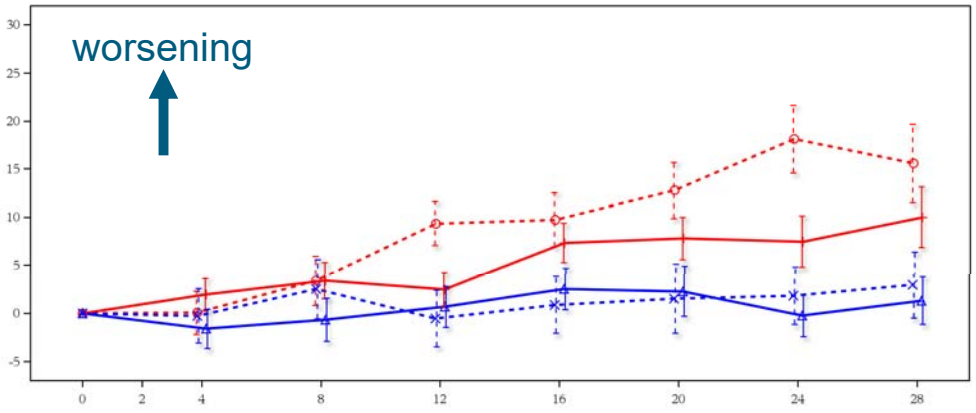
Effect on an ALS PRO

Adjusted mean (±SE) change from baseline in ALSAQ-5

Faster-progressing (mITT), tofersen (n=39)
Faster-progressing (mITT), placebo → tofersen (n=21)
Slower-progressing (non-mITT), tofersen (n=33)
Slower-progressing (non-mITT), placebo → tofersen (n=15)

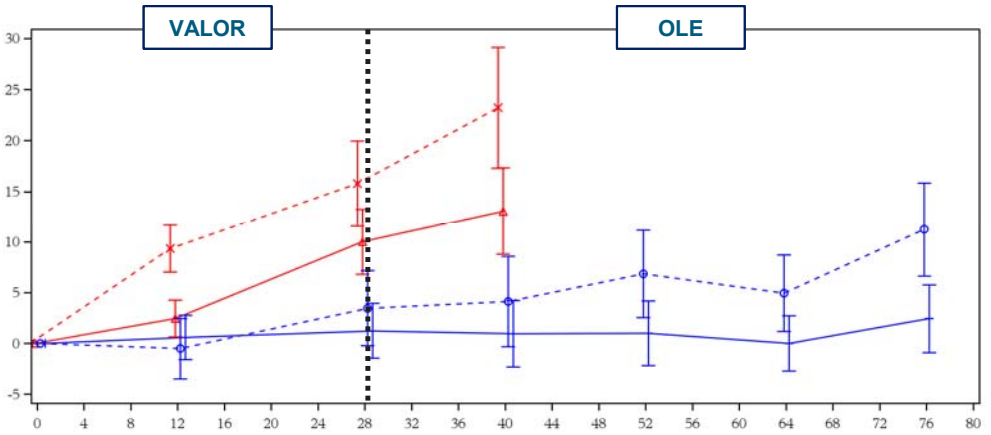
VALOR

(Exploratory endpoint)



Weeks from VALOR baseline

VALOR + OLE



Weeks from VALOR baseline

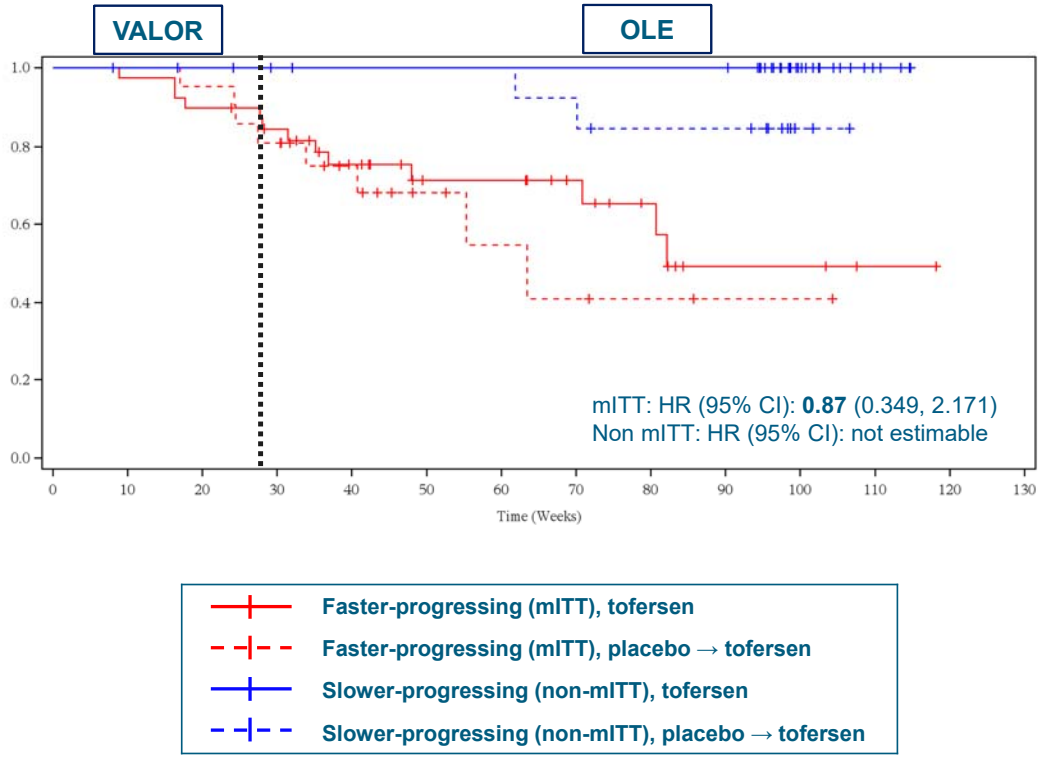
	Placebo	Tofersen	Difference Tofersen vs Placebo (95% CI)
Faster-progressing (mITT); Week 28	15.57	9.98	-5.6 (-15.55, 4.37)
Slower-progressing (non-mITT); Week 28	2.95	1.32	-1.6 (-9.55, 6.29)

	Placebo → tofersen	Early-start tofersen	Difference Tofersen vs Placebo (95% CI)
Faster-progressing (mITT); Week 40	23.2	13.1	-10.2 (-24.45, 4.14)
Slower-progressing (non-mITT); Week 76	11.2	2.4	-8.8 (-19.36, 1.75)

Time-to-event analyses

Median time to death and time to death or PV were non-estimable due to the number of events; a post-hoc analysis was performed to account for withdrawal due to disease progression

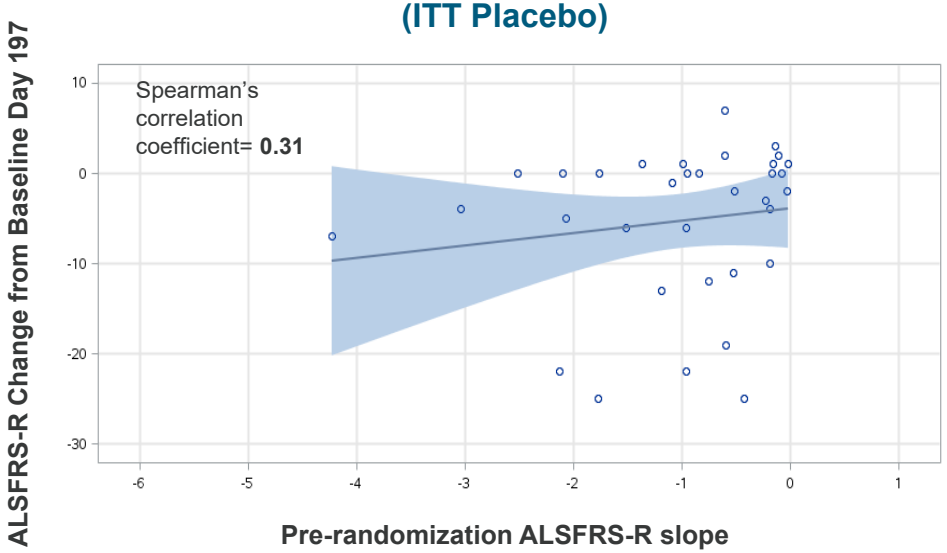
Event	Early (VALOR) start tofersen (n=72)	PBO + delayed-start tofersen (n=36)
Death	4 (5.6%)	3 (8.3%)
Permanent ventilation	6 (8.3%)	2 (5.6%)
Withdrawal due to disease progression	3 (4.2%)	5 (13.9%)
Total	13 (18.1%)	10 (27.8%)



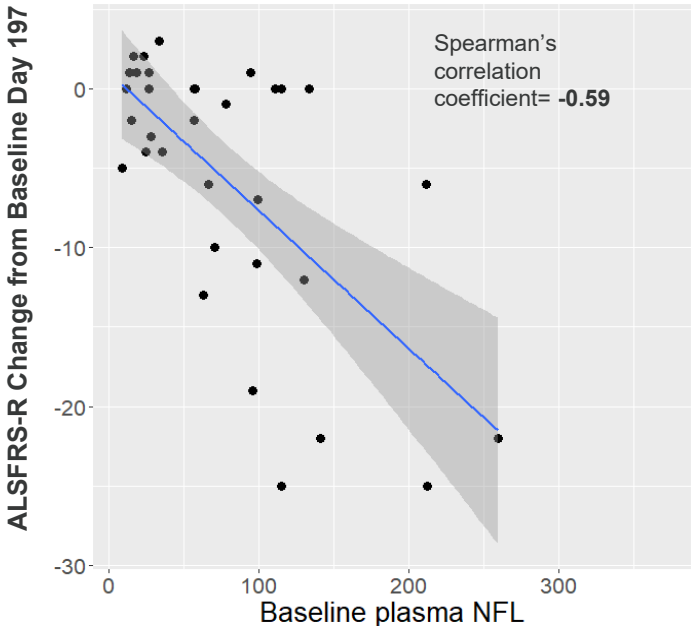
Enrichment markers

Baseline NfL was more strongly correlated with longitudinal changes in ALSFRS-R than ALSFRS-R pre-randomization slope

ALSFRS-R change by pre-randomization slope (ITT Placebo)



ALSFRS-R change by baseline plasma NfL (ITT Placebo)

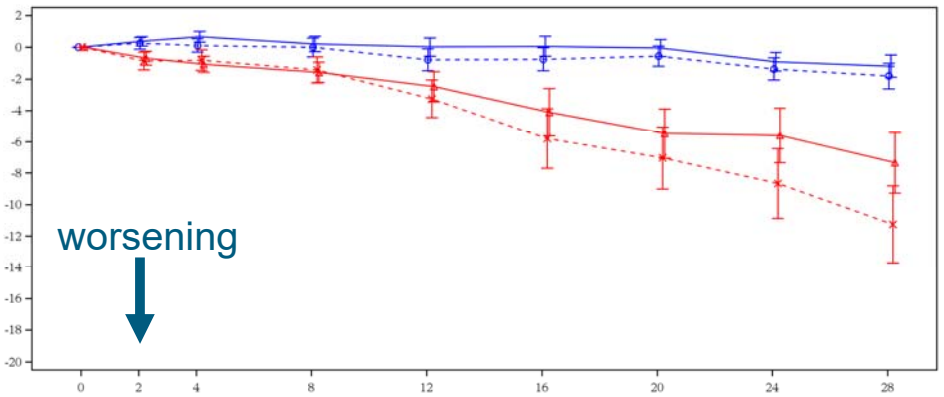


Clinical function by median plasma NfL*

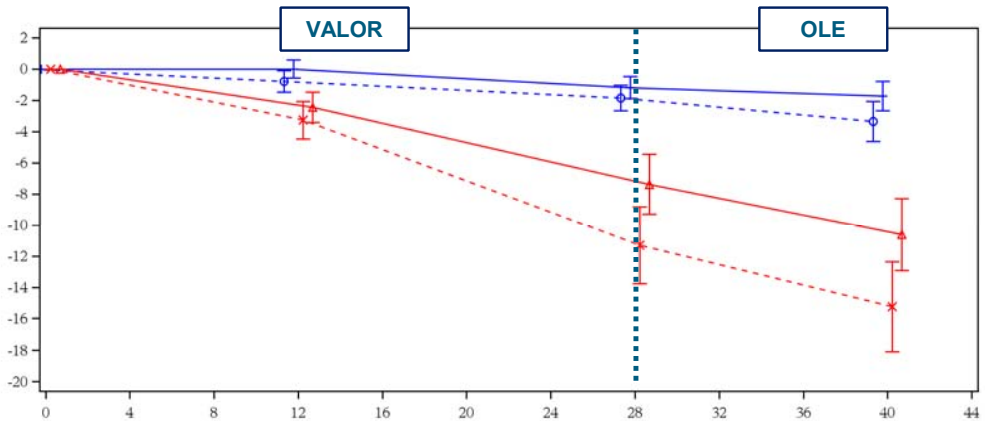
Change from baseline in ALSFRS-R

Faster-progressing (above median NfL), tofersen (n=38)
Faster-progressing (above median NfL), placebo → tofersen (n=16)
Slower-progressing (below median NfL), tofersen (n=34)
Slower-progressing (below median NfL), placebo → tofersen (n=20)

VALOR



VALOR + OLE



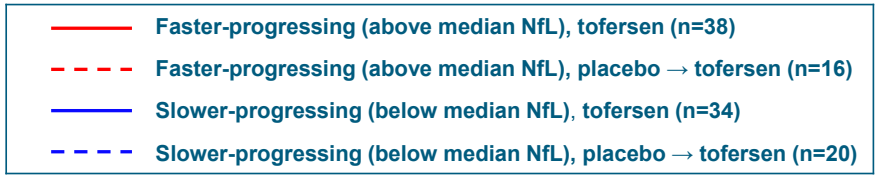
	Placebo	Tofersen	Difference Tofersen vs Placebo (95% CI)
Faster-progressing (≥ median); Week 28	**-11.3**	**-7.3**	**3.9 (-1.00, 8.86)**
Slower-progressing (< median); Week 28	**-1.8**	**-1.2**	**0.6 (-1.33, 2.58)**

	Placebo → tofersen	Early-start tofersen	Difference Tofersen vs Placebo (95% CI)
Faster-progressing (≥ median); Week 40	**-15.2**	**-10.6**	**4.6 (-1.2, 10.4)**
Slower-progressing (< median); Week 40	**-3.3**	**-1.7**	**1.6 (-1.3, 4.5)**

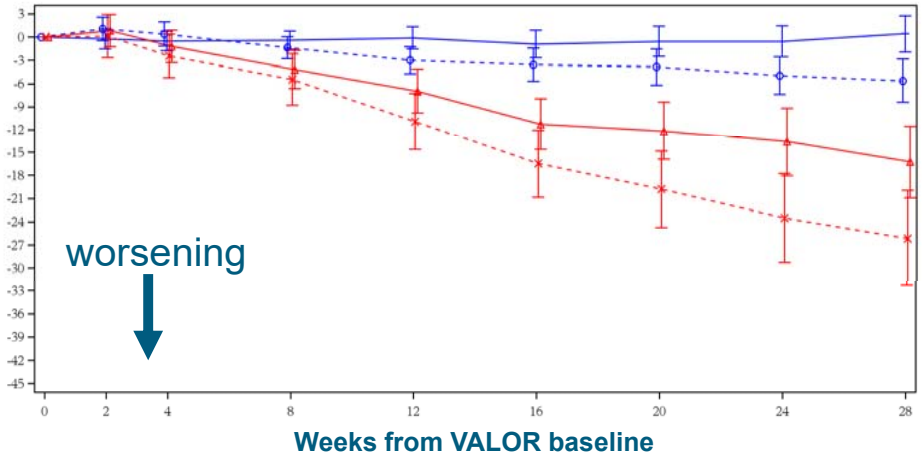
* Median plasma NfL = 75.6 pg/mL

Respiratory function by median plasma NfL*

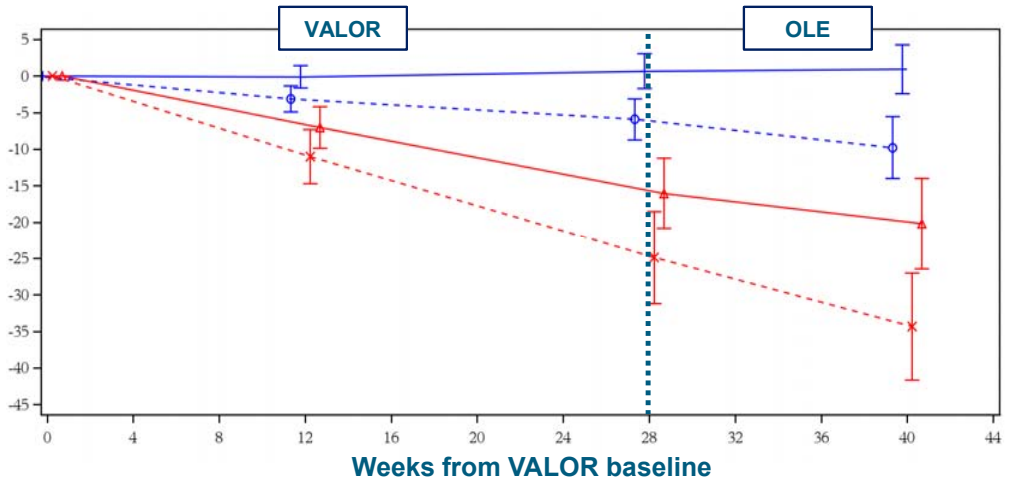
Change from baseline in SVC % predicted



VALOR



VALOR + OLE



	Placebo	Tofersen	Difference Tofersen vs Placebo (95% CI)
Faster-progressing (≥ median); Week 28	**-26.13%**	**-16.22%**	**9.91% (-2.27, 22.09)**
Slower-progressing (< median); Week 28	**-5.61%**	**0.44%**	**6.05% (-0.58, 12.68)**

	Placebo → tofersen	Early-start tofersen	Difference Tofersen vs Placebo (95% CI)
Faster-progressing (≥ median); Week 40	**-34.3%**	**-20.2%**	**14.1% (-0.6, 28.8)**
Slower-progressing (< median); Week 40	**-9.8%**	**0.9%**	**10.7% (0.6, 20.8)**

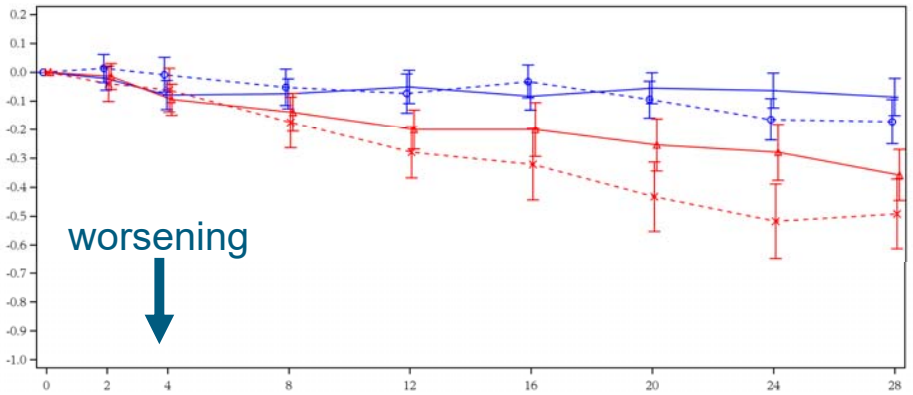
* Median plasma NfL = 75.6 pg/mL

Muscle strength by median NfL*

Change from baseline in HHD Megascore

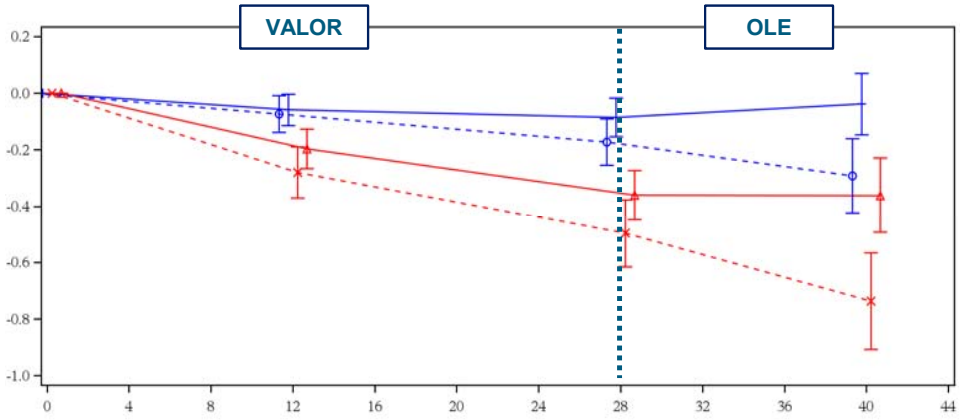
Faster-progressing (above median NfL), tofersen (n=38)
Faster-progressing (above median NfL), placebo → tofersen (n=16)
Slower-progressing (below median NfL), tofersen (n=34)
Slower-progressing (below median NfL), placebo → tofersen (n=20)

VALOR



Weeks from VALOR baseline

VALOR + OLE



Weeks from VALOR baseline

	Placebo	Tofersen	Difference Tofersen vs Placebo (95% CI)
Faster-progressing (≥ median); Week 28	**-0.49**	**-0.36**	**0.13 (-0.11, 0.37)**
Slower-progressing (< median); Week 28	**-0.17**	**-0.09**	**0.09 (-0.10, 0.27)**

	Placebo → tofersen	Early-start tofersen	Difference Tofersen vs Placebo (95% CI)
Faster-progressing (≥ median); Week 40	**-0.74**	**-0.36**	**0.38 (0.03, 0.72)**
Slower-progressing (< median); Week 40	**-0.29**	**-0.04**	**0.25 (-0.07, 0.58)**

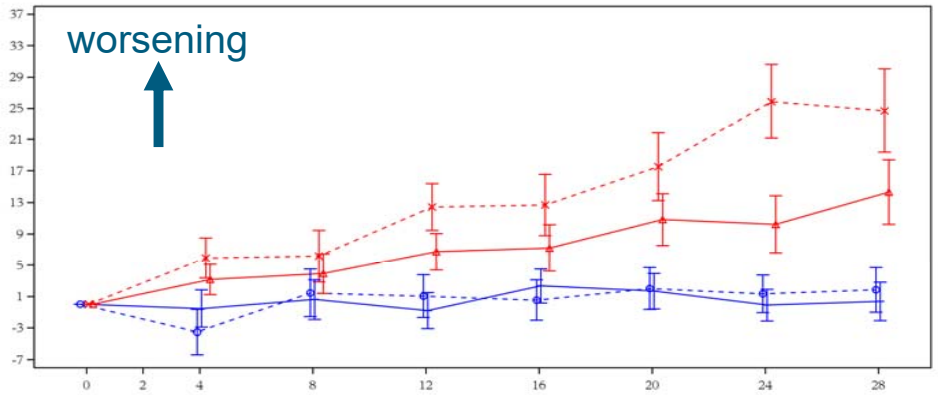
* Median plasma NfL = 75.6 pg/mL

ALS PRO by median NfL*

Change from baseline in ALSAQ-5

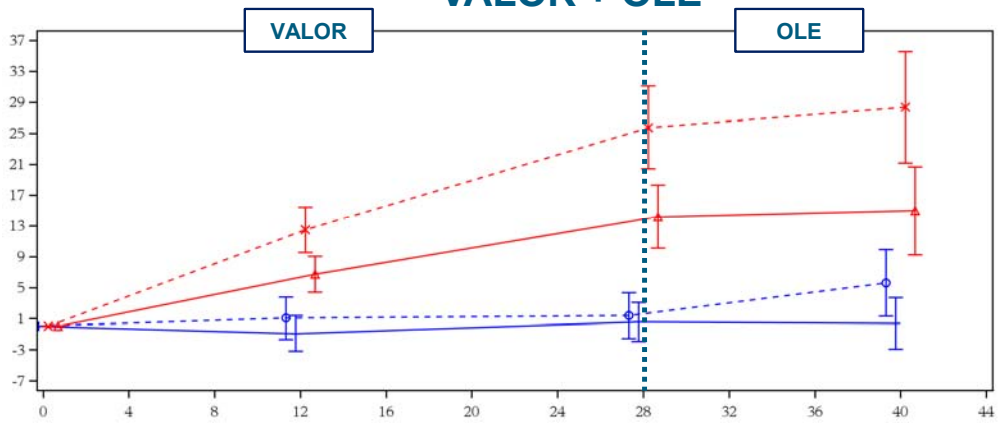
Faster-progressing (above median NfL), tofersen (n=38)
Faster-progressing (above median NfL), placebo → tofersen (n=16)
Slower-progressing (below median NfL), tofersen (n=34)
Slower-progressing (below median NfL), placebo → tofersen (n=20)

VALOR



Weeks from VALOR baseline

VALOR + OLE



Weeks from VALOR baseline

	Placebo	Tofersen	Difference Tofersen vs Placebo (95% CI)
Faster-progressing (≥ median); Week 28	24.7	14.3	-10.4 (-20.99, 0.21)
Slower-progressing (< median); Week 28	1.9	0.4	-1.5 (-8.32, 5.29)

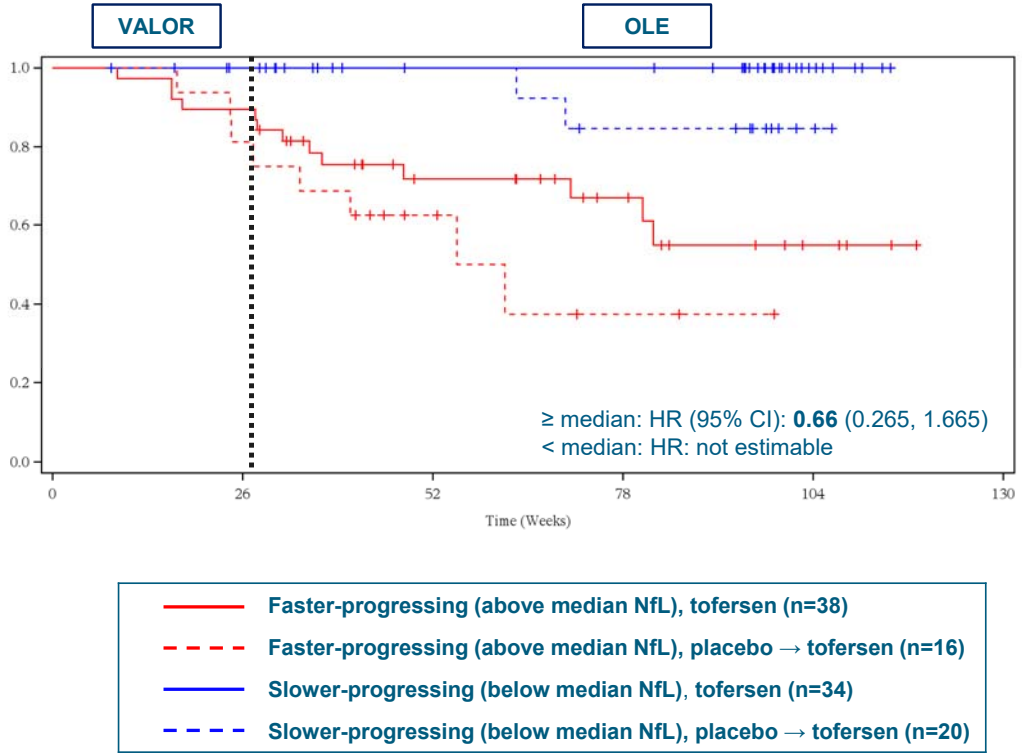
	Placebo → tofersen	Early-start tofersen	Difference Tofersen vs Placebo (95% CI)
Faster-progressing (≥ median); Week 40	28.4	14.9	-13.4 (-28.04, 1.22)
Slower-progressing (< median); Week 40	5.6	0.4	-5.2 (-15.20, 4.75)

* Median plasma NfL = 75.6 pg/mL

Time-to-event analyses by median NfL*

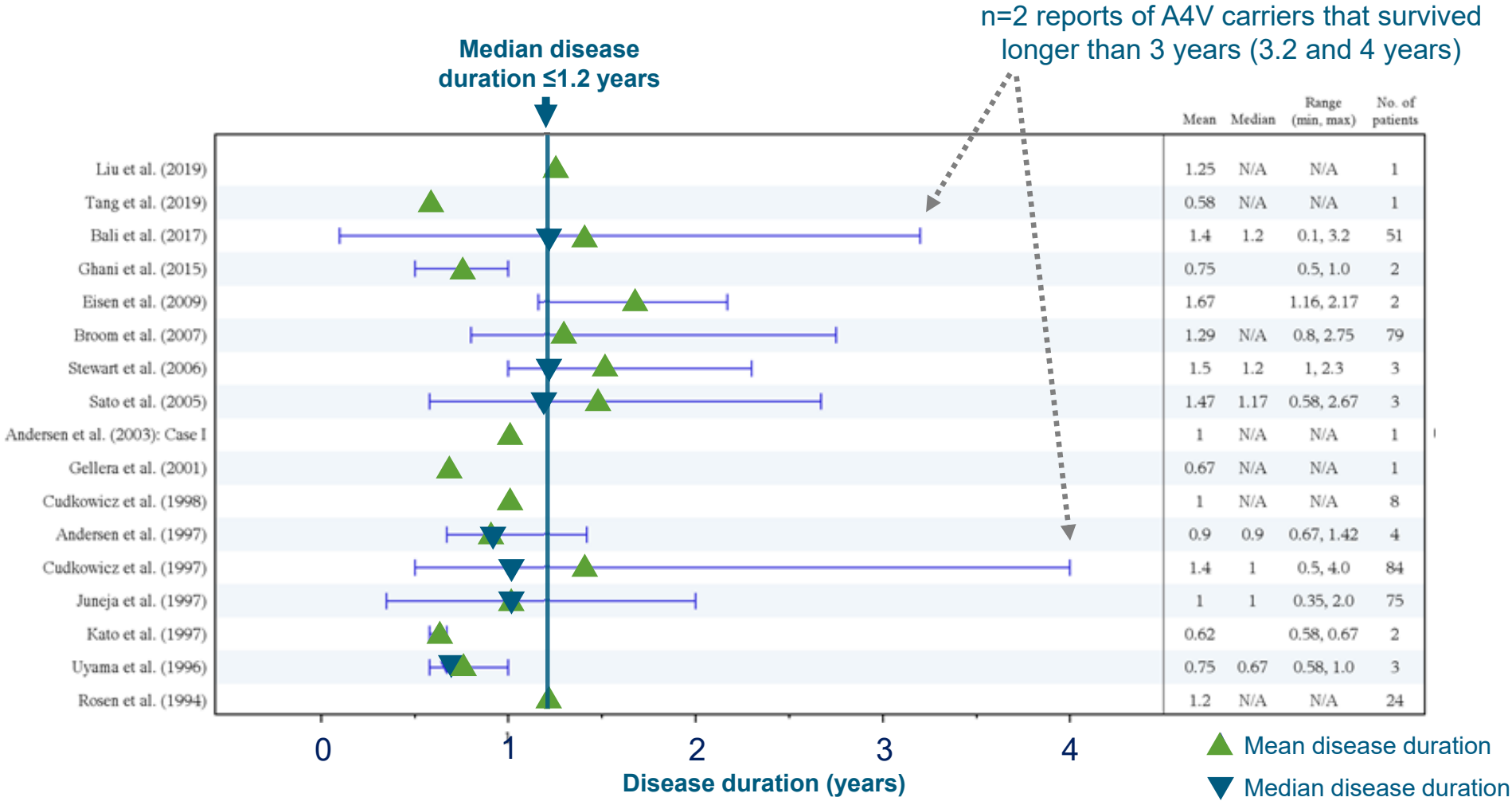
Median time to death and time to death or PV were non-estimable due to the number of events; a post-hoc analysis was performed to account for withdrawal due to disease progression

Event	Early (VALOR) start tofersen (n=72)	PBO + delayed-start tofersen (n=36)
Death	4 (5.6%)	3 (8.3%)
Permanent ventilation	6 (8.3%)	2 (5.6%)
Withdrawal due to disease progression	3 (4.2%)	5 (13.9%)
Total	13 (18.1%)	10 (27.8%)



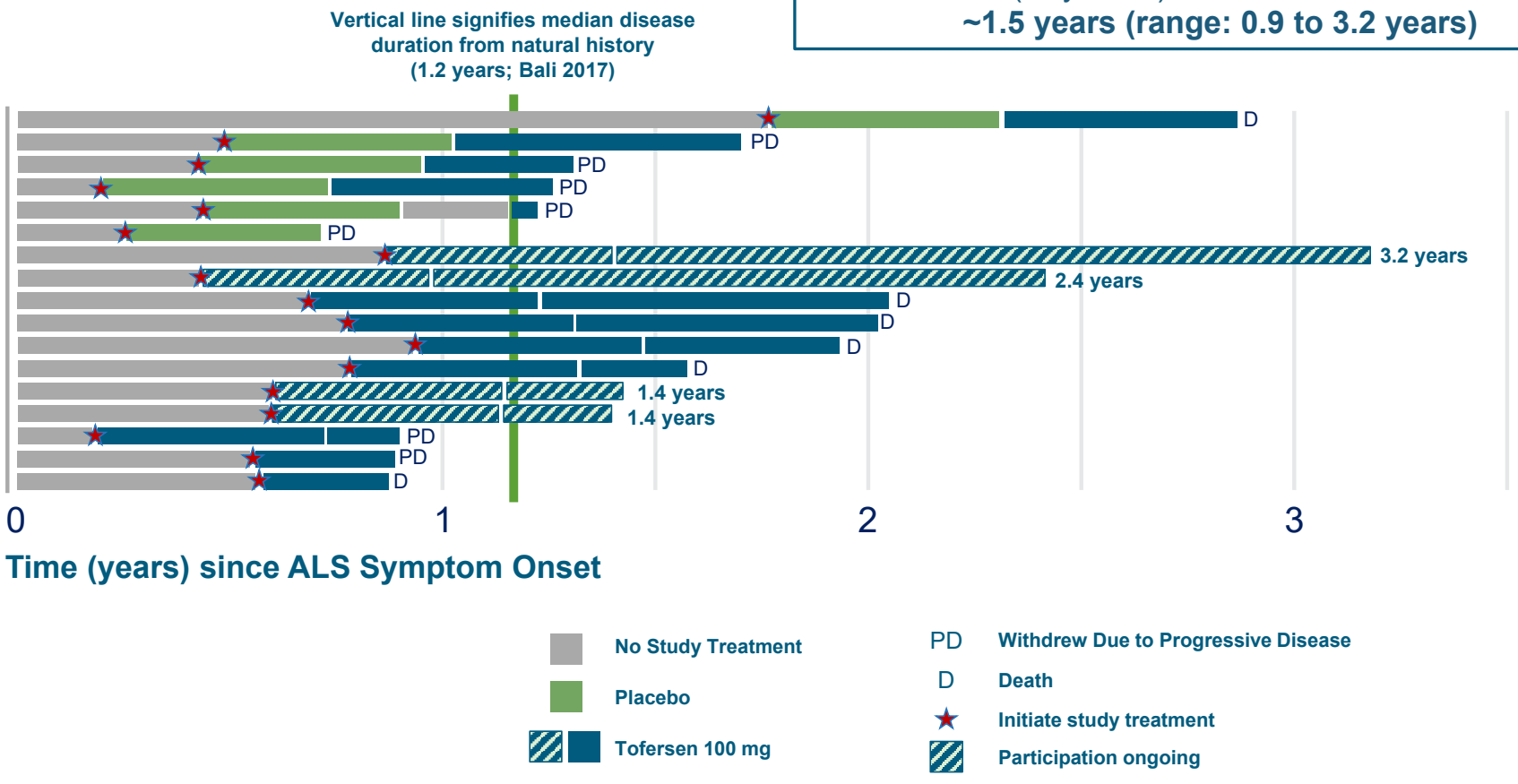
* Median plasma NfL = 75.6 pg/mL

Natural history in A4V carriers



Disease duration in tofersen-treated A4V carriers

Median time from onset of symptoms to death, withdrawal, or data cutoff (July 2021) in tofersen-treated A4V carriers: **~1.5 years (range: 0.9 to 3.2 years)**



Overview of safety

- Nearly all subjects had at least 1 TEAE; most events were mild-moderate in severity
- Many of the AEs were consistent with ALS disease progression or the LP procedure
- Most common events: procedural pain, headache, pain in extremity, back pain, and fall
- Overall safety profile in the OLE was comparable to VALOR
- Several participants treated with tofersen had SAEs involving the CNS
  - No similar events in the placebo group
  - Myelitis with sensory/motor deficits was clinically monitorable and reversible
- Many in the tofersen group had treatment-emergent CSF abnormalities; most of these were not reported as AEs

Serious neurologic events

Adverse event	VALOR		VALOR and OLE (Treated period)
	Placebo (N=36) n (%)	Tofersen 100 mg (N=72) n (%)	Tofersen 100 mg (N=104) n (%)
Subjects with serious neurologic events	0	4 (5.6)	5 (4.8)
Myelitis / Transverse myelitis	0	2 (2.8)	2 (2.0)
Meningitis chemical	0	1 (1.4)	1 (1.0)
Lumbar radiculopathy	0	1 (1.4)	1 (1.0)
Nervous system disorder	0	0	1 (1.0)

CSF parameter shift from baseline

CSF Shift to high leukocytes (10^6/L)	9/36 (25.0)	54/69 (78.3)	88/100 (88.0)
CSF Shift to high protein (mg/L)	6/20 (30.0)	31/46 (67.4)	54/68 (79.4)

AE = adverse event; SAE = serious adverse event; TEAE = treatment emergent adverse event

Summary

VALOR

VALOR did not achieve statistical significance on its primary endpoint of ALSFRS-R at 6 months; however, consistent effects were seen across key secondary and exploratory clinical outcome measures

These effects became more apparent with longer-term follow-up in the extension, as earlier initiation of tofersen led to:

- A slowing of decline in faster progressing participants
- An apparent stabilization of clinical function in slower progressing participants

Tofersen administration led to sustained reductions in total CSF SOD1 protein demonstrating target engagement, and plasma NfL suggestive of a slowing in neuronal degeneration

Most AEs were mild to moderate in severity and many were consistent with ALS disease progression or LP-related events

Serious neurologic events, including myelitis, were seen in tofersen-treated participants

Many thanks!

Thank you to the **study participants** and their **caregivers and families**, the VALOR/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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