Tofersen for the Treatment of *SOD1*-ALS

Peripheral and Central Nervous System Drugs Advisory Committee

Biogen

March 22, 2023

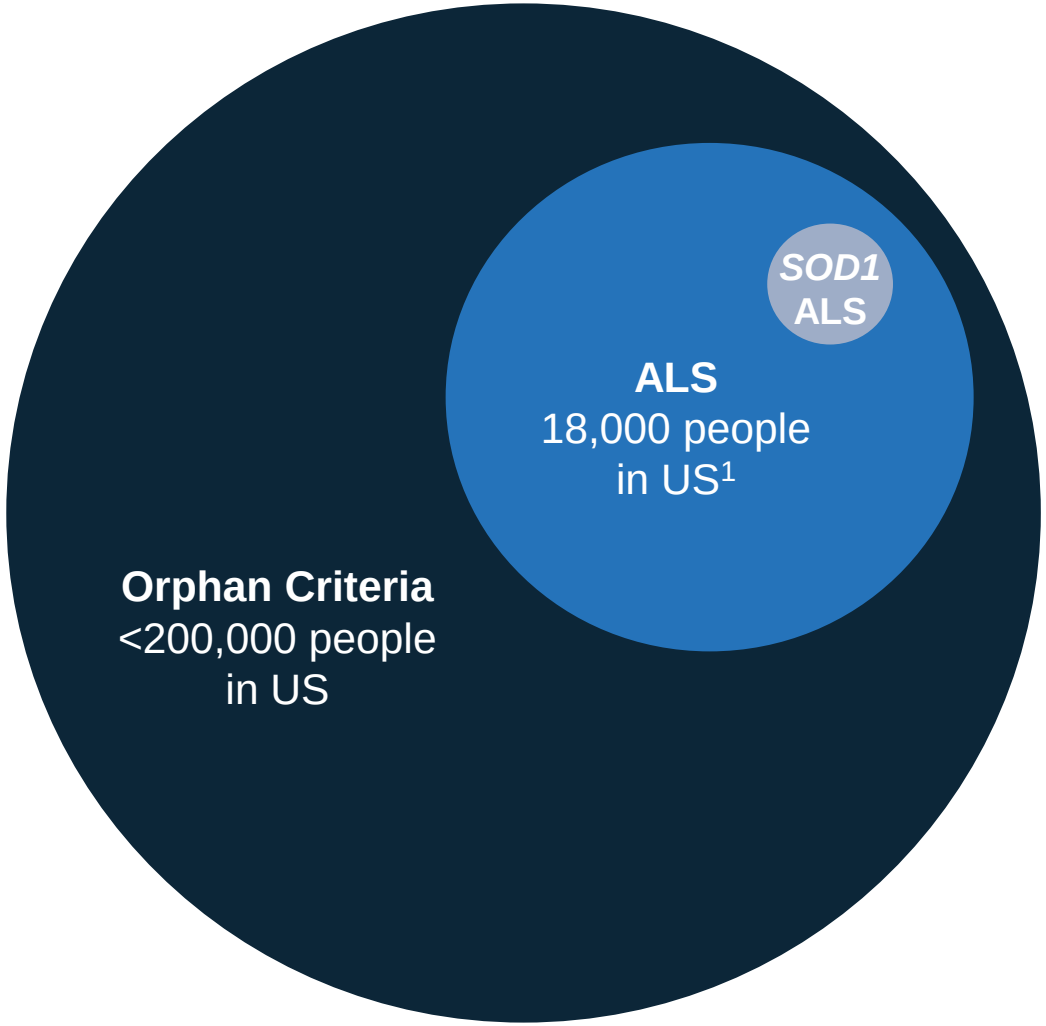
Introduction

Toby Ferguson, MD, PhD
Vice President, Head of Neuromuscular Development Unit
Biogen

Proposed indication

QALSODY (tofersen) is indicated for the treatment of adults with amyotrophic lateral sclerosis associated with a mutation in the superoxide dismutase 1 gene (SOD1-ALS)

SOD1-ALS is a rare, progressive, and fatal disease



- *SOD1*-ALS
  - Caused by a mutation in the superoxide dismutase-1 (*SOD1*) gene
  - Affects ~330 people in the US[2,3]
  - Median survival 2.7 years from diagnosis[4]
- Remains a progressive, fatal disease with a high unmet medical need

1. Mehta P, et al. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration.* 2023;24:108-116. 2. Zou ZY, et al. *J Neurol Neurosurg Psychiatry.* 2017;88:540-549. 3. Brown CA, et al. *Neuroepidemiology.* 2021;55:342-353. 4. Bali T, et al. *J Neurol Neurosurg Psychiatry.* 2017;88:99-105.

Tofersen targets underlying genetic pathophysiology for *SOD1*-ALS

Antisense oligonucleotide facilitates specific degradation of *SOD1* mRNA

↓

Reduces production of SOD1 protein (toxic and native)

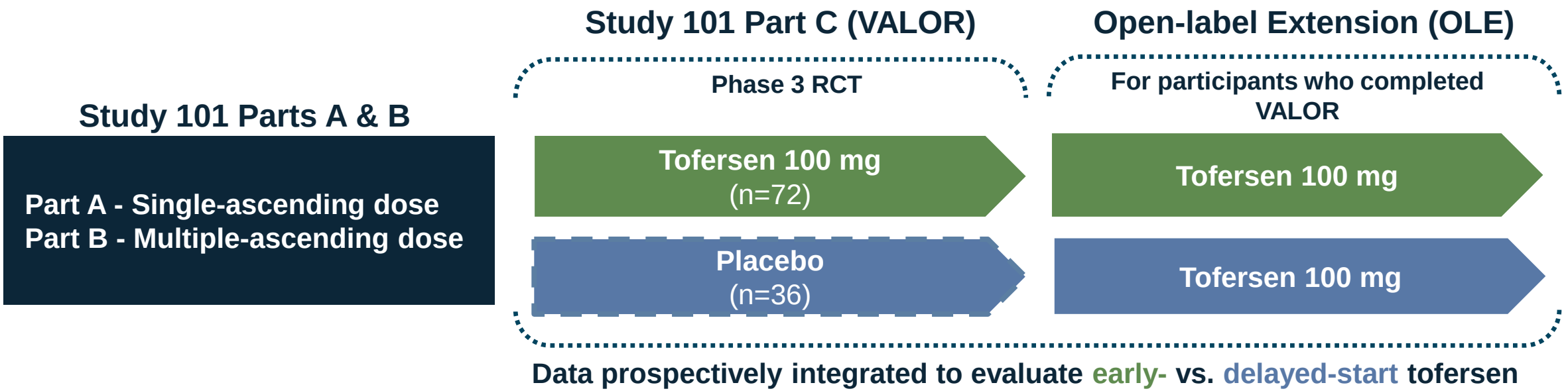
↓

Prevents accumulation of new toxic SOD1 and allows clearance of existing toxic SOD1

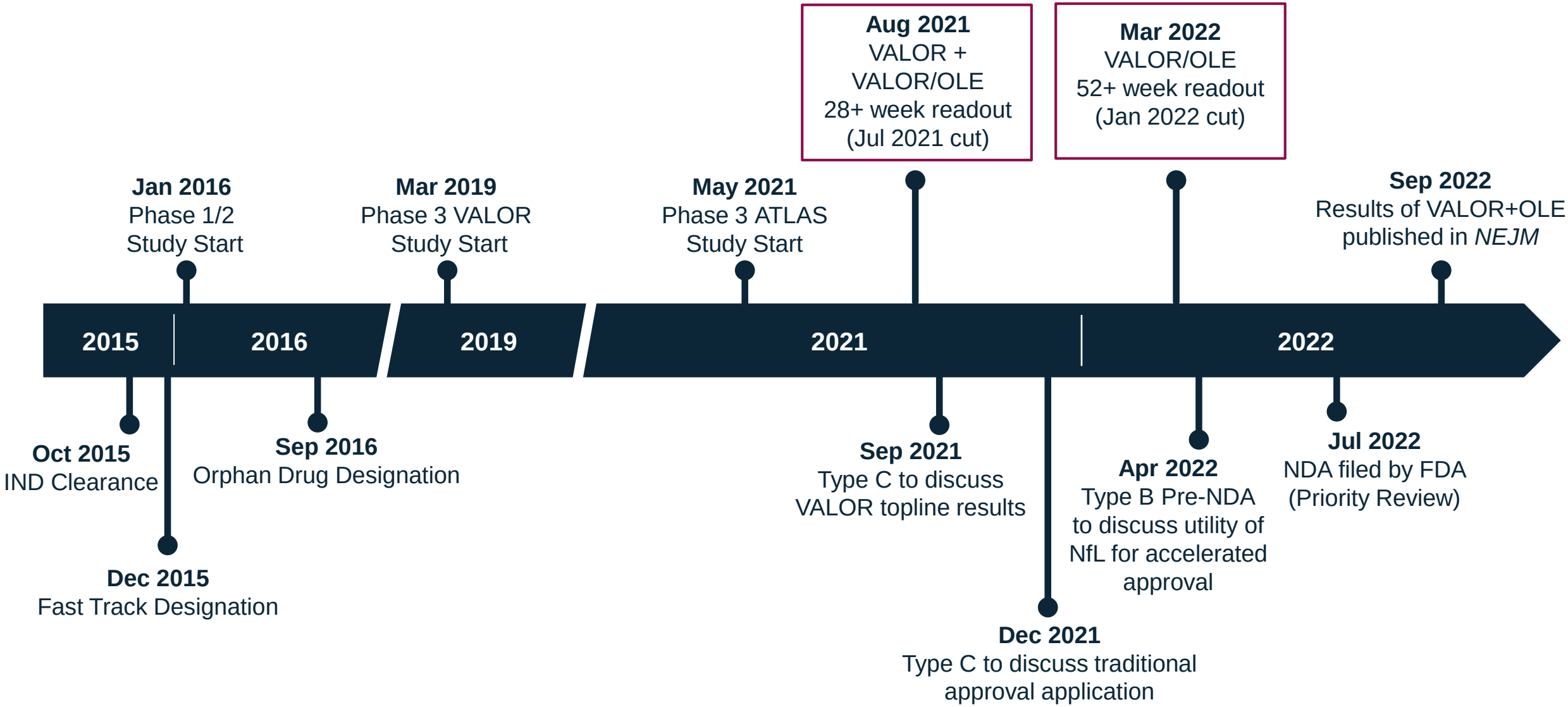
↓

Preserves motor neuron integrity, as evidenced by reductions in neurofilament

Tofersen clinical development program



Clinical development and regulatory timeline



FDA Accelerated Approval

Provisions of FDASIA in Section 506(c) of the FD&C Act provide that FDA may grant accelerated approval to:

. . . a product for a serious or life-threatening disease or condition . . . upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments.[1]

1. Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics.

FDA guidance on expedited programs for serious conditions

- Determining a reasonably likely surrogate endpoint depends on:
  - Biological plausibility of the relationship between the disease, the endpoint, and the desired effect
  - Empirical evidence to support that relationship
- “Reasonably likely” surrogate endpoint does not yet have sufficient evidence to be considered a validated surrogate endpoint

1. Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics.

What you will hear today

- ***SOD1*-ALS is a rare, life-threatening condition with critical unmet medical need**
- **Evidence that substantial reductions in NfL are reasonably likely to predict clinical benefit in *SOD1*-ALS**
- **An overview of efficacy and safety in support of the benefit-risk evaluation for tofersen**
- **An overview of Biogen's long-term data generation plans for tofersen**

Agenda

Presentation	Presenter
Introduction	**Toby Ferguson, MD, PhD** Vice President, Head of Neuromuscular Development Unit
Disease Background & Unmet Need	**Timothy M. Miller, MD, PhD** David Clayson Professor of Neurology Washington University in St. Louis
Efficacy	**Stephanie Fradette, PharmD** Clinical Development Lead and ALS Portfolio Head
Safety	**Laura Fanning, MD** Executive Medical Director, Global Medical Safety
Clinical Perspective	**Timothy M. Miller, MD, PhD** David Clayson Professor of Neurology Washington University in St. Louis
Conclusion	**Stephanie Fradette, PharmD** Clinical Development Lead and ALS Portfolio Head

Subject matter experts

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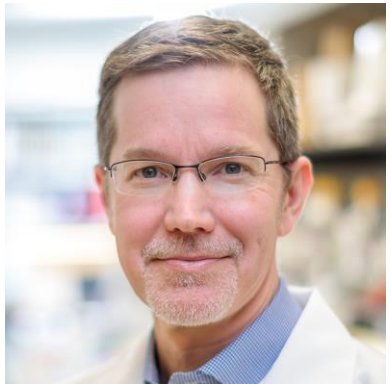
Senior Director of Biostatistics, Biogen



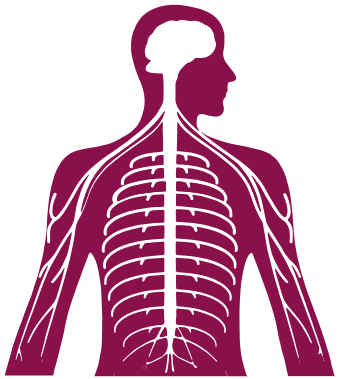
Disease Background and Unmet Need

Timothy M. Miller, MD, PhD

David Clayson Professor of Neurology

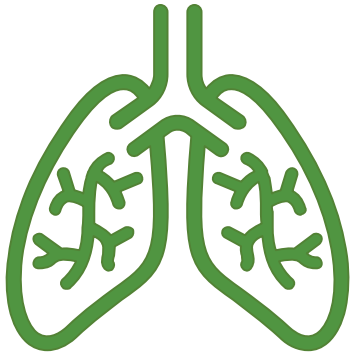
Washington University in St. Louis

ALS is a rare, fatal neurodegenerative disease characterized by loss of upper and lower motor neurons



ALS is a **progressive, adult-onset disease**[1]

Weakness leads to difficulty breathing, swallowing, moving limbs, walking



ALS is uniformly fatal

typically due to **respiratory failure** within

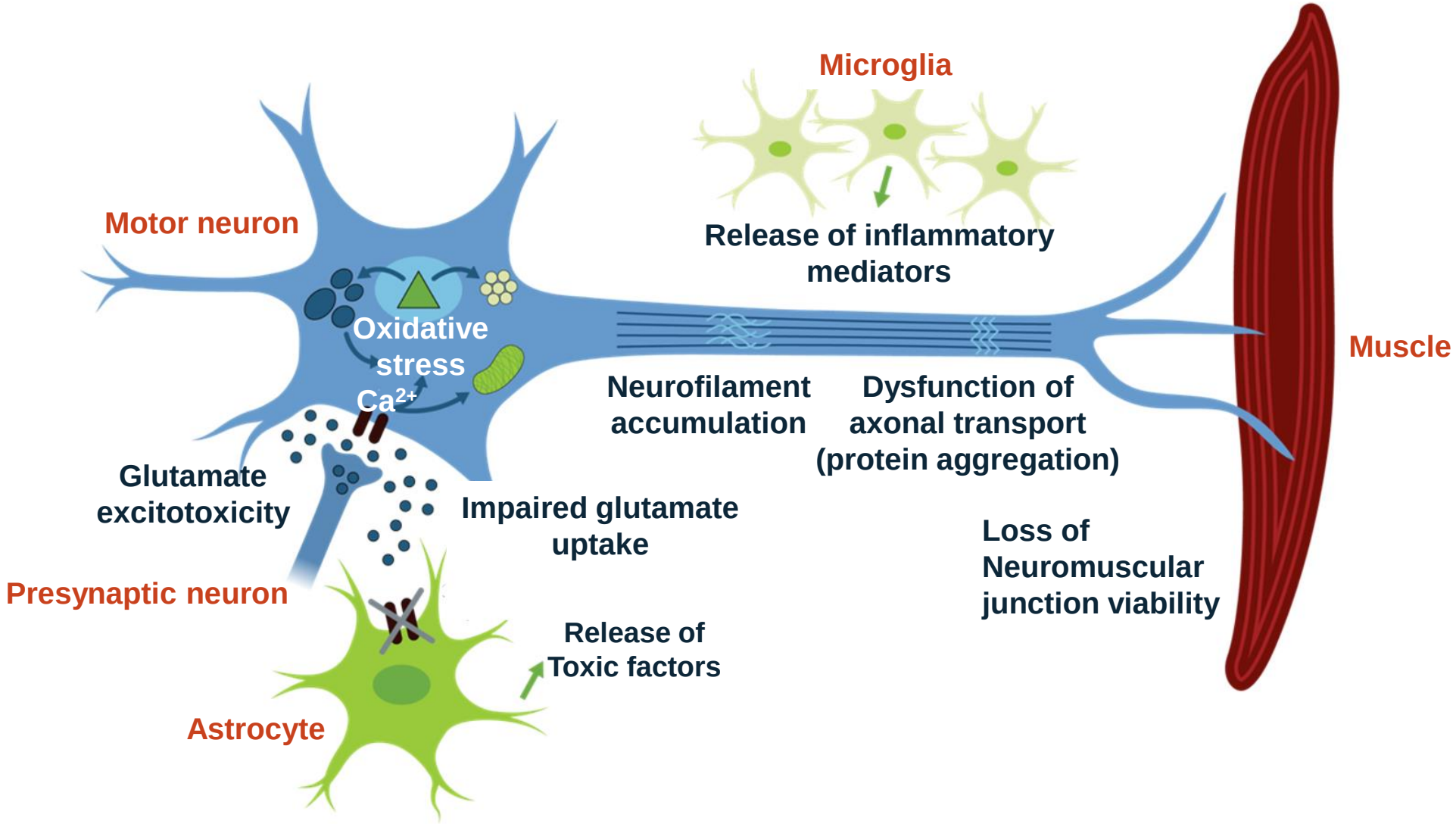
3 to 5 years

from symptom onset[2]

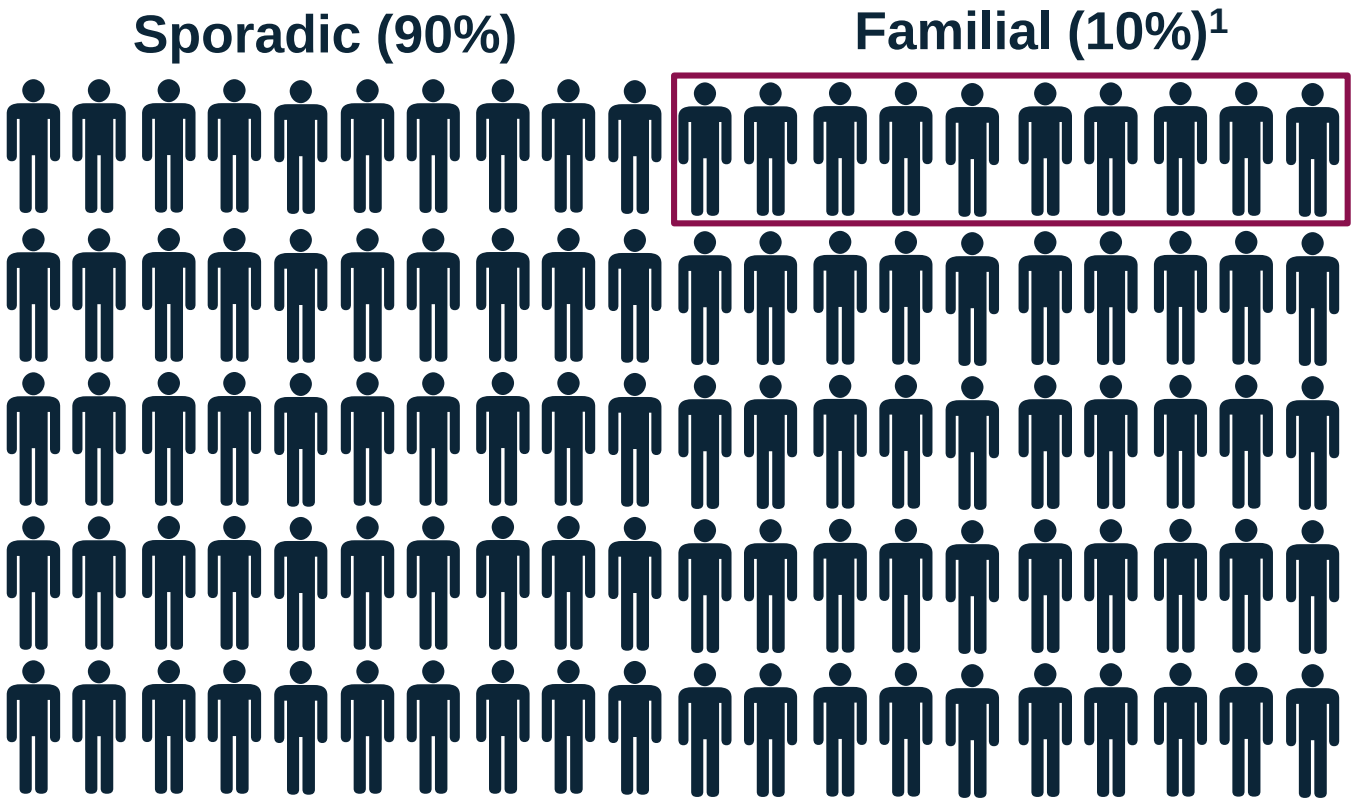
ALS, amyotrophic lateral sclerosis

1. Al-Chalabi A, Hardiman O. *Nat Rev Neurol.* 2013;9(11):617-628. 2. Brown RH, Al-Chalabi A. *N Engl J Med*. 2017;377(2):162-172.

There are multiple mechanisms implicated in ALS



Causative mutations are found in people with and without a known family history of ALS



1. Zou ZY, et al. *J Neurol Neurosurg Psychiatry*. 2017;88(7):540-549.

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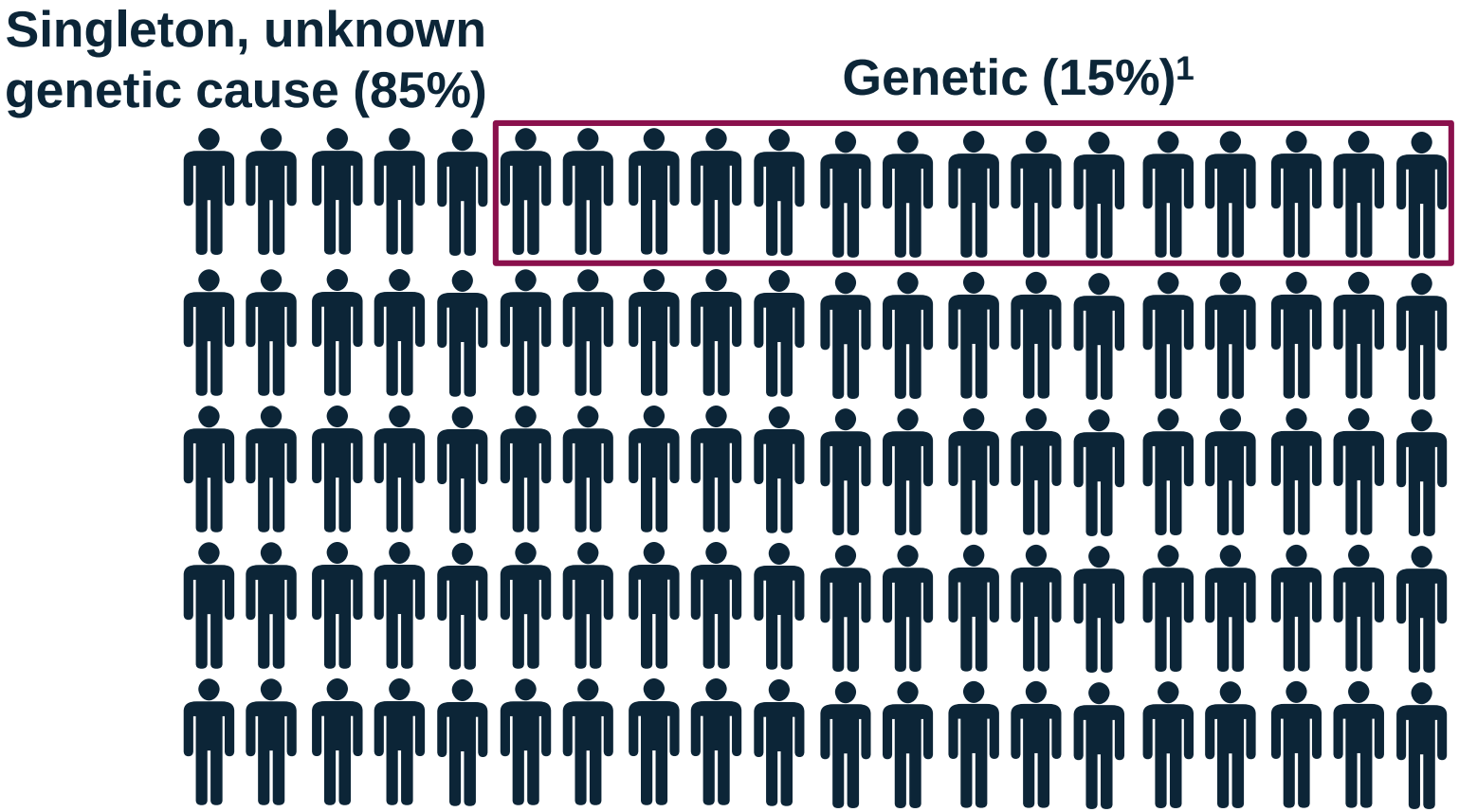


1. Goutman SA, et al. *Lancet Neurol.* 2022;21:480-493.

Causative mutations are found in people with and without a known family history of ALS

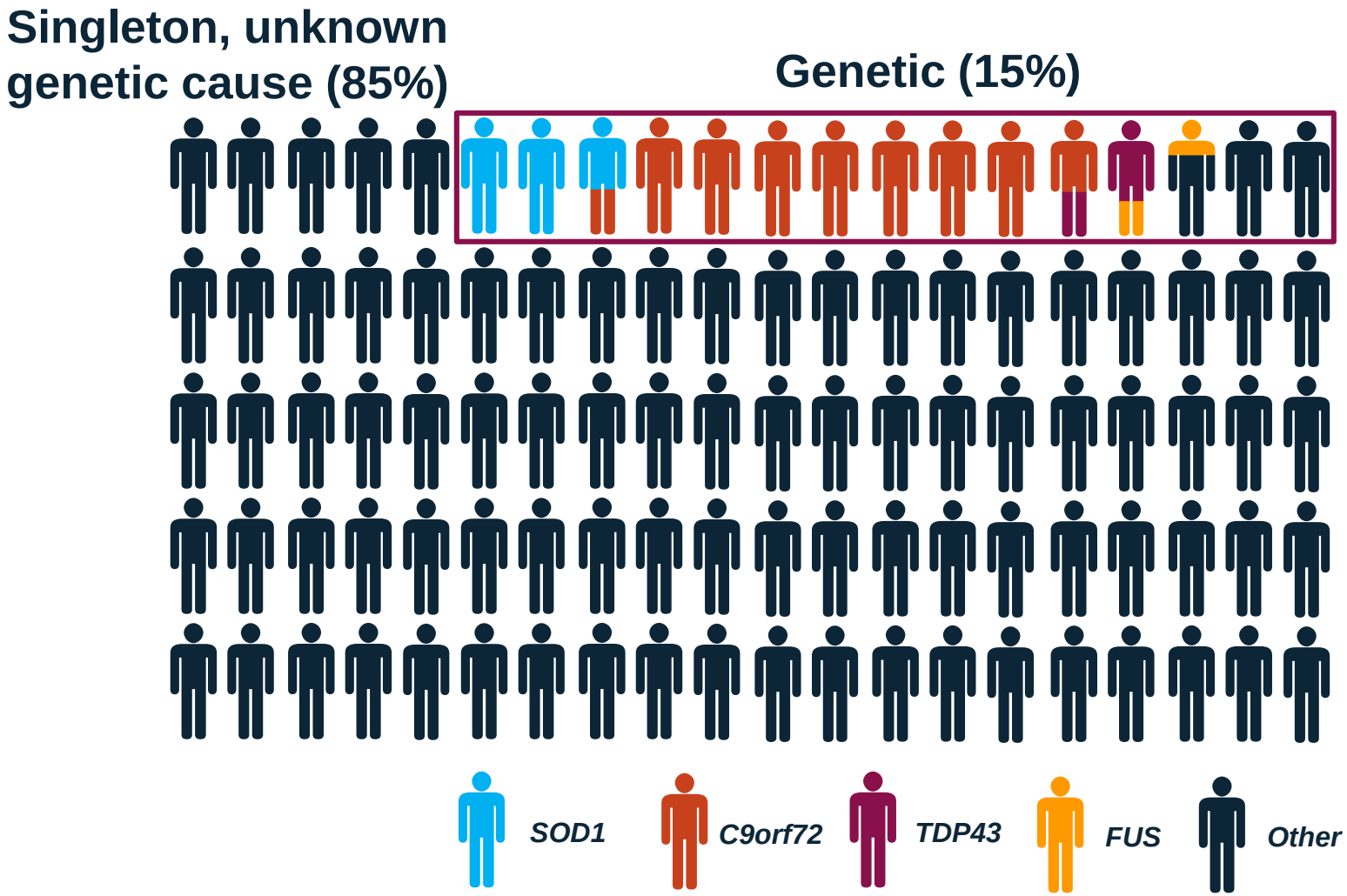
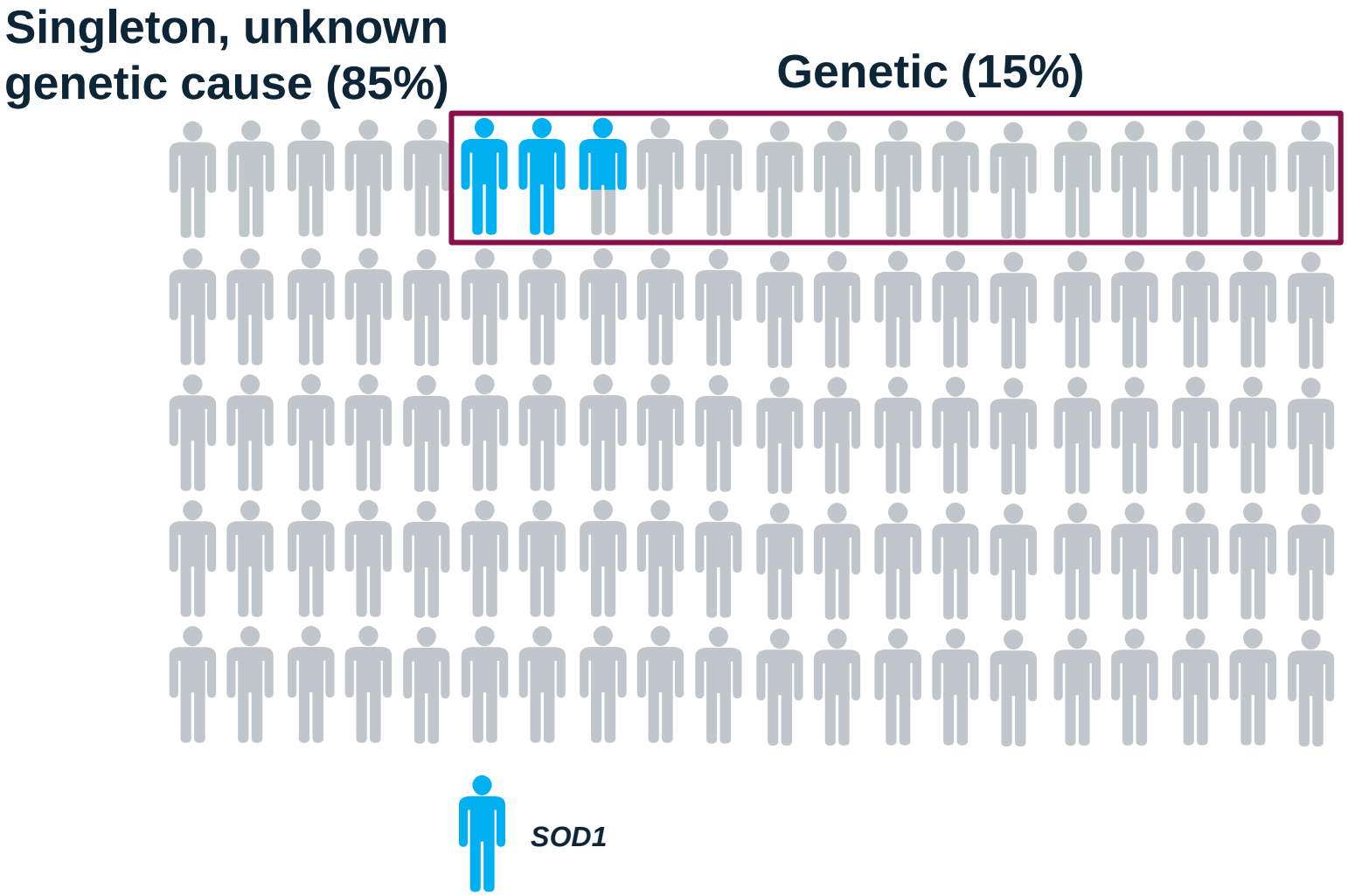


Figure based on Zou ZY, et al. *J Neurol Neurosurg Psychiatry*. 2017;88(7):540-549.

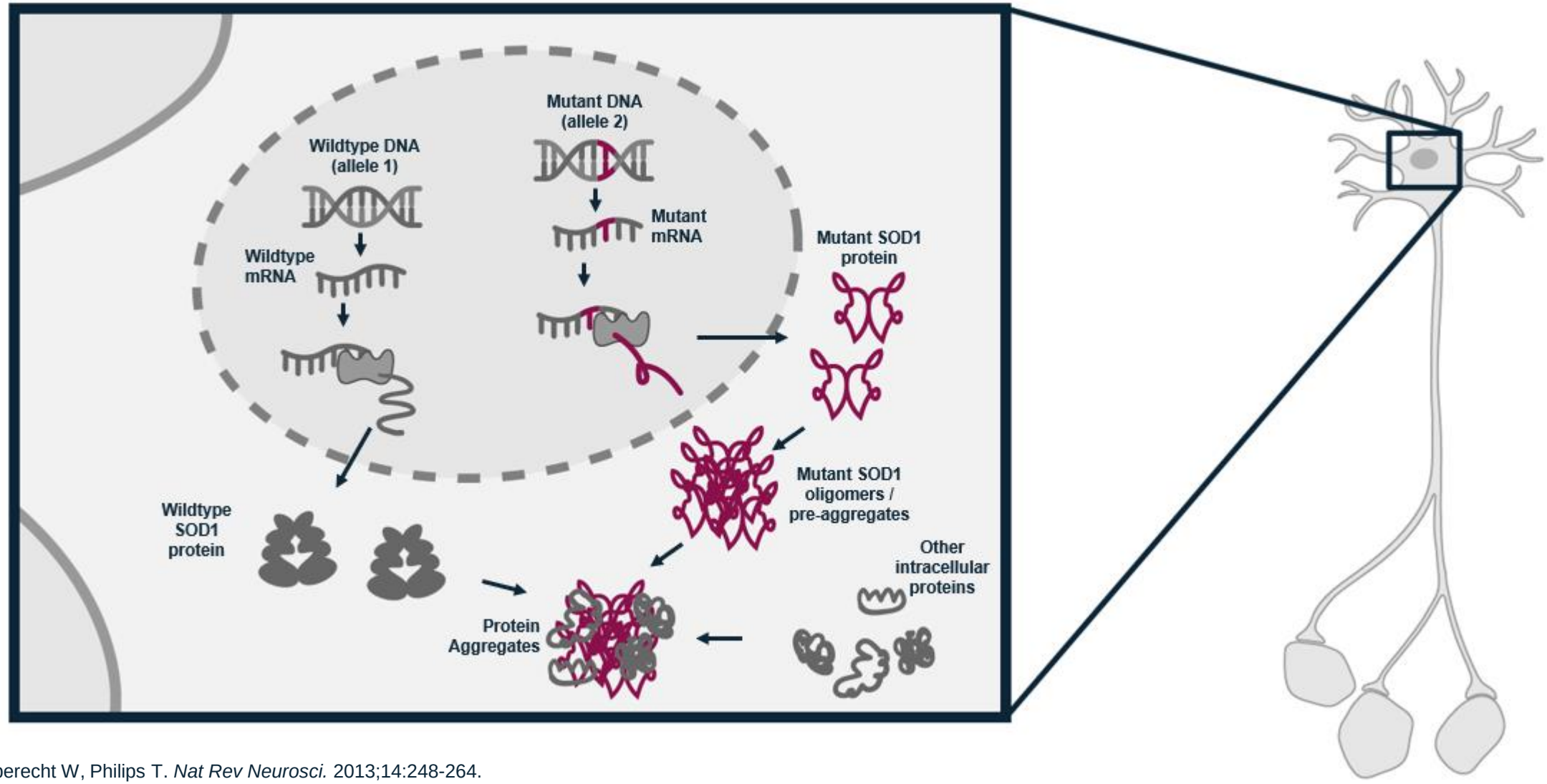
Causative mutations are found in people with and without a known family history of ALS



***SOD1*-ALS is estimated to affect ~330 people in the US[1]**

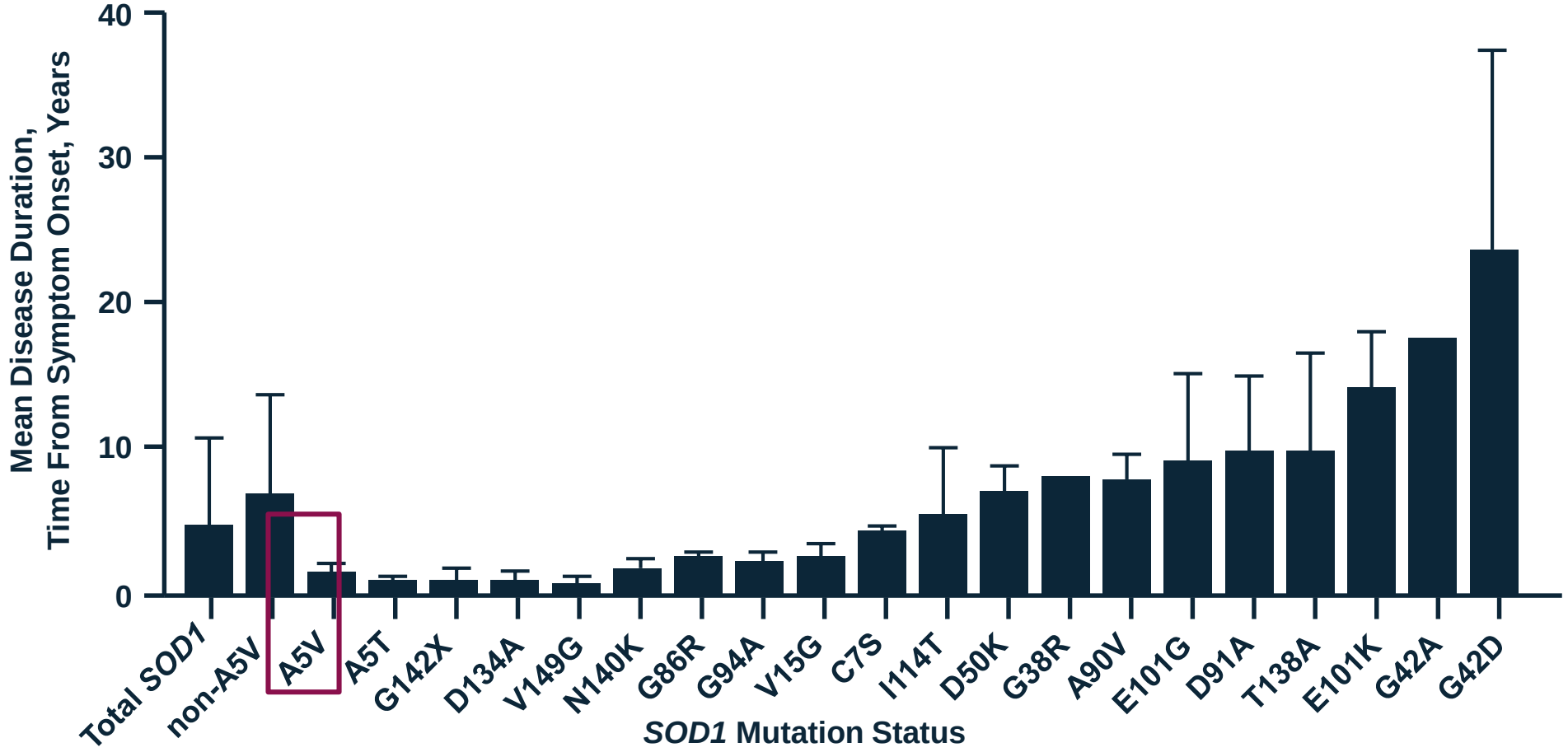
1. Brown CA, et al. *Neuroepidemiology.* 2021;55:342-353.
Figure based on Zou ZY, et al. *J Neurol Neurosurg Psychiatry*. 2017;88(7):540-549.

Mutations in the *SOD1* gene lead to production of a toxic form of SOD1 protein



Based on Robberecht W, Philips T. *Nat Rev Neurosci.* 2013;14:248-264.

SOD1-ALS natural history is highly heterogenous



Disease duration varies by mutation type

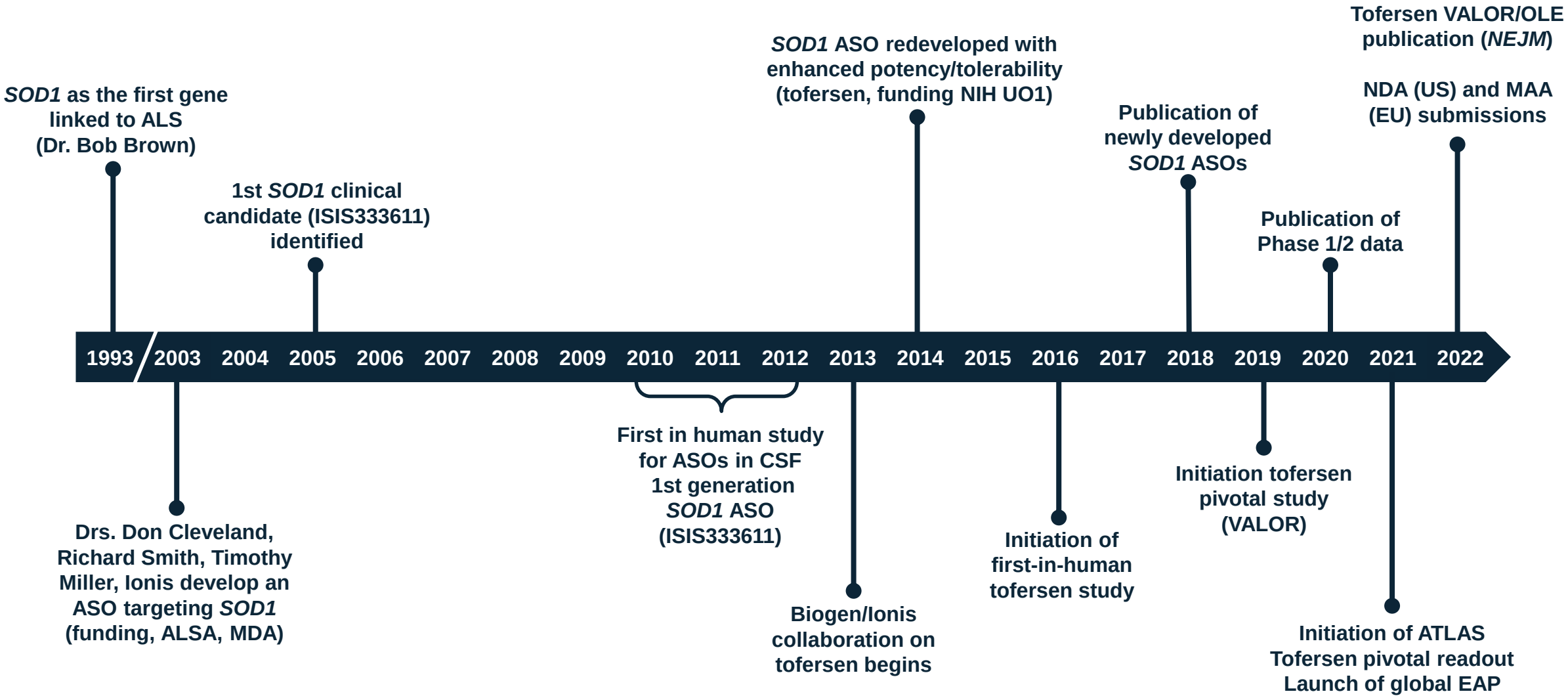
Current therapies do not address *SOD1*-ALS pathophysiology

1995	2011	2017	2022
Rilutek® (riluzole)	**Nuedexta® (dextromethorphan hydrobromide and quinidine sulfate)**	**Radicava® (edaravone)**	**Relyvrio™ (sodium phenylbutyrate and taurursodiol)**
Indicated for the treatment of ALS	Indicated for the treatment of pseudobulbar affect (PBA)	Indicated for the treatment of ALS	Indicated for the treatment of ALS

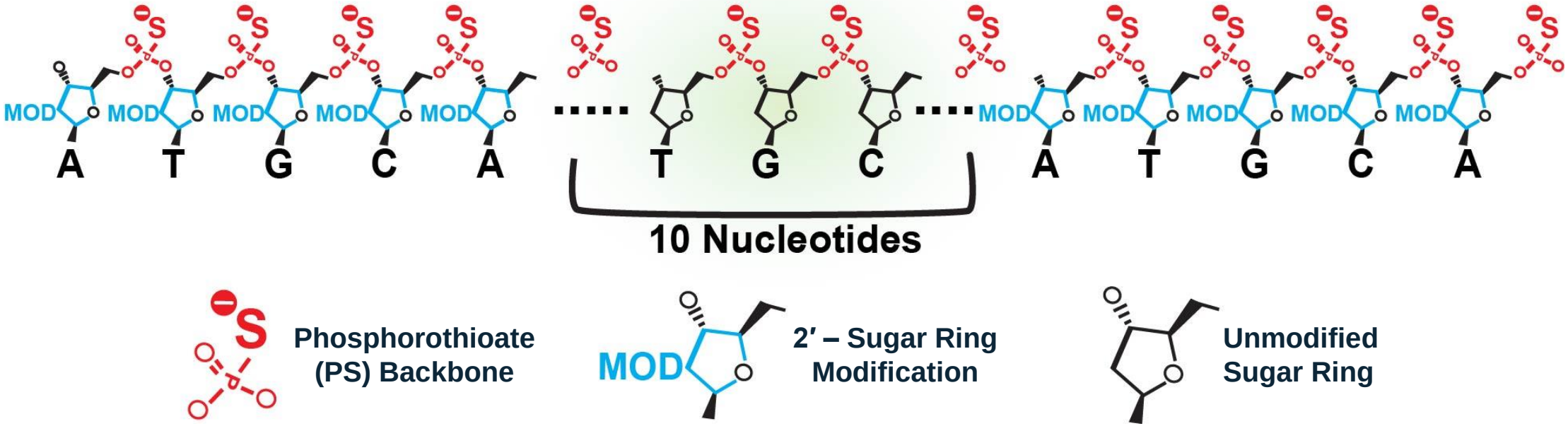
No available therapies target underlying disease pathology of *SOD1*-ALS

Based on initial US approvals. www.fda.gov/.

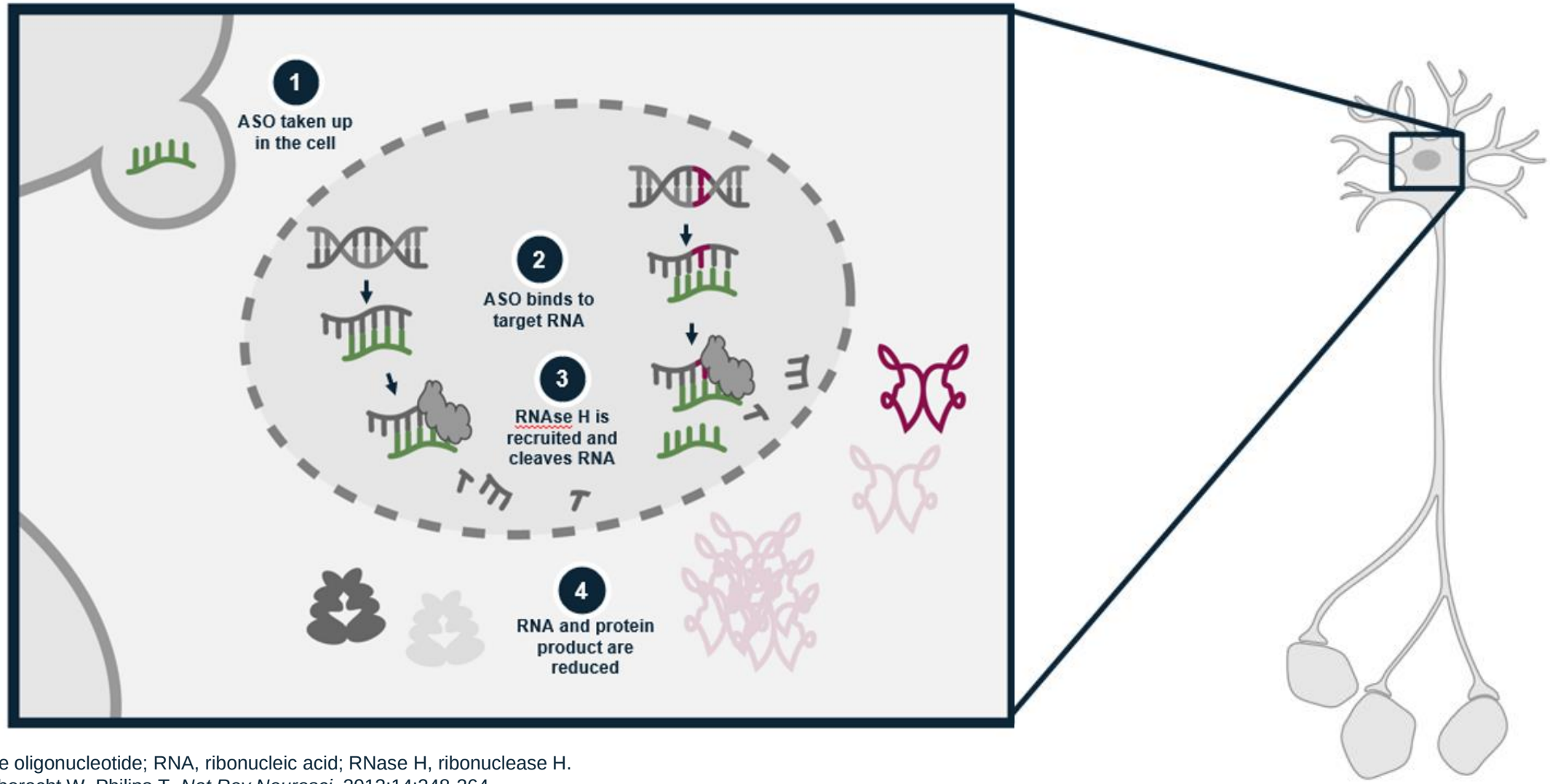
The discovery of tofersen spans two decades



Antisense oligonucleotides (ASOs)

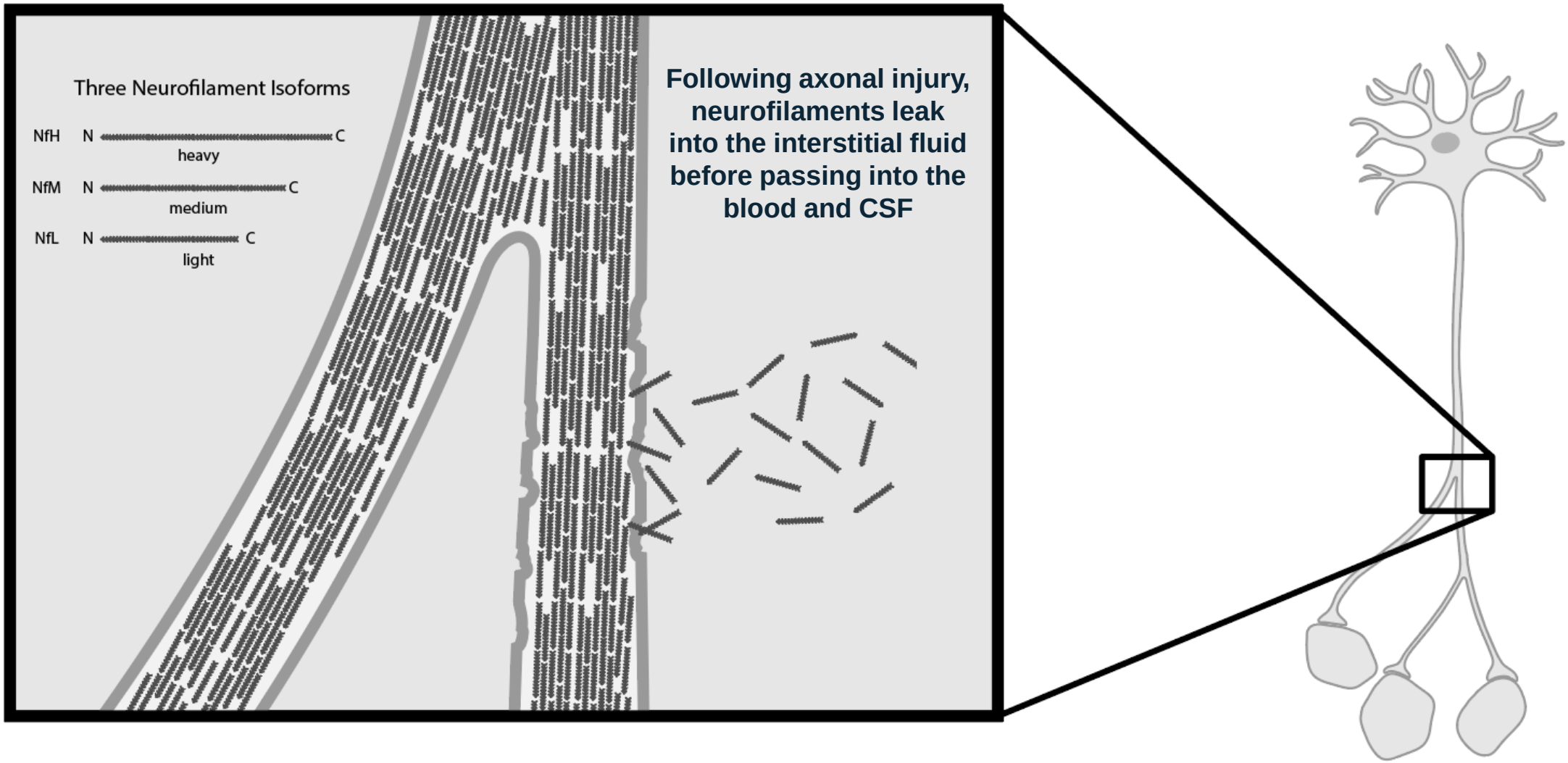


Tofersen is an ASO that targets the *SOD1* gene



ASO, antisense oligonucleotide; RNA, ribonucleic acid; RNase H, ribonuclease H.
Based on Robberecht W, Philips T. *Nat Rev Neurosci.* 2013;14:248-264.

Neurofilaments are a marker of motor neuron integrity



Based on Gagliardi D, et al. *Int J Mol Sci.* 2019;20:4152.

The behavior of neurofilament is well characterized in the ALS literature

1990

Rosengren 1996

2000

Norgren 2003
Brettschneider 2006
Zetterberg 2007
Boylan 2009
Rejin 2009

2010

Ganesalingam 2011
Steinacker 2011
Tortelli 2012
Boylan 2013
Gaiottino 2013
Ganesalingam 2013
Lehnert 2014
Gonçalves 2015
Lu 2015
McCombe 2015
Menke 2015
Tortelli 2015
Chen 2016
Oeckl 2016
Steinacker 2016
Weydt 2016
Wilke 2016
Xu 2016
Gaiani 2017
Gendron 2017
Kaiserova 2017

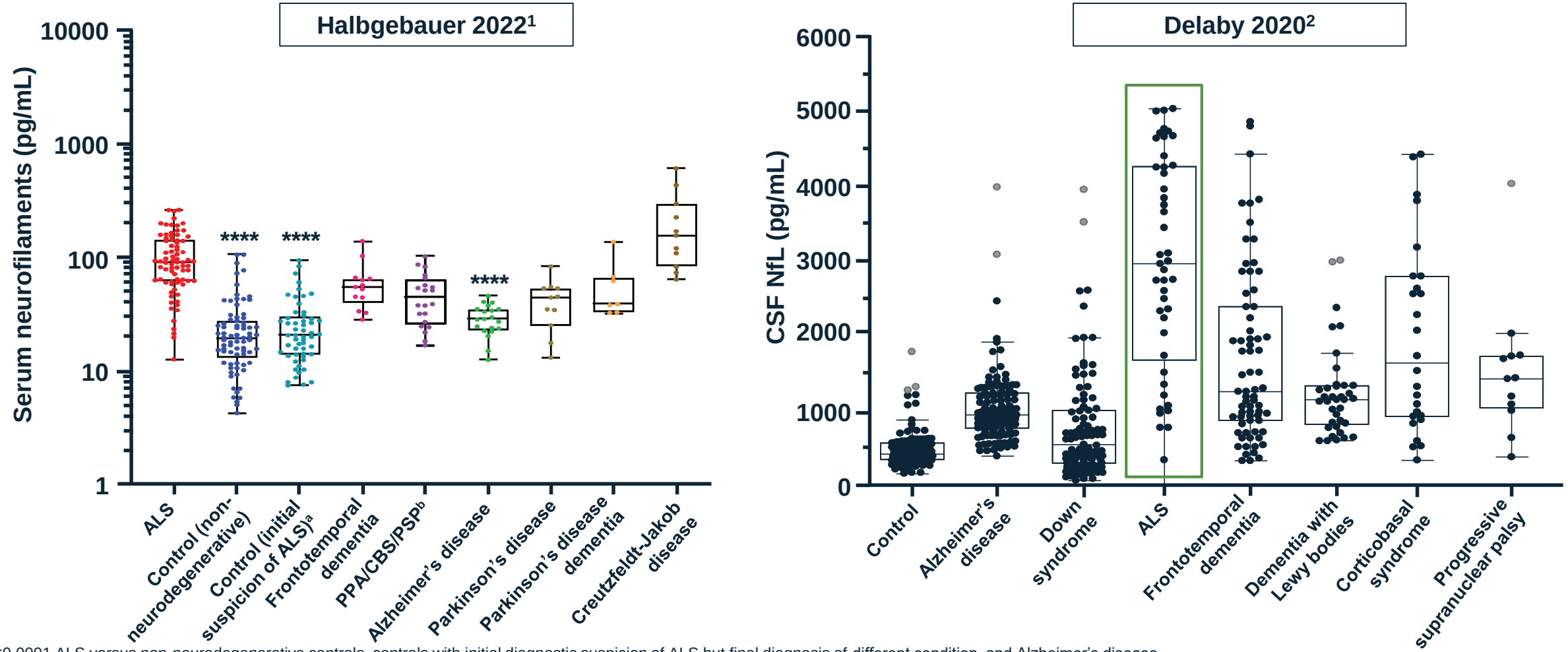
2020

Poesen 2017
Steinacker 2017
Andrés Benito 2018
Benatar 2018
De Schaepdryver 2018
Feneberg 2018
Gong 2018
Illán-Gala 2018
Khalil 2018
Li 2018
Rossi 2018
Scarafino 2018
Schreiber 2018
Bridel 2019
De Schaepdryver 2019
Forgrave 2019
Gille 2019
Kasai 2019
Verde 2019a
Verde 2019b

Abu-Rumeileh 2020
Benatar 2020
Delaby 2020
De Schaepdryver 2020
Huang 2020
Khalil 2020
Sugimoto 2020
Sun 2020
Thouvenot 2020
Yang 2020
Behzadi 2021
Bjornevik 2021
Brodovitch 2021
Gagliardi 2021
Kojima 2021
Simonini 2021
Vacchiano 2021
Verde 2021
Zhou 2021
Escal 2022
Falzone 2022

Haji 2022
Halbgebauer 2022
Heckler 2022
Kmezic 2022
Masrori 2022
Sferruzza 2022
Shi 2022
Thompson 2022
Yildiz 2022
Zecca 2022
Zhang 2022
De Shaepdryver 2023
Meyer 2023
Smith 2023

Neurofilament levels are elevated in ALS and exceed levels in nearly all other neurodegenerative diseases



****p<0.0001 ALS versus non-neurodegenerative controls, controls with initial diagnostic suspicion of ALS but final diagnosis of different condition, and Alzheimer's disease.

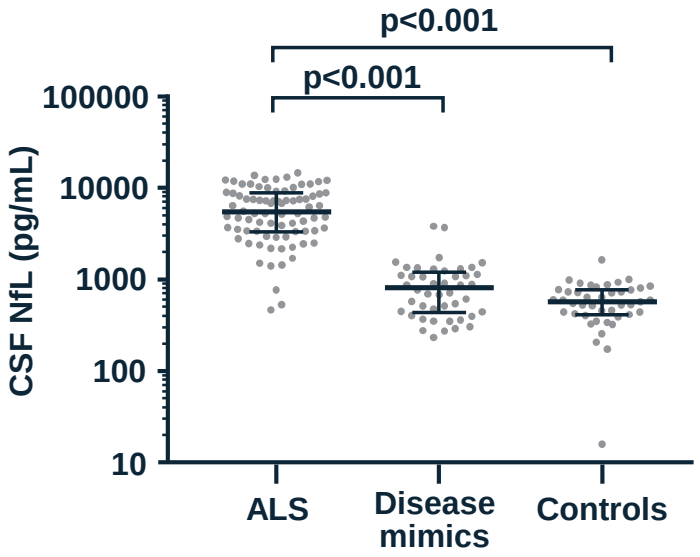
[a] Control participants with initial diagnostic suspicion of ALS but final diagnosis of different condition.

[b] PPA/CBS/PSP, primary progressive aphasia/ corticobasal syndrome/ progressive supranuclear palsy.

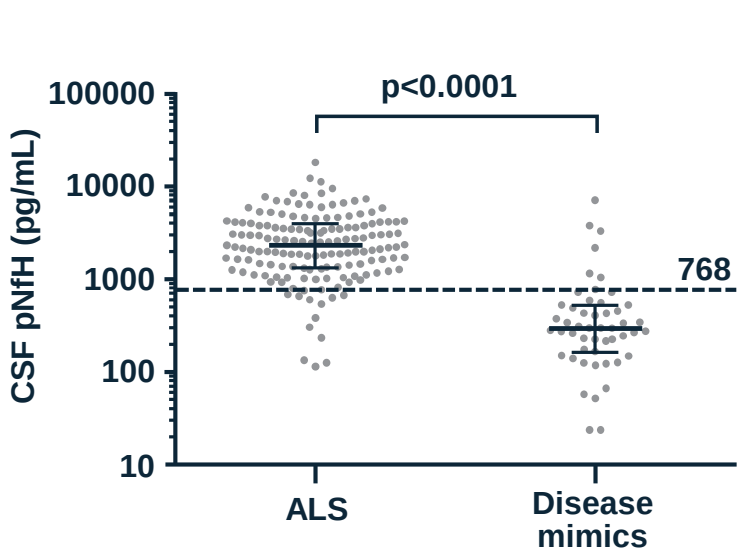
1. Reprinted from Halbgebauer S, et al. *Neurology.* 2022;98(14):e1434-e1445. 2. Reprinted from Delaby C, et al. *Sci Rep.* 2020;10(1):9161. https://creativecommons.org/licenses/by/4.0/.

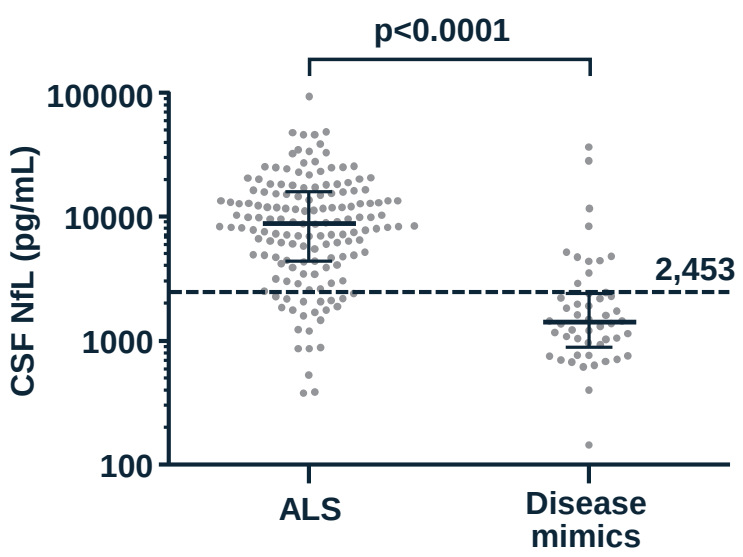
Neurofilament elevations in ALS are distinguishable from disease mimics

Abu-Rumeileh 2020[1]



Poesen 2017[2]

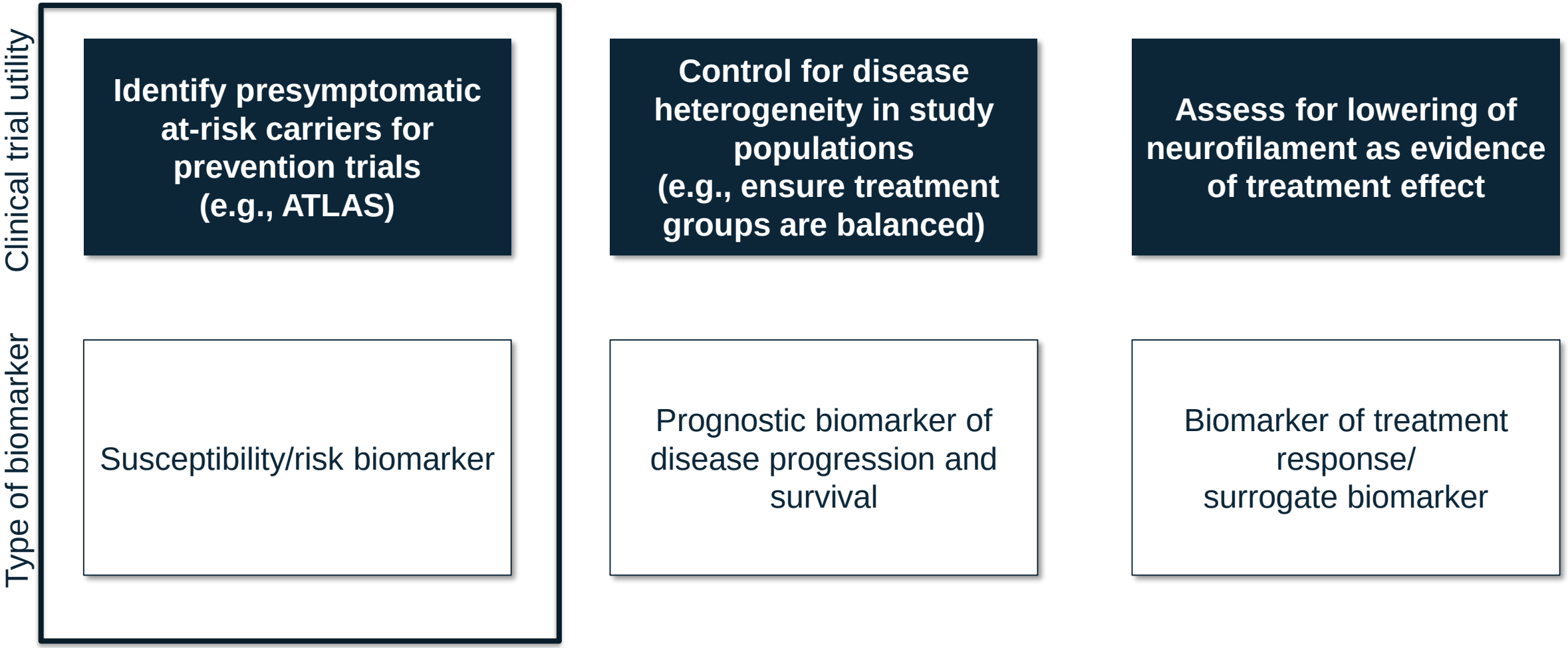




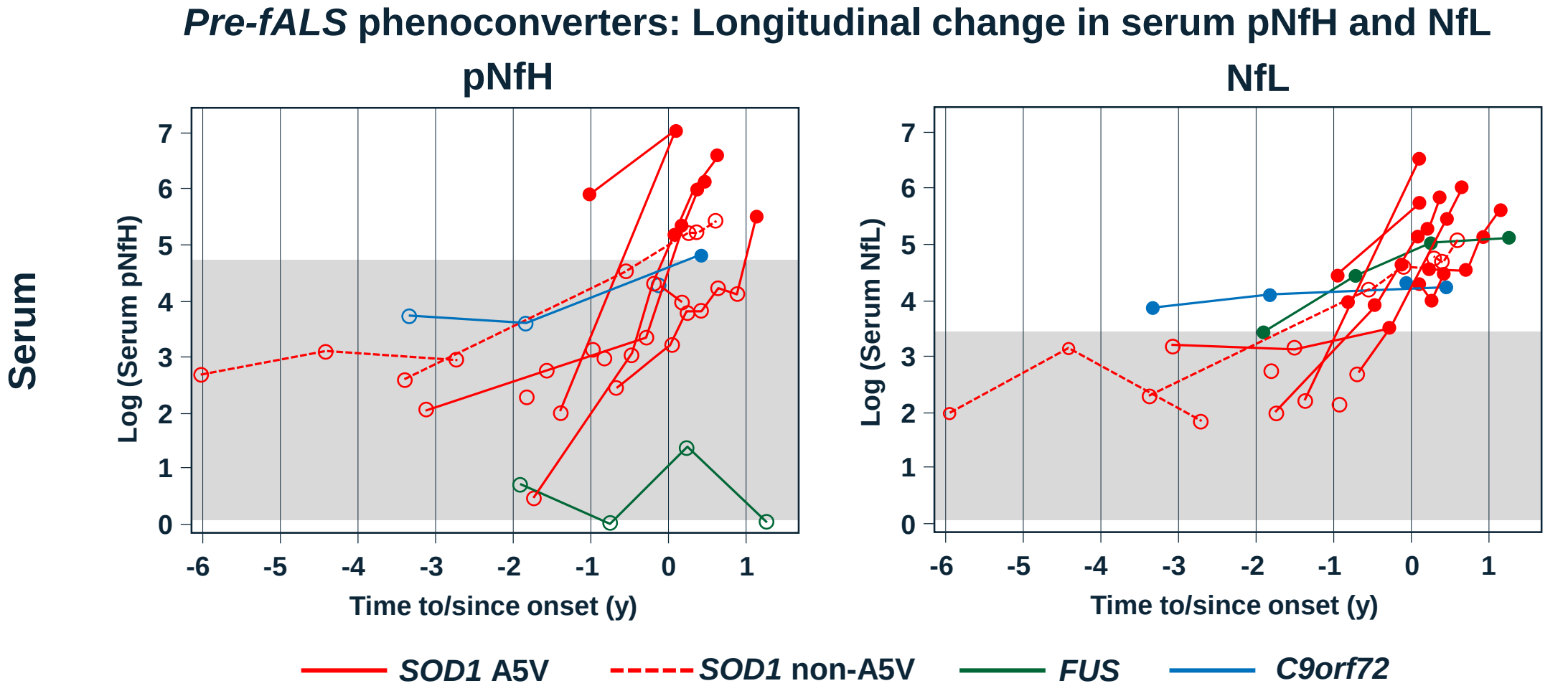
Disease mimics: Conditions that can mimic the symptoms associated with ALS (e.g., multifocal motor neuropathy, multiple sclerosis, and Parkinson's disease)

1. Reprinted from Abu-Rumeileh S, et al. *J Neurol.* 2020;267(6):1699-1708. Springer Nature.
2. Reprinted from Poesen K, et al. *Neurology.* 2017;88(24):2302-2309.

Utility of neurofilament in ALS trials



Neurofilament levels are elevated prior to emergence of clinically manifest ALS



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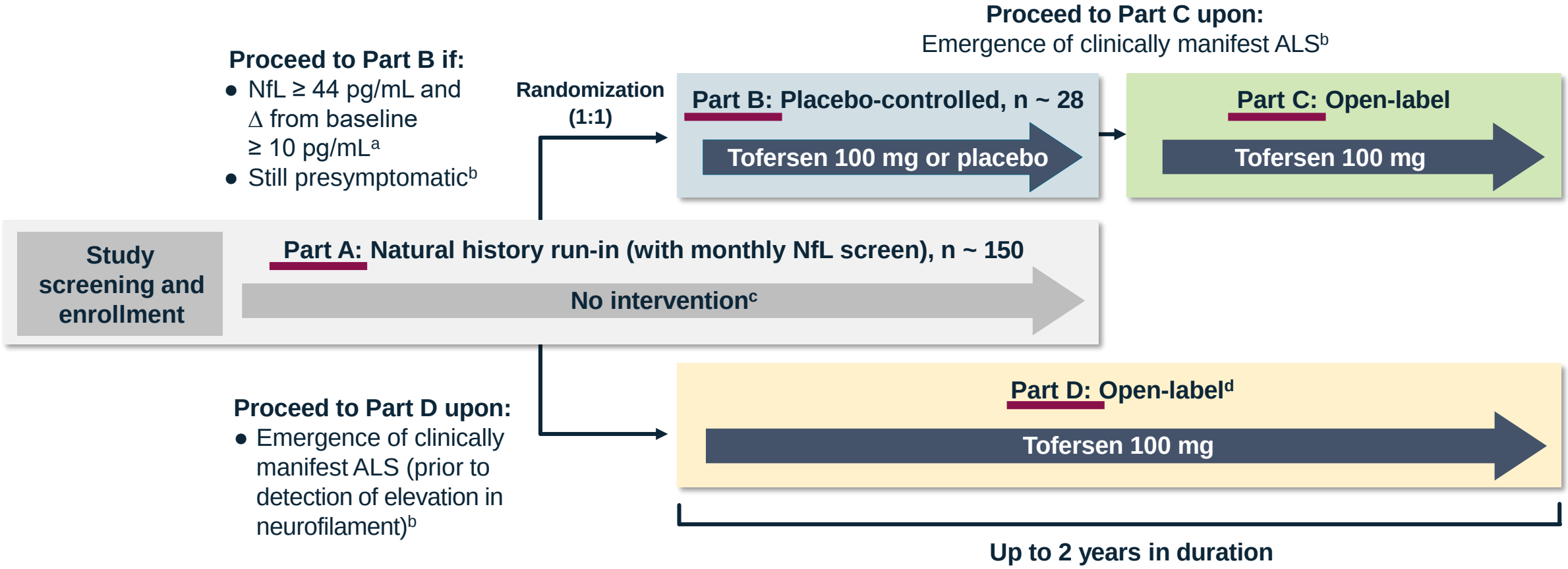
ATLAS study design

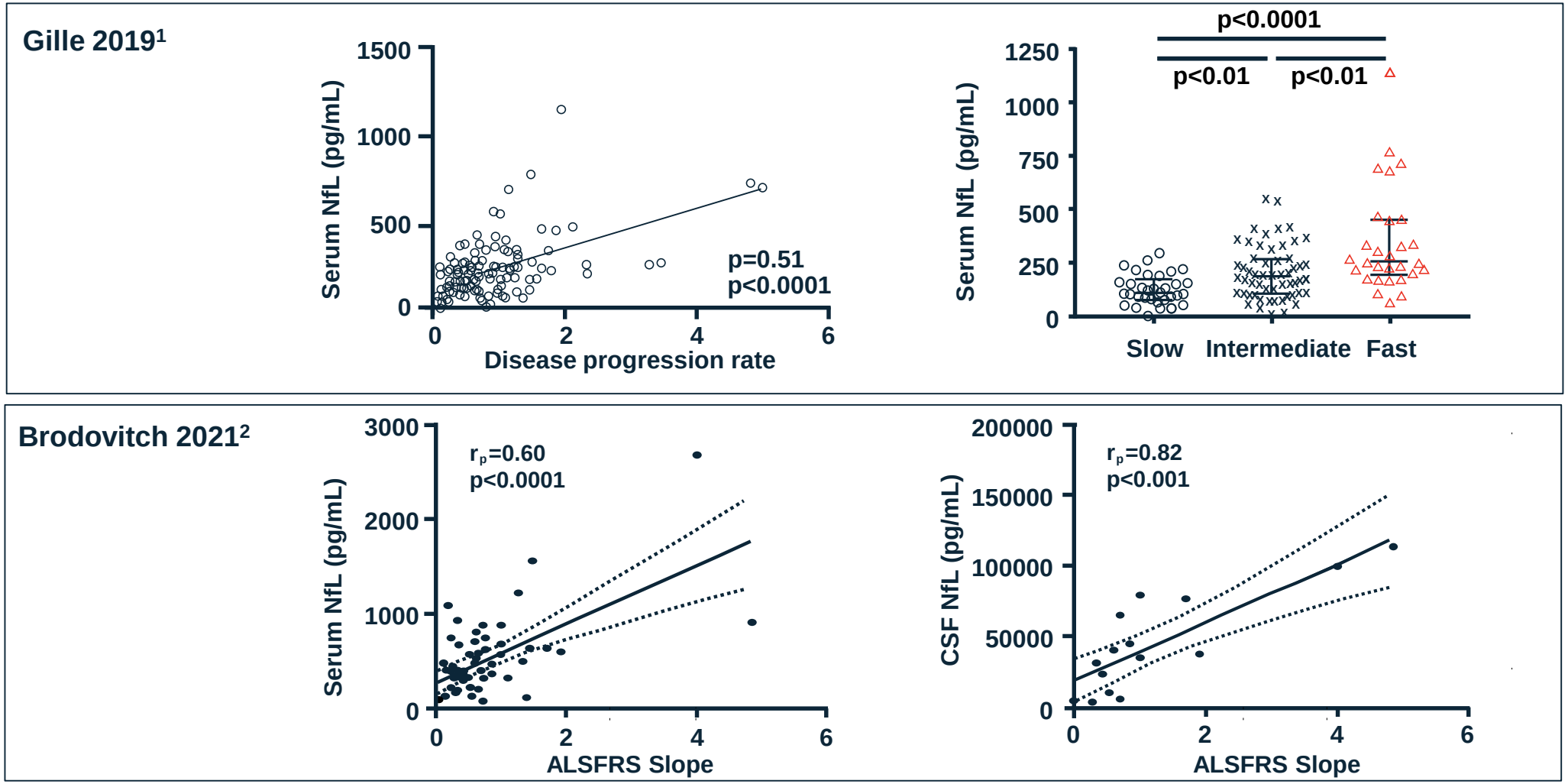


[a] Measured using Siemens Healthineers NfL Assay; [b] Assuming other eligibility criteria are met; [c] Follow-up in Part A will end once 28 participants have been enrolled in Part B; [d] Part D was originally designed with a placebo-control but was transitioned to open-label following the sponsor's review of the results of the Phase 3 VALOR study.

Utility of neurofilament in ALS trials

Clinical trial utility	Identify presymptomatic at-risk carriers for prevention trials (e.g., ATLAS)	Control for disease heterogeneity in study populations (e.g., ensure treatment groups are balanced)	Assess for lowering of neurofilament as evidence of treatment effect
Type of biomarker	Susceptibility/risk biomarker	Prognostic biomarker of disease progression and survival	Biomarker of treatment response/ surrogate biomarker

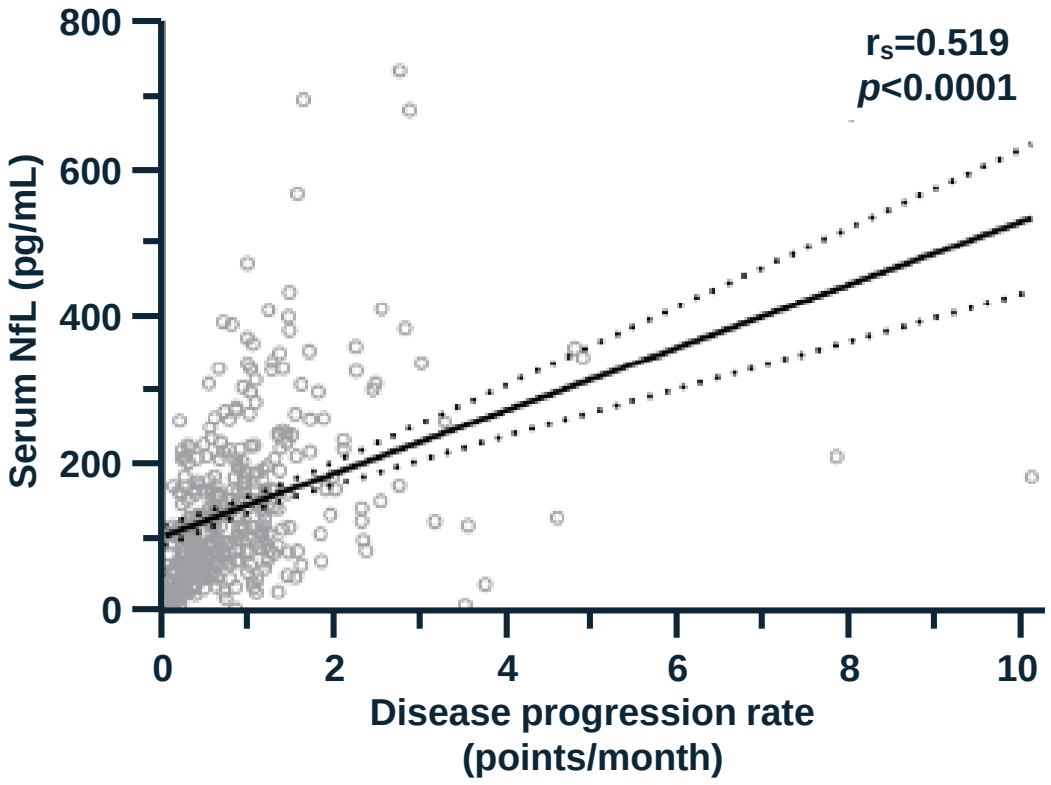
Neurofilament levels correlate with disease progression rate in ALS



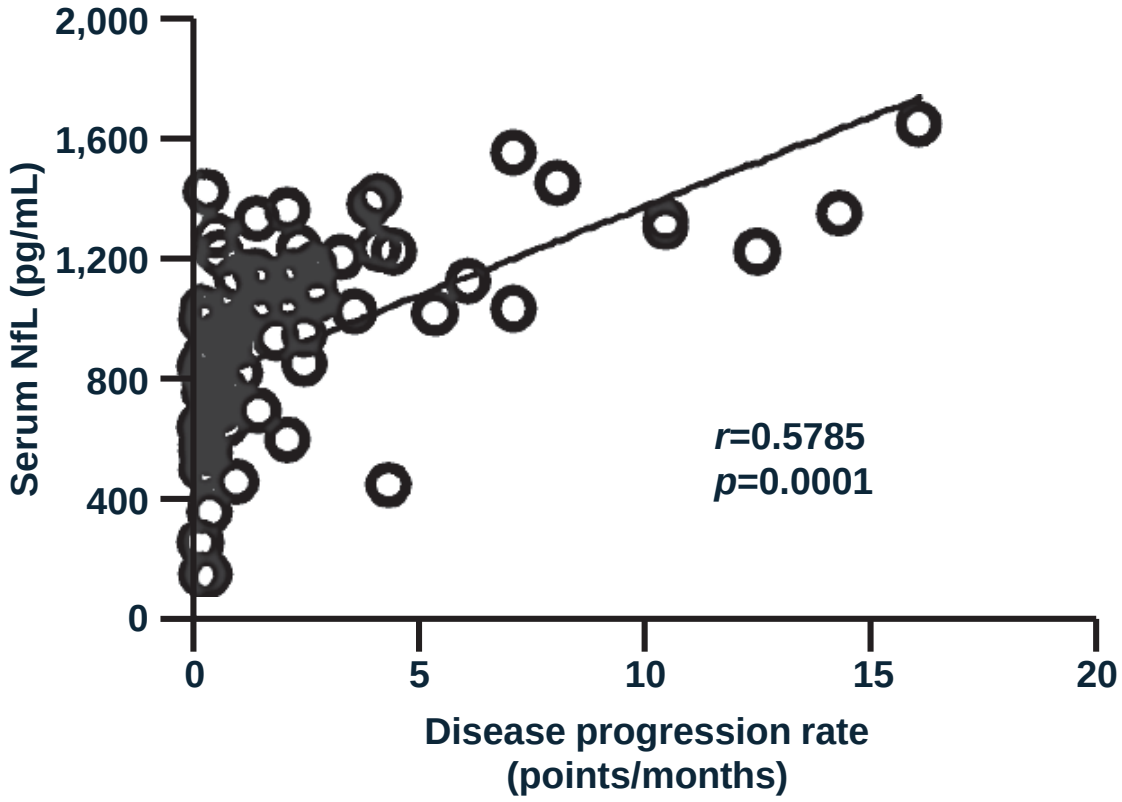
1. Reprinted from Gille B, et al. *Neuropathol Appl Neurobiol.* 2019;45(3):291-304; Copyright © 2018 Wiley. Reproduced with permission from John Wiley & Sons Inc.
2. Reprinted from Brodovitch A, et al. *Sci Rep.* 2021;11(1):703. https://creativecommons.org/licenses/by/4.0.

Neurofilament levels correlate with disease progression rate in ALS

De Schaepdryver 2020[1]



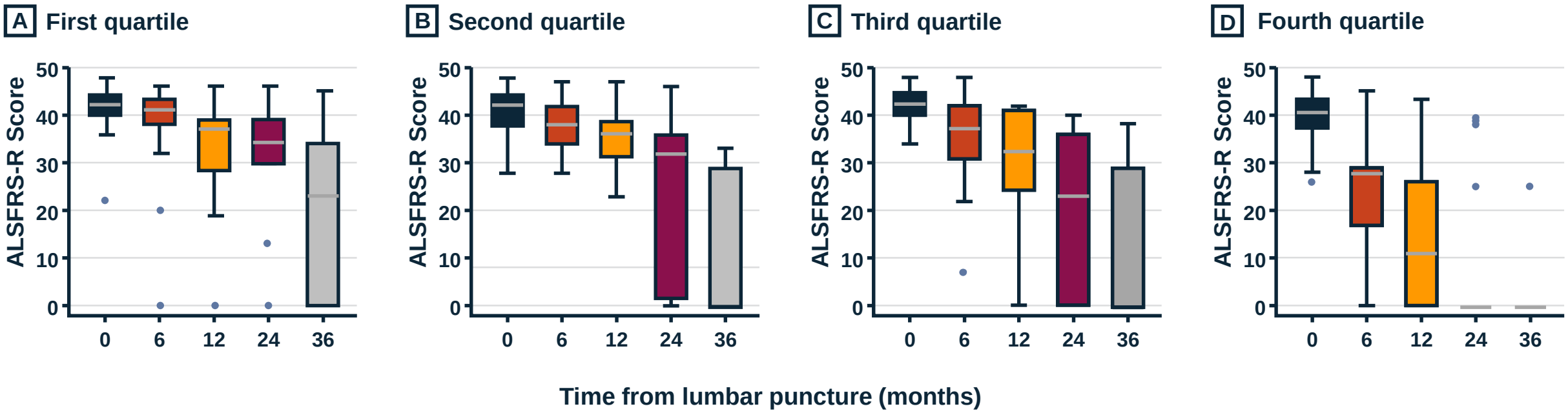
Gong 2018[2]



1. Reproduced from De Schaepdryver M, et al. *J Neurol Neurosurg Psychiatry.* 2020;91(4):436-437. Copyright 2020 with permission from BMJ Publishing Group Ltd.
2. Reproduced from Gong ZY, et al. *Neurodegener Dis.* 2018;18(2-3):165-172. Copyright © 2018 Karger Publishers, Basel, Switzerland.

Neurofilament levels are prognostic for decline in clinical function in ALS

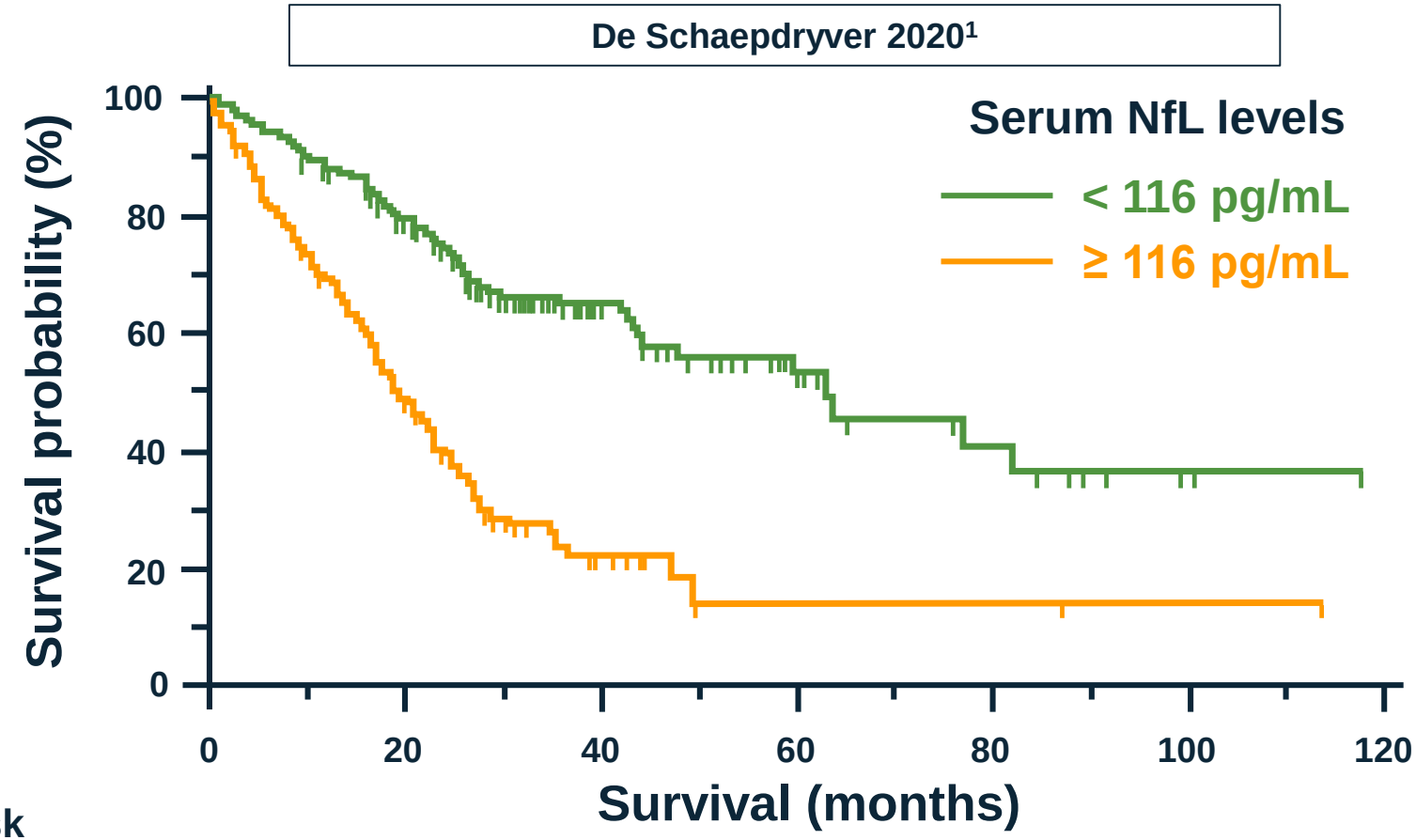
Gaiani 2017[1]



N=92, Quartiles defined by CSF NfL concentration measured by commercially available ELISA kit (NfL, Uman Diagnostics, Umea, Sweden)

1. Reproduced from Gaiani A, et al. *JAMA Neurol.* 2017;74(5):525-532. Copyright © 2017 American Medical Association. All rights reserved.

Neurofilament levels are prognostic for survival in ALS

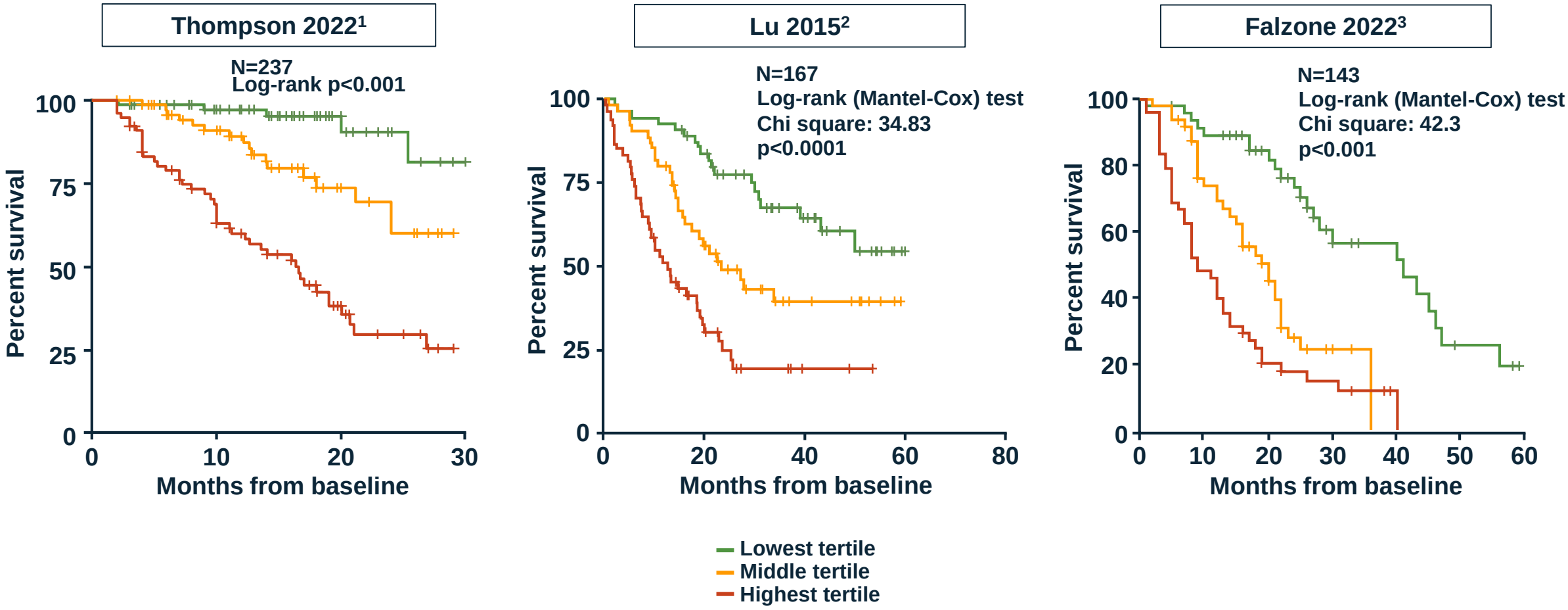


Number at risk

Group: < 116 pg/mL	191	134	48	16	9	2	0
Group: ≥ 116 pg/mL	191	75	13	2	2	1	0

1. Reprinted from De Schaepdryver M, et al. *J Neurol Neurosurg Psychiatry*. 2020;91(4):436-437. Copyright 2020 with permission from BMJ Publishing Group Ltd.

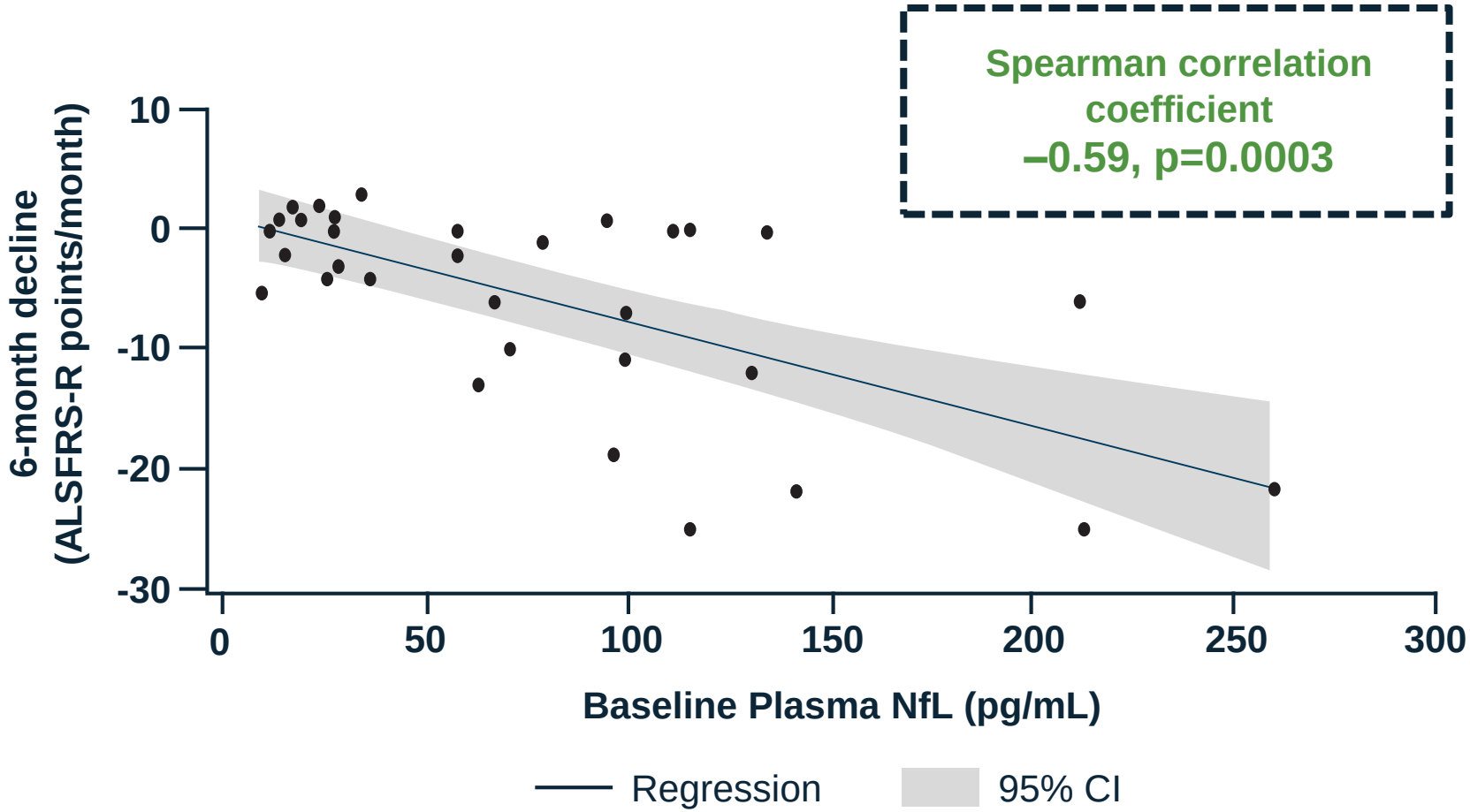
Neurofilament levels are prognostic for survival in ALS



1. Reprinted from Thompson AG, et al. *Brain Commun.* 2022;4(1):fcac029. https://creativecommons.org/licenses/by/4.0/.
2. Reprinted from Lu CH, et al. *Neurology.* 2015;84(22):2247-2257.
3. Reprinted from Falzone YM, et al. *Eur J Neurol.* 2022;29(7):1930-1939. Copyright © 2019 Wiley. Reproduced with permission from John Wiley & Sons Inc.

Prognostic utility of NF appears similar in *SOD1*-ALS

Baseline plasma NfL correlates with ALSFRS-R decline in VALOR placebo participants (n=33)



Reprinted from Miller T, et al. Presented at: American Neurological Association Annual Meeting; October 17-19, 2021.

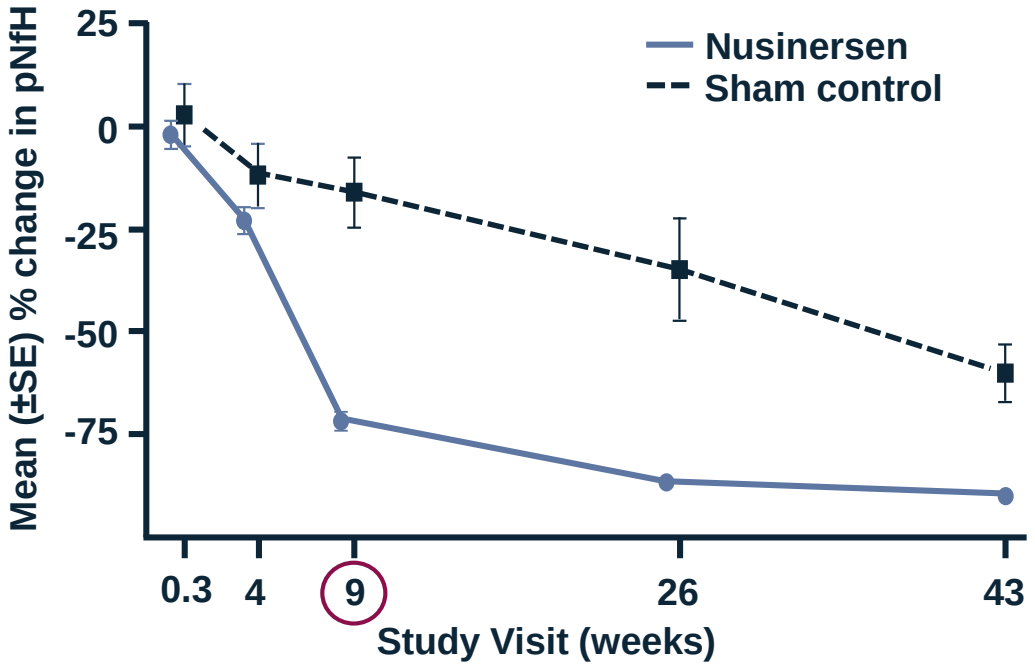
Utility of neurofilament in ALS trials

Clinical trial utility	Identify presymptomatic at-risk carriers for prevention trials (e.g., ATLAS)	Control for disease heterogeneity in study populations (e.g., ensure treatment groups are balanced)	Assess for lowering of neurofilament as evidence of treatment effect
Type of biomarker	Susceptibility/risk biomarker	Prognostic biomarker of disease progression and survival	Biomarker of treatment response/ surrogate biomarker

Treatment-driven reductions in neurofilament preceded clinical benefit in other neurodegenerative diseases

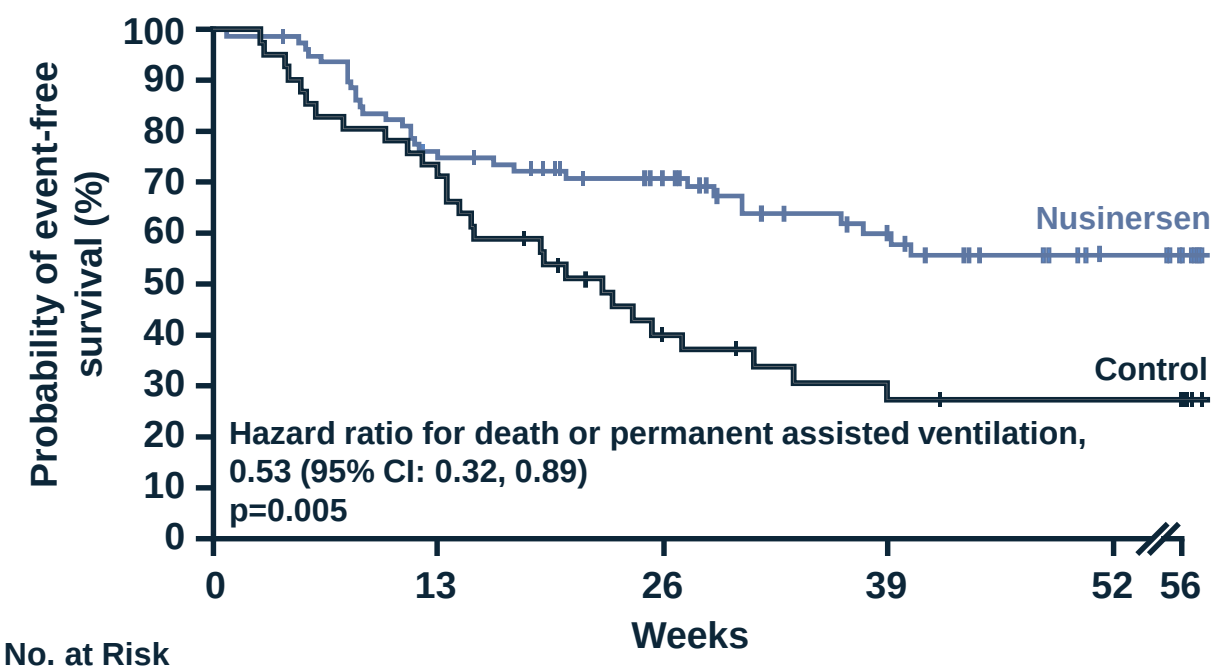
Spinraza (Nusinersen) ENDEAR study in infantile-onset SMA

Plasma pNfH, Darras 2019[1]



Nusinersen	76	73	69	47	30
Sham control	39	36	30	17	15

Event-free survival, Finkel 2017[2]

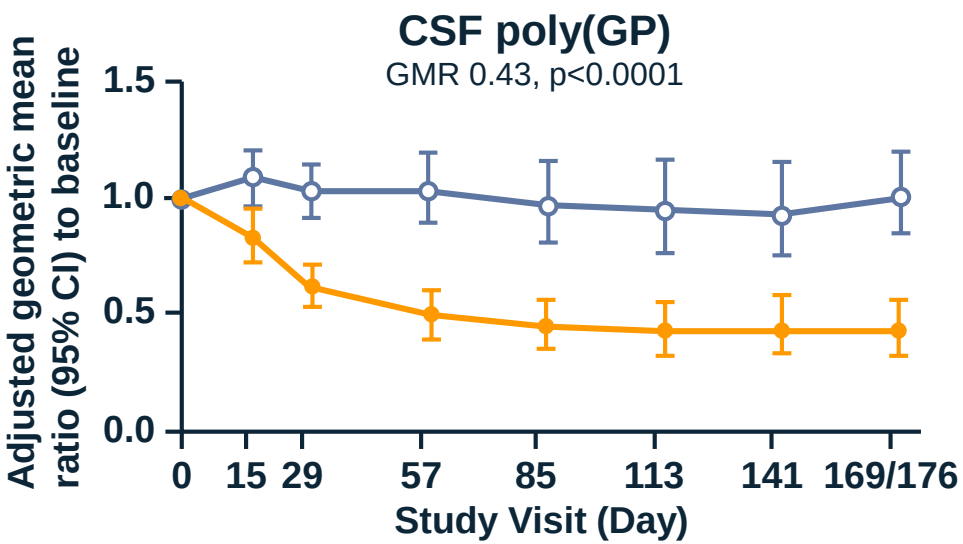


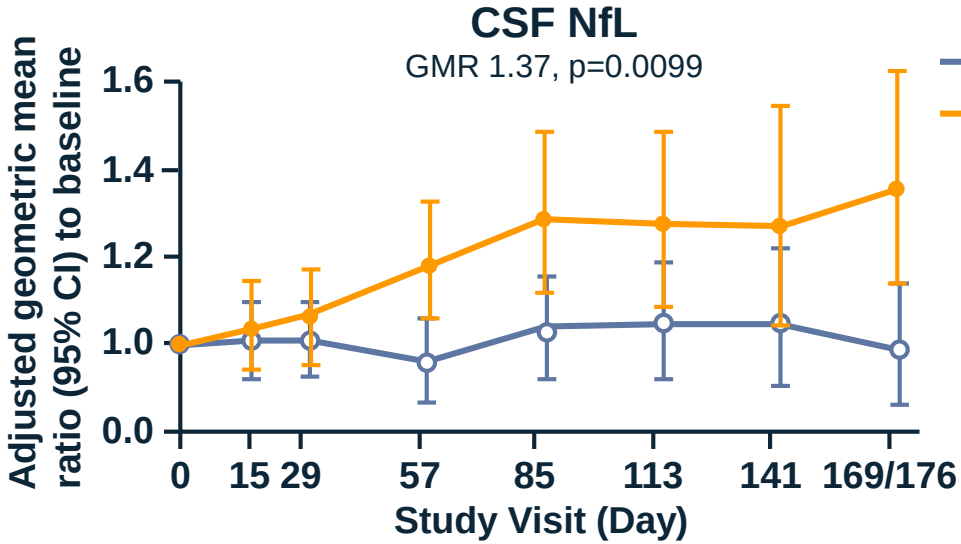
No. at Risk						
Nusinersen	80	59	46	29	16	13
Control	41	30	14	9	7	7

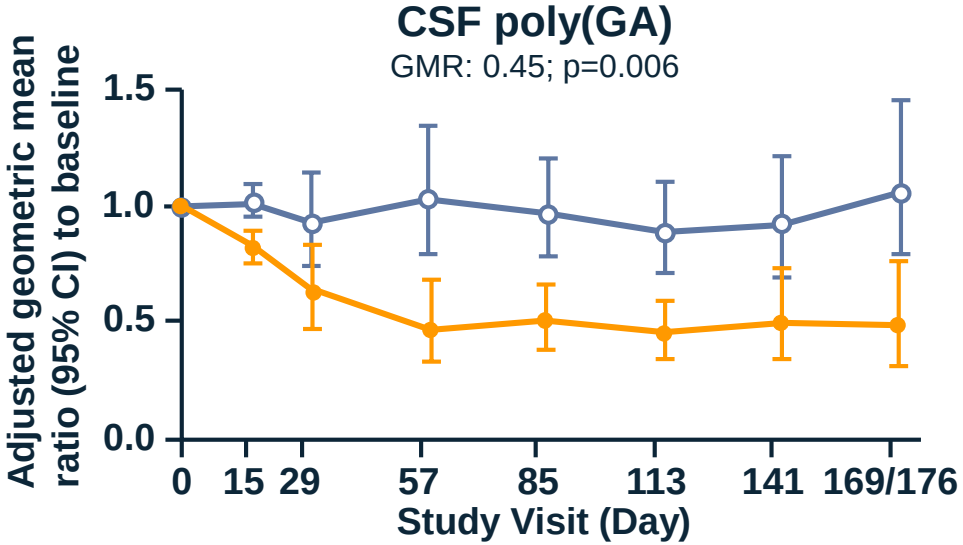
1. Reprinted from Darras BT, et al. *Ann Clin Transl Neurol.* 2019;6(5):932-944. Copyright © 2019 Wiley. Reproduced with permission from John Wiley & Sons Inc.
2. Reprinted from Finkel RS, et al. *N Engl J Med*. 2017;377(18):1723-1732. Copyright © 2017 Massachusetts Medical Society. All rights reserved.

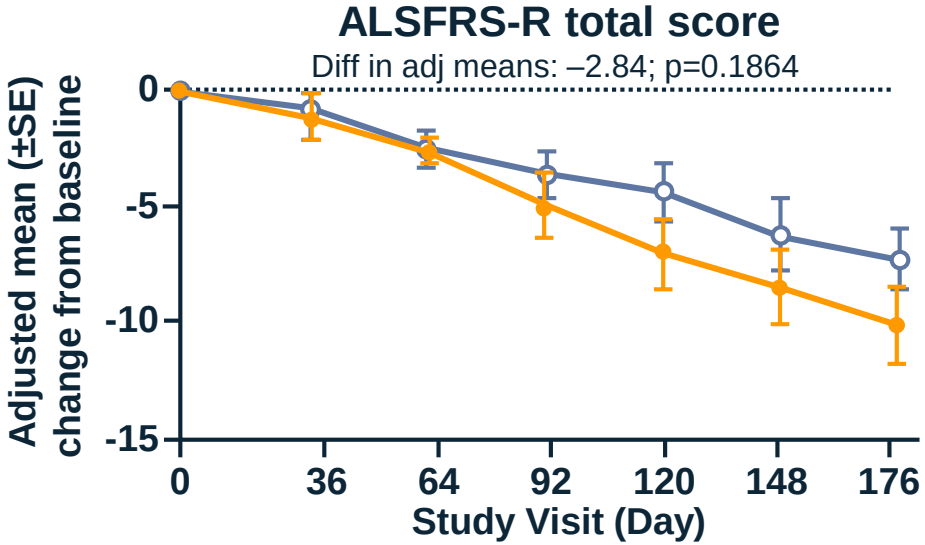
Treatment-driven increases in NfL were associated with worse clinical outcomes in *C9orf72*-ALS

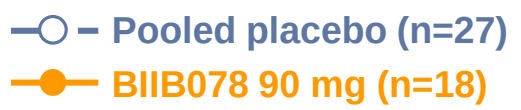
BIIB078 Phase 1 multiple-ascending-dose study in adults with *C9orf72*-ALS





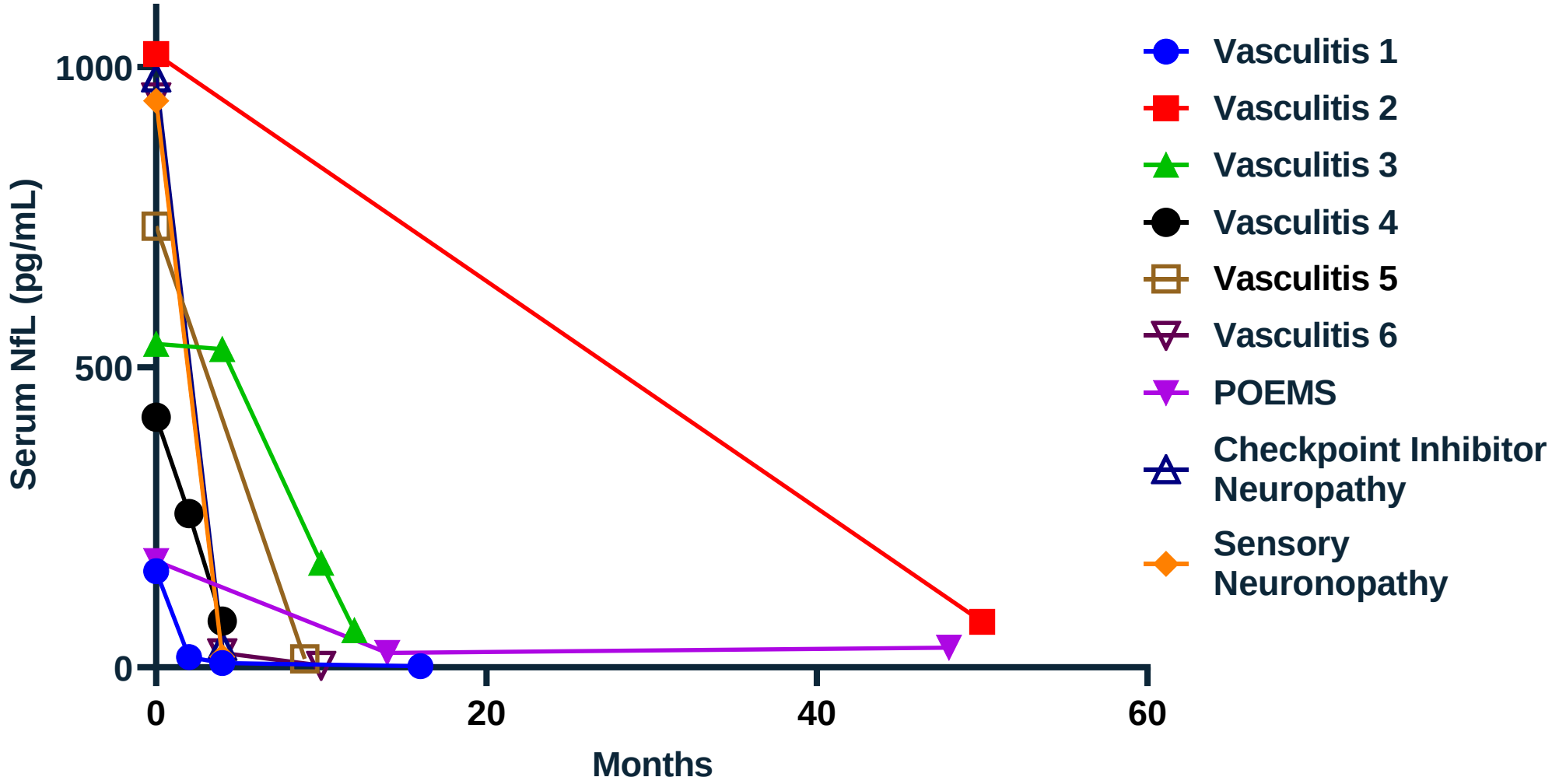






ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS Functional Rating Scale-Revised; CSF, cerebrospinal fluid; NfL, neurofilament light.

NfL is elevated in some neuropathies and decreases with treatment



NfL, neurofilament light.
Unpublished data, Washington University Neuromuscular Clinic.

Neurofilament can play a critical role in ALS trials

Clinical trial utility

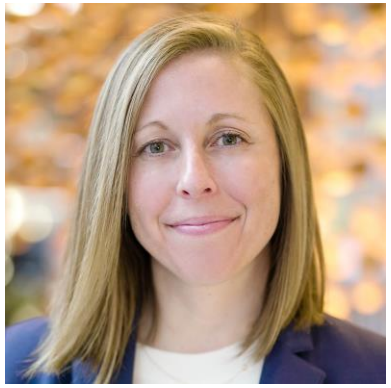
Identify presymptomatic at-risk carriers for prevention trials (e.g., ATLAS)

Control for disease heterogeneity in study populations (e.g., ensure treatment groups are balanced)

Assess for lowering of neurofilament as evidence of treatment effect

- *SOD1*-ALS is a disease associated with motor neuron death
- Neurofilament is a marker of motor neuron integrity, as degenerating motor neurons leak neurofilament, primarily from their injured axons
- Consistently, neurofilament levels have been found to be prognostic for disease progression and survival in ALS— higher levels associated with faster disease progression and shortened survival
- Treatment-driven lowering of neurofilament is thought to represent a slowing of axonal injury and neurodegeneration

ALS, amyotrophic lateral sclerosis; SOD1, superoxide dismutase-1.



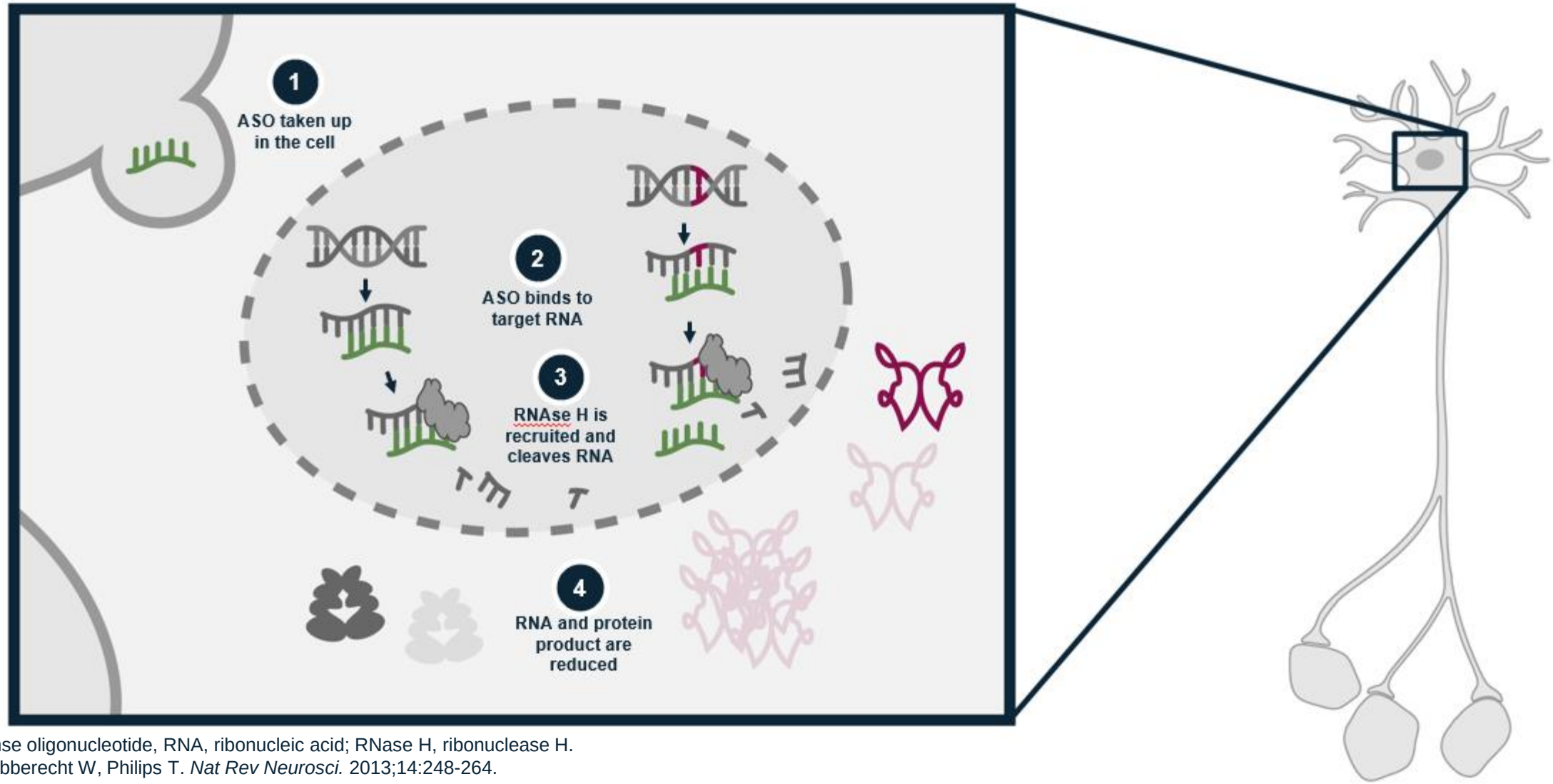
Efficacy

Stephanie Fradette, PharmD

Clinical Development Lead and ALS Portfolio Head

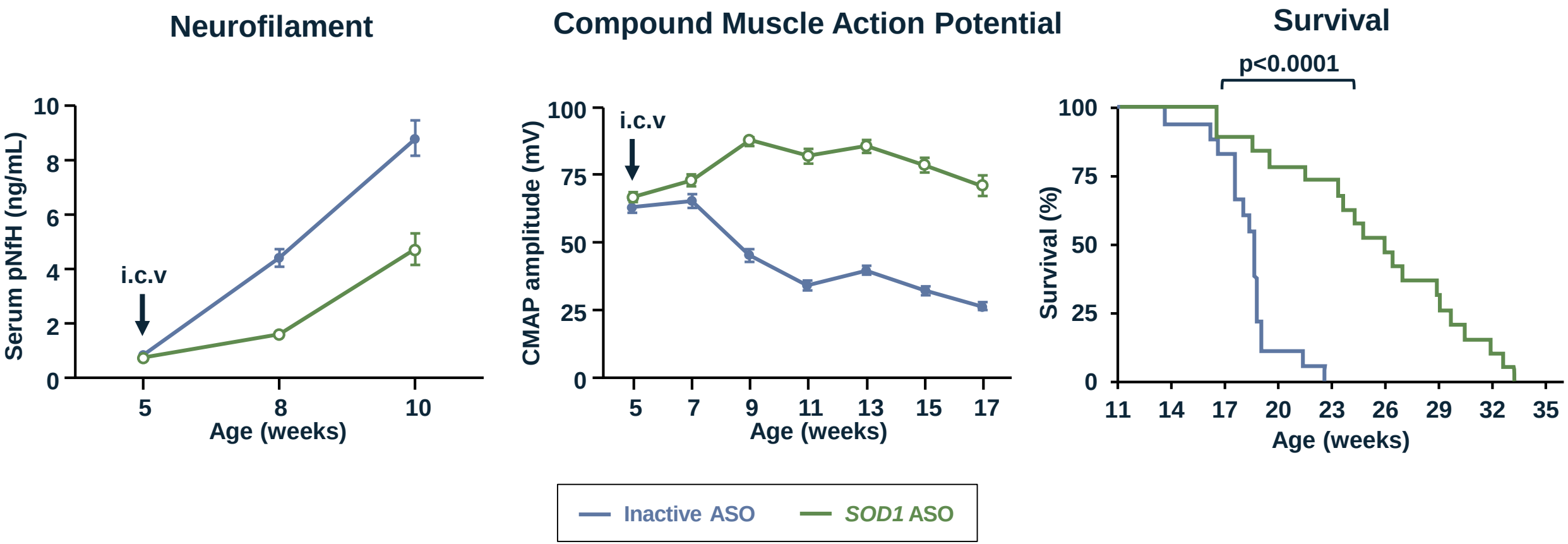
Biogen

Tofersen mediates degradation of *SOD1* mRNA to reduce synthesis of SOD1 protein



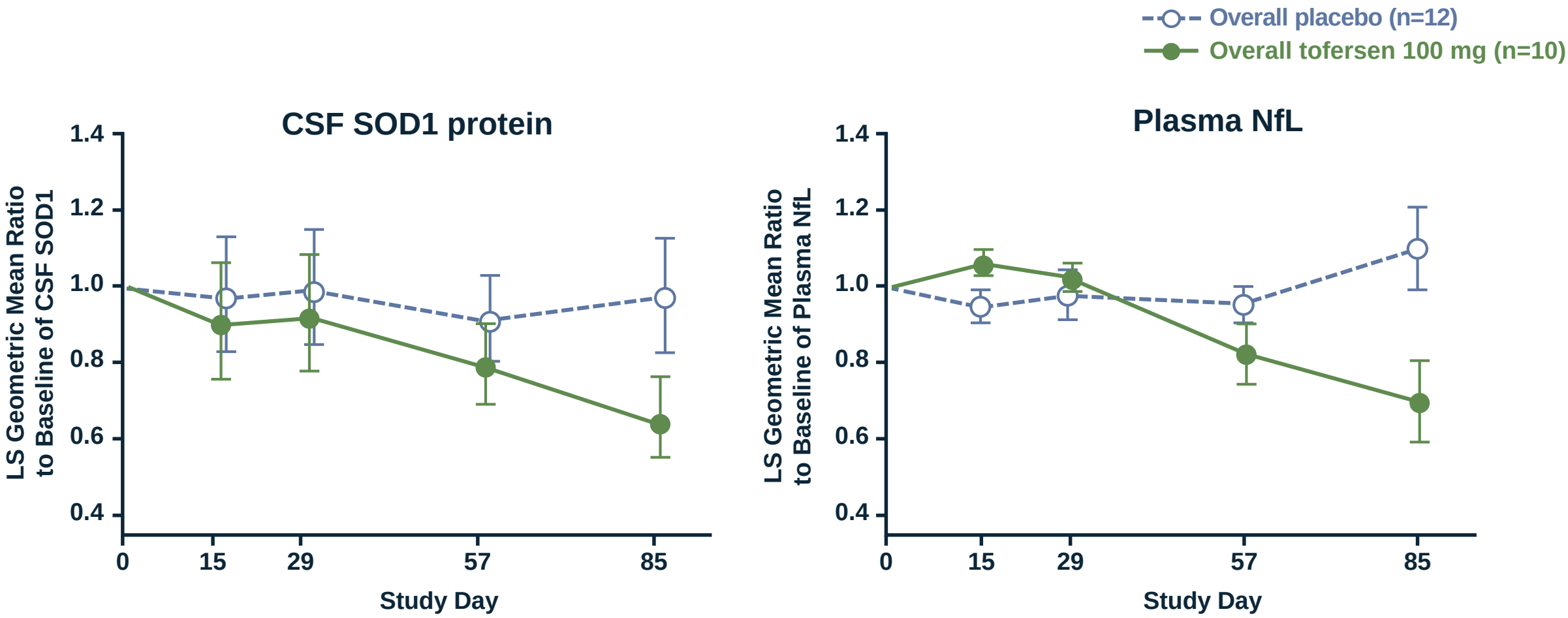
ASO, antisense oligonucleotide, RNA, ribonucleic acid; RNase H, ribonuclease H.
Based on Robberecht W, Philips T. *Nat Rev Neurosci.* 2013;14:248-264.

In *SOD1*-G93A transgenic mice, tofersen reduced NF levels, preserved motor units, and prolonged survival



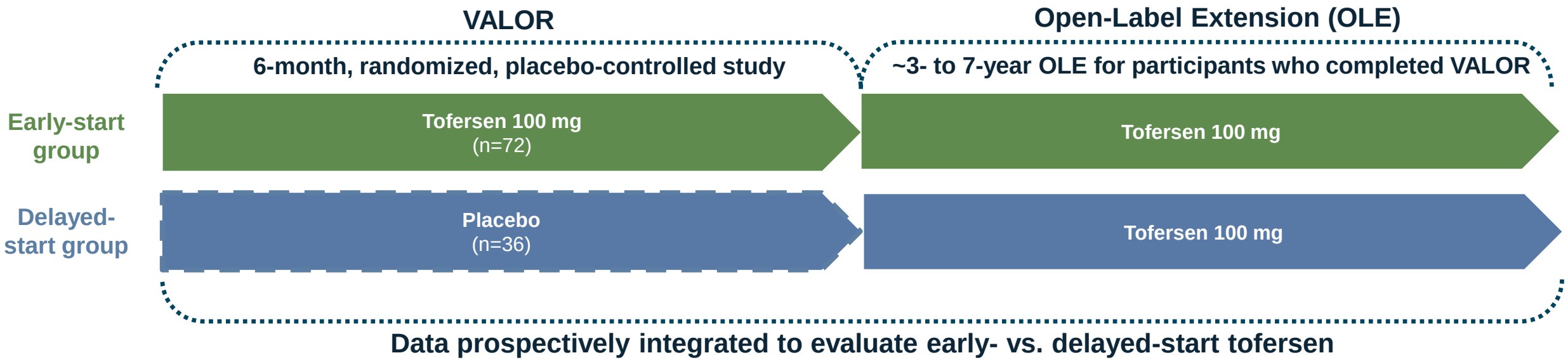
ASO, antisense oligonucleotide, i.c.v., intracerebroventricular infusion.

In the Phase 1/2 clinical study, tofersen was generally safe and found to reduce levels of CSF SOD1 and plasma NfL



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

VALOR and its Open-Label Extension were conducted to evaluate tofersen in adults with *SOD1*-ALS



Population (n=108)

- Adults with weakness attributable to ALS and a confirmed *SOD1* mutation

Primary analysis population

- Faster Progression Subgroup; "FPS (mutation/slope)" composed of n=60 participants predicted to have faster progressing disease based on *SOD1* mutation type and/or pre-randomization ALSFRS-R slope

Primary endpoint

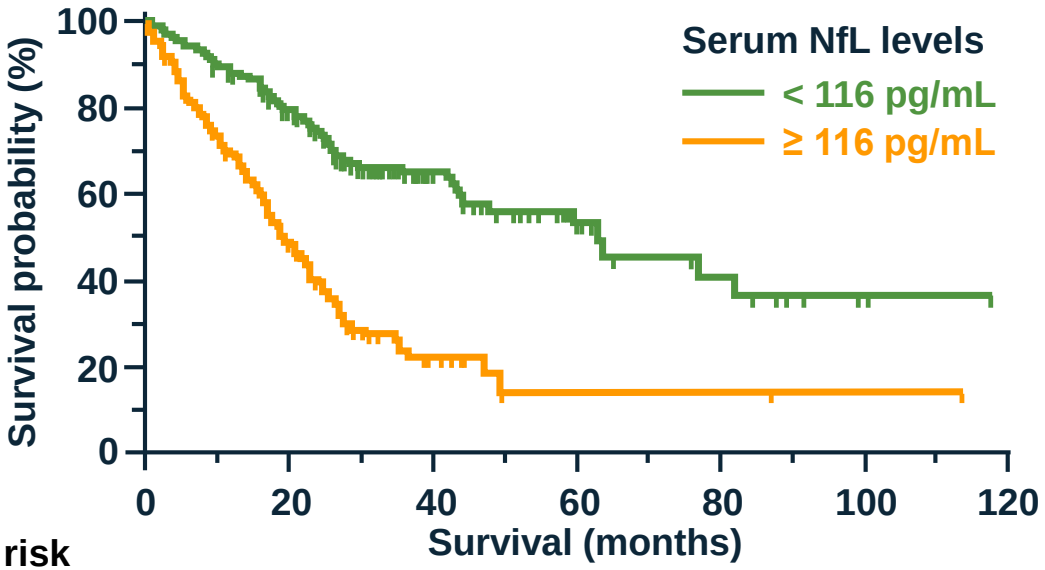
- ALSFRS-R total score

Secondary endpoints (in order of testing)

- Total SOD1 protein
- Plasma NfL
- Percent-predicted slow vital capacity (SVC)
- HHD megascore
- Ventilation assistance-free survival
- Overall survival

Baseline NfL levels were also utilized to control for disease heterogeneity

Multivariate Cox Regression Survival Curves



Number at risk

Group: < 116 pg/mL	191	134	48	16	9	2	0
Group: ≥ 116 pg/mL	191	75	13	2	2	1	0

De Schaepdryver 2020[1]

Cox Proportional Hazards Modeling

	Blood ($n = 248$)		
	HR [95% confidence interval]	*P*	Adj *P*
Age of onset	1.39 [0.96–2.02]	0.087	0.347
FVC	0.62 [0.40–0.98]	0.051	0.308
Spinal onset	1.39 [0.96–2.02]	0.087	0.347
PR	0.77 [0.38–1.57]	0.483	0.828
ALS-specific ECAS score	1.16 [0.71–1.89]	0.572	0.858
Latency from symptom onset	0.74 [0.50–1.11]	0.159	0.477
Plasma NFL	**2.99 [1.65–5.41]**	**0.001**	**0.016**
CSF NFL	–	–	–
CSF CHIT1	–	–	–
C3	1.38 [0.70–2.69]	0.367	0.735
C4	0.97 [0.50–1.88]	0.918	0.918
CRP	0.96 [0.54–1.68]	0.876	0.918
Ferritin	0.91 [0.51–1.61]	0.741	0.918
CK	0.78 [0.50–1.20]	0.268	0.644

Thompson 2022[2]

1. Reprinted from De Schaepdryver M, et al. *J Neurol Neurosurg Psychiatry.* 2020;91(4):436-437; Copyright 2020 with permission from BMJ Publishing Group Ltd.
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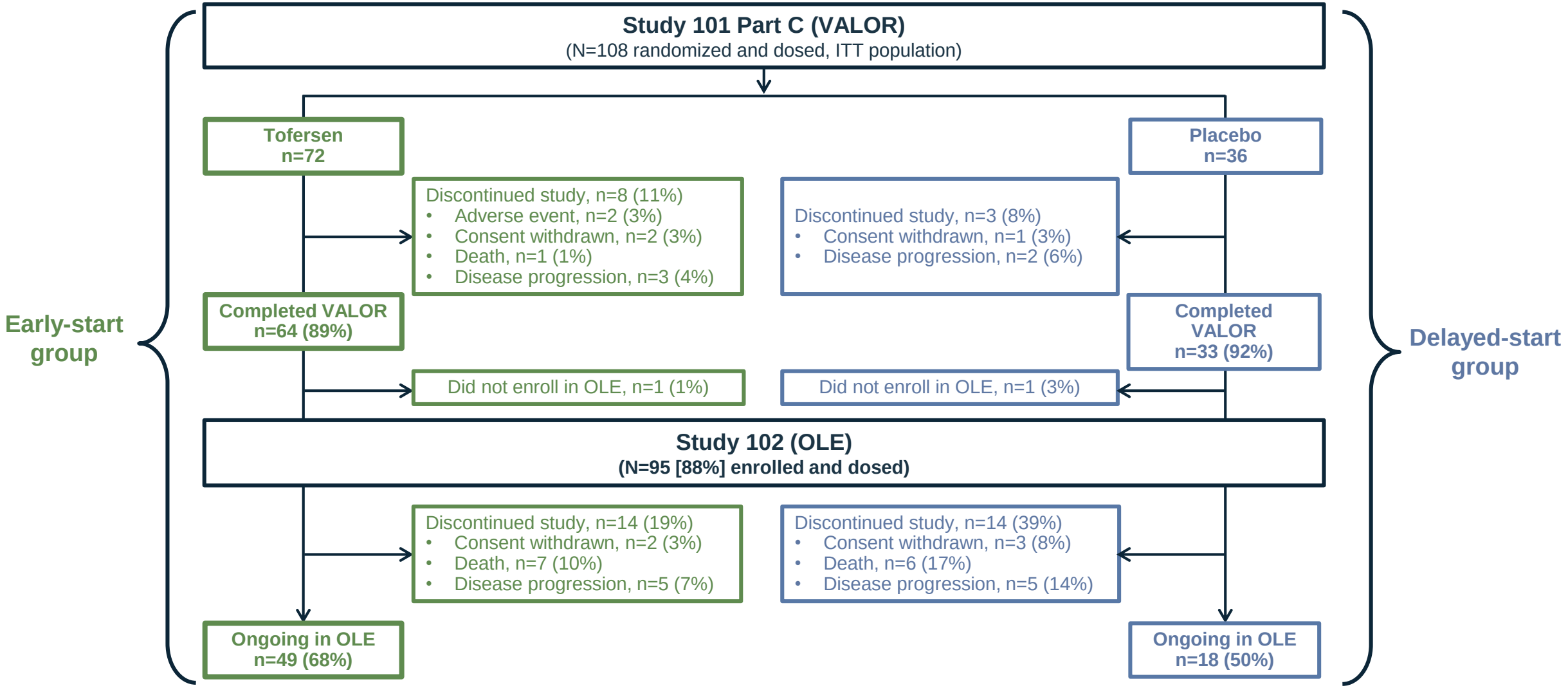
Participant disposition

Combined VALOR + OLE; ITT population



ITT, intent-to-treat; OLE, open-label extension.

Baseline demographics and disease characteristics

Combined VALOR + OLE; ITT population

	VALOR+OLE Integrated (ITT; N=108)	
	VALOR: Placebo VALOR/OLE: Delayed-start tofersen (n=36)	VALOR: Tofersen VALOR/OLE: Early-start tofersen (n=72)
Most common *SOD1* mutations		
p.Ile114Thr	10 (27.8)	10 (13.9)
p.Ala5Val	6 (16.7)	11 (15.3)
p.Gly94Cys	2 (5.6)	4 (5.6)
p.His47Arg	4 (11.1)	1 (1.4)
Riluzole use n (%)	22 (61)	45 (63)
Edaravone use n (%)	3 (8)	6 (8)
Time from symptom onset (m)		
median (Q1, Q3)	14.6 (6.6, 32.0)	11.4 (7.2, 28.9)
min, max	2.4, 103.2	1.7, 145.7
% predicted SVC at baseline		
mean (SD)	85.1 (16.5)	82.1 (16.6)
min, max	54.8, 120.4	46.7, 134.7
ALSFRS-R baseline total score		
mean (SD)	37.3 (5.8)	36.9 (5.9)
min, max	24, 47	15, 48
ALSFRS-R pre-randomization slope		
mean (SD)	–1.2 (1.2)	–1.1 (1.4)
min, max	–4.9, –0.02	–8.3, 0.0
ALSFRS-R run-in slope		
mean (SD)	–0.7 (3.3)	–1.0 (2.2)
min, max	–11, 10	–9, 4
Plasma NfL (pg/mL)		
mean (SD)	89.7 (86.5)	100.4 (82.8)
median (min, max)	64.6 (8, 370)	78.5 (5, 329)

ALSFRS-R, ALS Functional Rating Scale-Revised; ITT, intent-to-treat; OLE, open-label extension; SOD1, superoxide dismutase-1; SVC, slow vital capacity.

Baseline demographics and disease characteristics

Combined VALOR + OLE; FPS and SPS (mutation/slope)

	VALOR + OLE Integrated (FPS (mutation/slope); N=60)		VALOR + OLE Integrated (SPS (mutation/slope); N=48)	
	VALOR: Placebo Integrated: Delayed-start tofersen (n=21)	VALOR: Tofersen Integrated: Early-start tofersen (n=39)	VALOR: Placebo Integrated: Delayed-start tofersen (n=15)	VALOR: Tofersen Integrated: Early-start tofersen (n=33)
ALSFRS-R run-in slope				
mean (SD)	–1.3 (3.91)	–1.8 (2.47)	0.1 (1.87)	–0.1 (1.34)
min, max	–11, 10	–9, 3	–3, 4	–3, 4
Plasma NfL (pg/mL)				
mean (SD)	127.3 (94.40)	146.2 (82.63)	37.0 (29.51)	47.6 (41.80)
median (min, max)	110.8 (9, 370)	129.7 (12, 329)	26.8 (8, 99)	41.7 (5, 211)

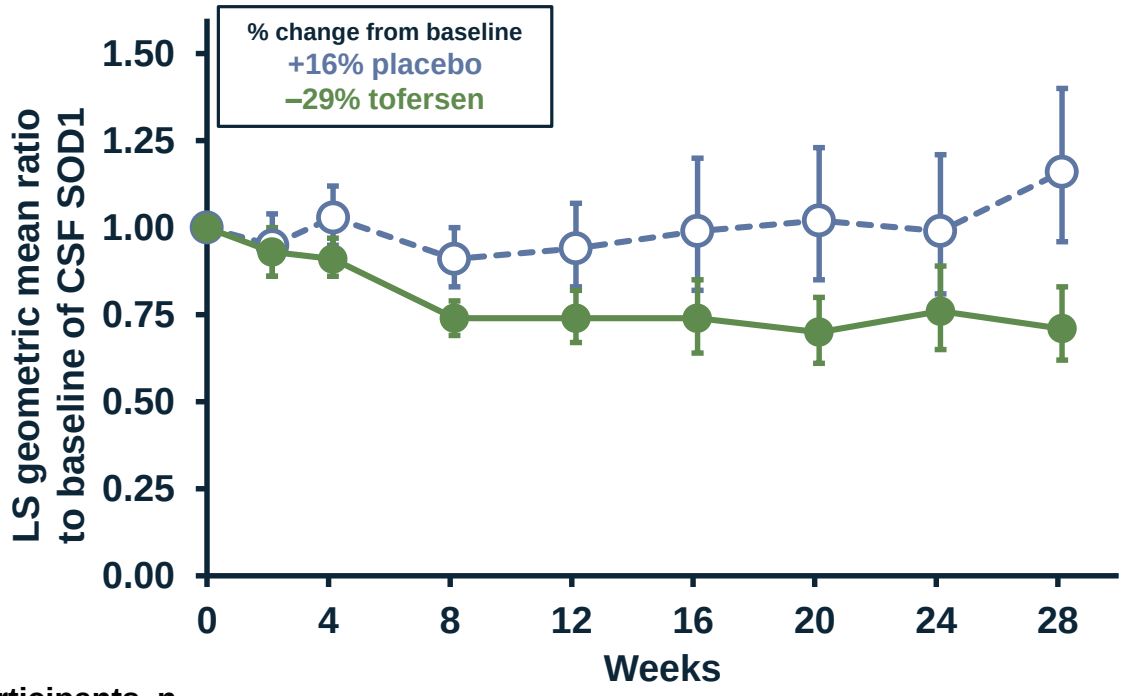
ALSFRS-R, ALS Functional Rating Scale-Revised; ITT, intent-to-treat; NfL, neurofilament light; OLE, open-label extension; SOD1, superoxide dismutase-1; SVC, slow vital capacity.

Tofersen reduced levels of CSF SOD1 and plasma NfL

VALOR, FPS (mutation/slope)

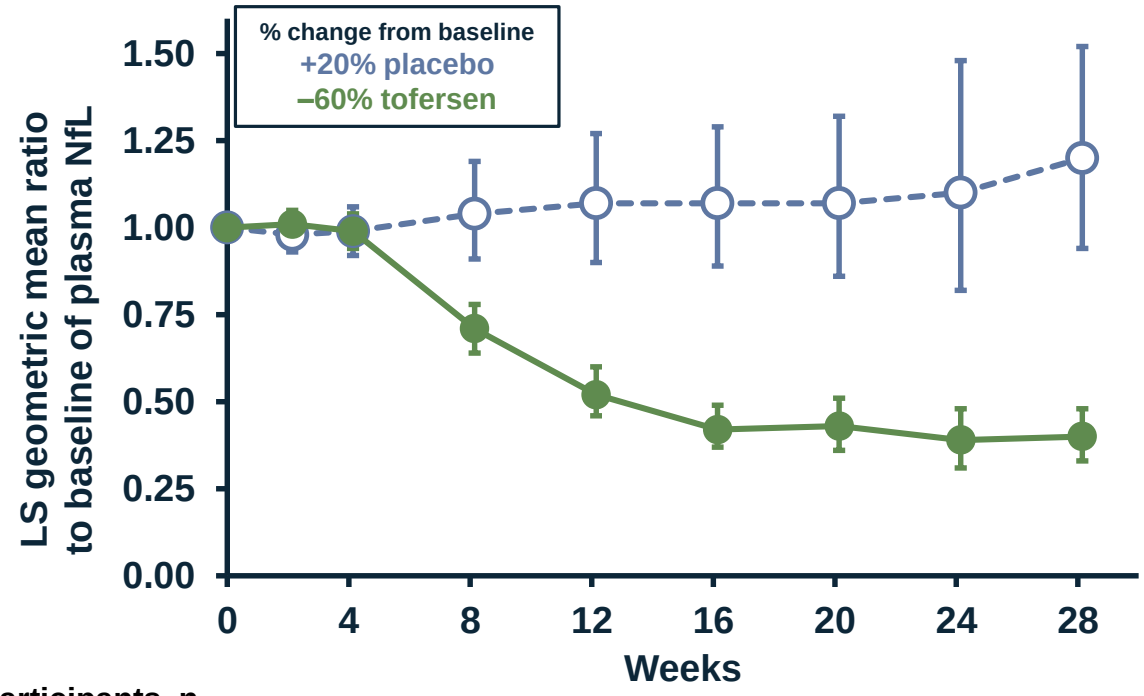
Placebo
Tofersen

Total SOD1 protein in CSF



Participants, n								
Placebo	21	20	18	21	19	19	19	17
Tofersen	38	37	34	33	34	32	32	31

Plasma NfL

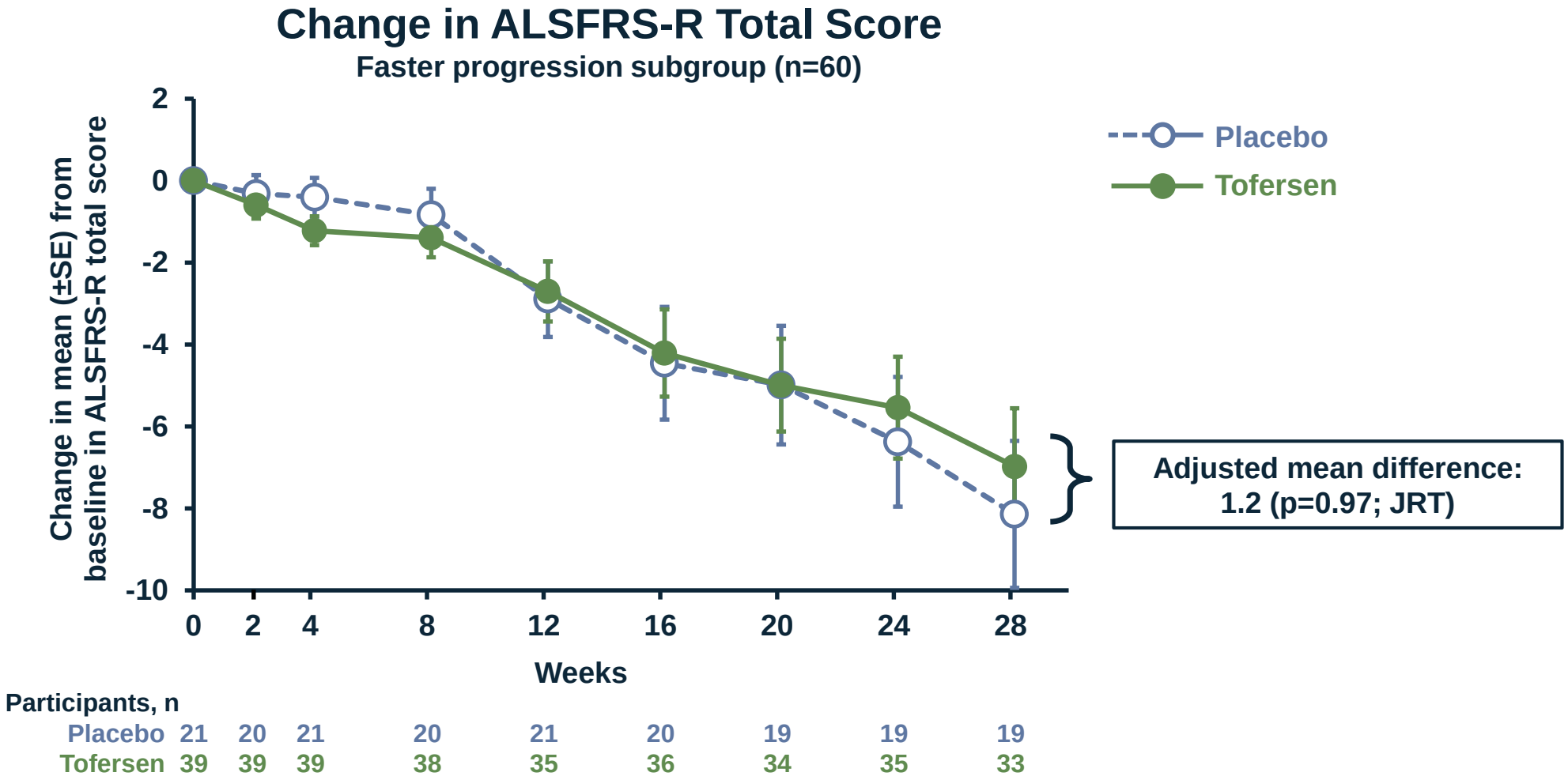


Participants, n								
Placebo	21	20	17	20	19	19	18	17
Tofersen	38	37	34	32	33	32	34	27

CSF, cerebrospinal fluid; FPS, faster progression subgroup; NfL, neurofilament light; SOD1, superoxide dismutase-1.

Statistical significance was not achieved on the primary analysis in VALOR

VALOR, FPS (mutation/slope)



Trends favoring tofersen observed across secondary and exploratory analyses

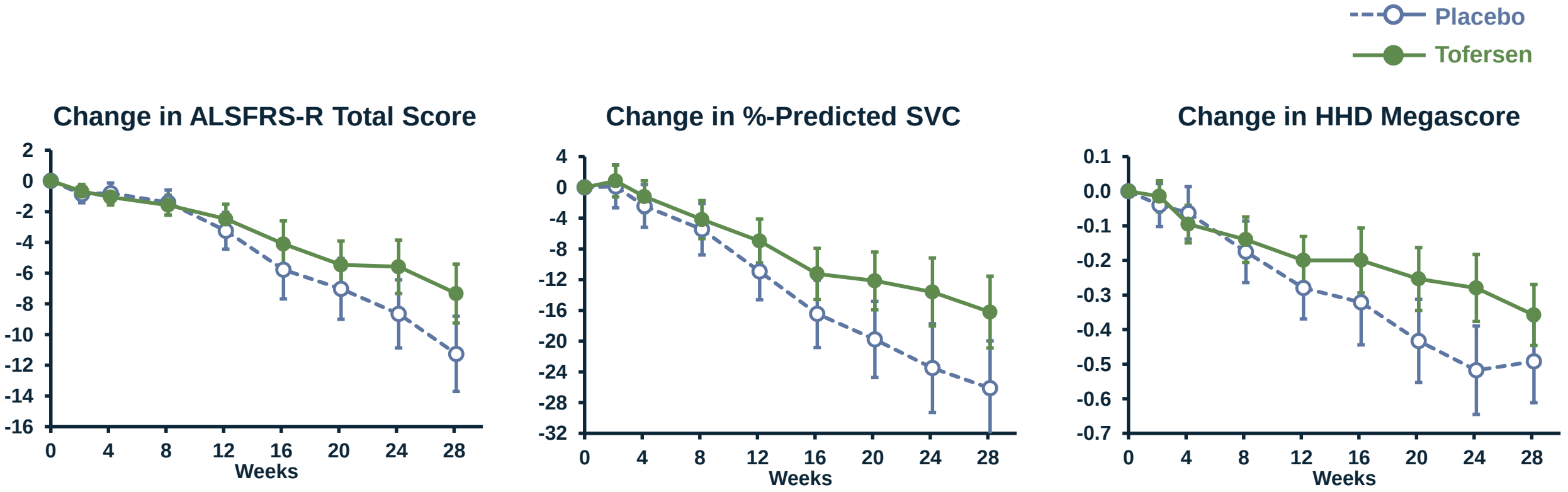
VALOR, FPS (mutation/slope) & SPS (mutation/slope)

Key secondary endpoints	Analysis population	Placebo	Tofersen	Absolute difference
CSF SOD1 protein *% change from baseline in geometric mean*	FPS (mutation/slope)	16% increase	29% reduction	45% (p<0.0001*)
	SPS (mutation/slope)	19% reduction	40% reduction	21% (p=0.0007*)
Plasma NfL *% change from baseline in geometric mean*	FPS (mutation/slope)	20% increase	60% reduction	80% (p<0.0001*)
%-Predicted Slow Vital Capacity *Adjusted mean (±SE) change from baseline*	FPS (mutation/slope)	–22.2%-predicted	–14.3%-predicted	7.9 (p=0.32; JRT)
HHD Megascore *Adjusted mean (±SE) change from baseline*	FPS (mutation/slope)	–0.37	–0.34	0.02 (p=0.84; ANCOVA)
Event-free survival *Median time to death or PV*	FPS (mutation/slope)	Median not reached in either group due to limited number of events		
Overall survival *Median time to death*	FPS (mutation/slope)	Median not reached in either group due to limited number of events		

*Nominal p value due to lack of statistical significance on the primary analysis.

Greater differentiation observed in faster progression subgroup defined by baseline plasma NfL levels

VALOR, FPS (NF-based)



Difference: 3.9 (95% CI: –1.00, 8.86)

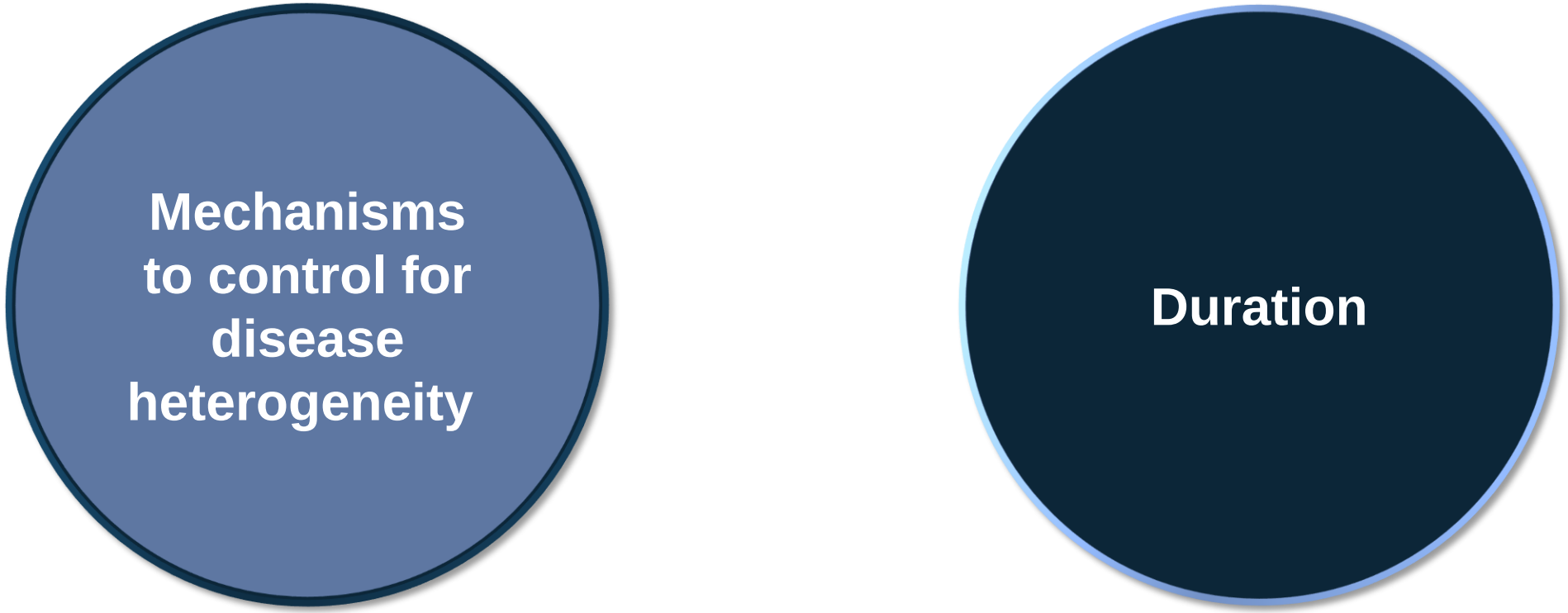
Difference: 9.91 (95% CI: –2.27, 22.09)

Difference: 0.13 (95% CI: –0.11, 0.37)

* Median plasma NfL = 75.6 pg/mL.

ALSFRS-R, ALS Functional Rating Scale-Revised; FPS, faster progression group; HHD, handheld dynamometry; NfL, neurofilament light; SVC, slow vital capacity.

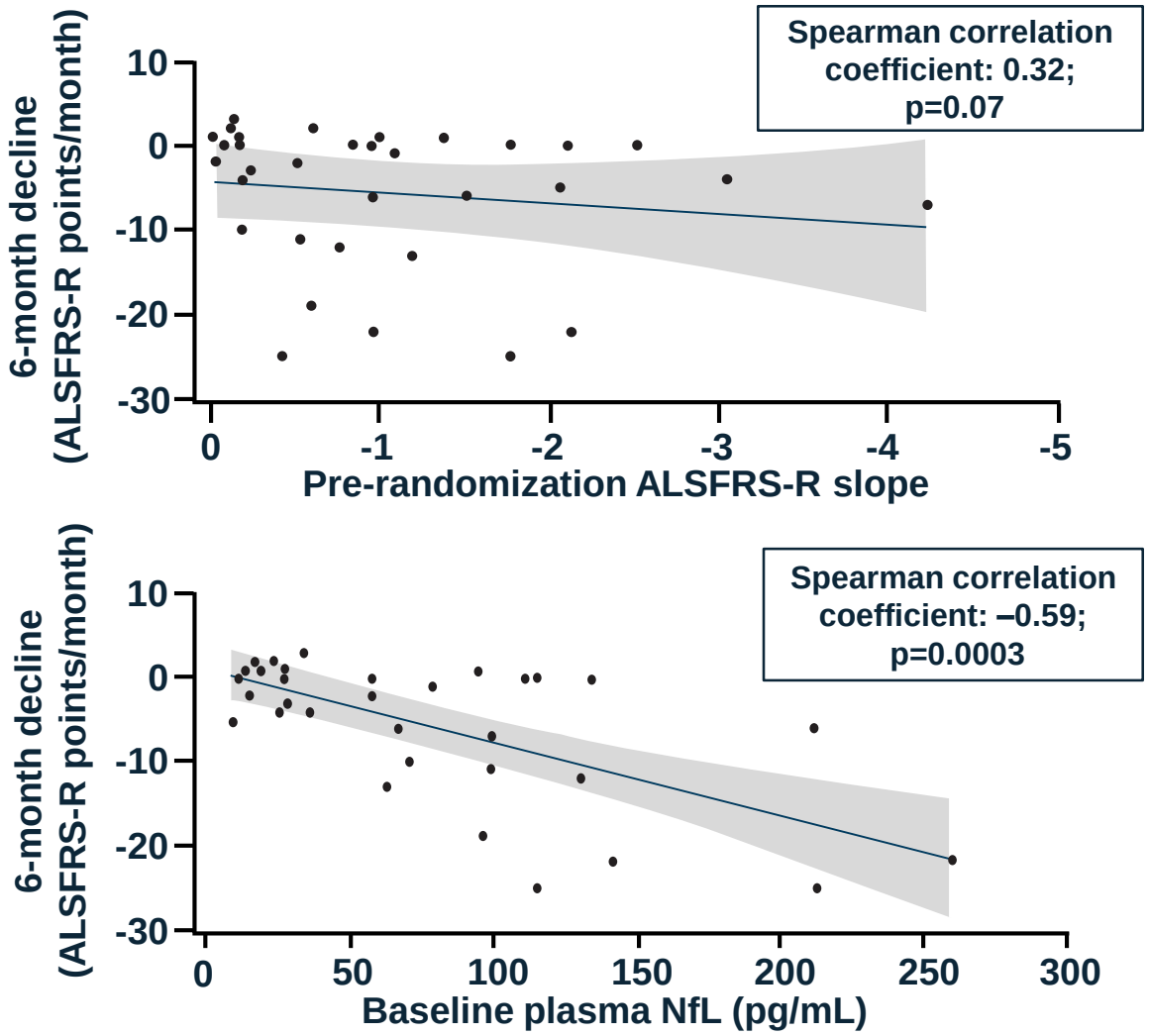
Factors affecting the primary analysis



Factors affecting the primary analysis

Mechanisms to control for disease heterogeneity

Correlation Between Key Baseline Characteristics and Change in ALSFRS-R in VALOR Placebo Participants



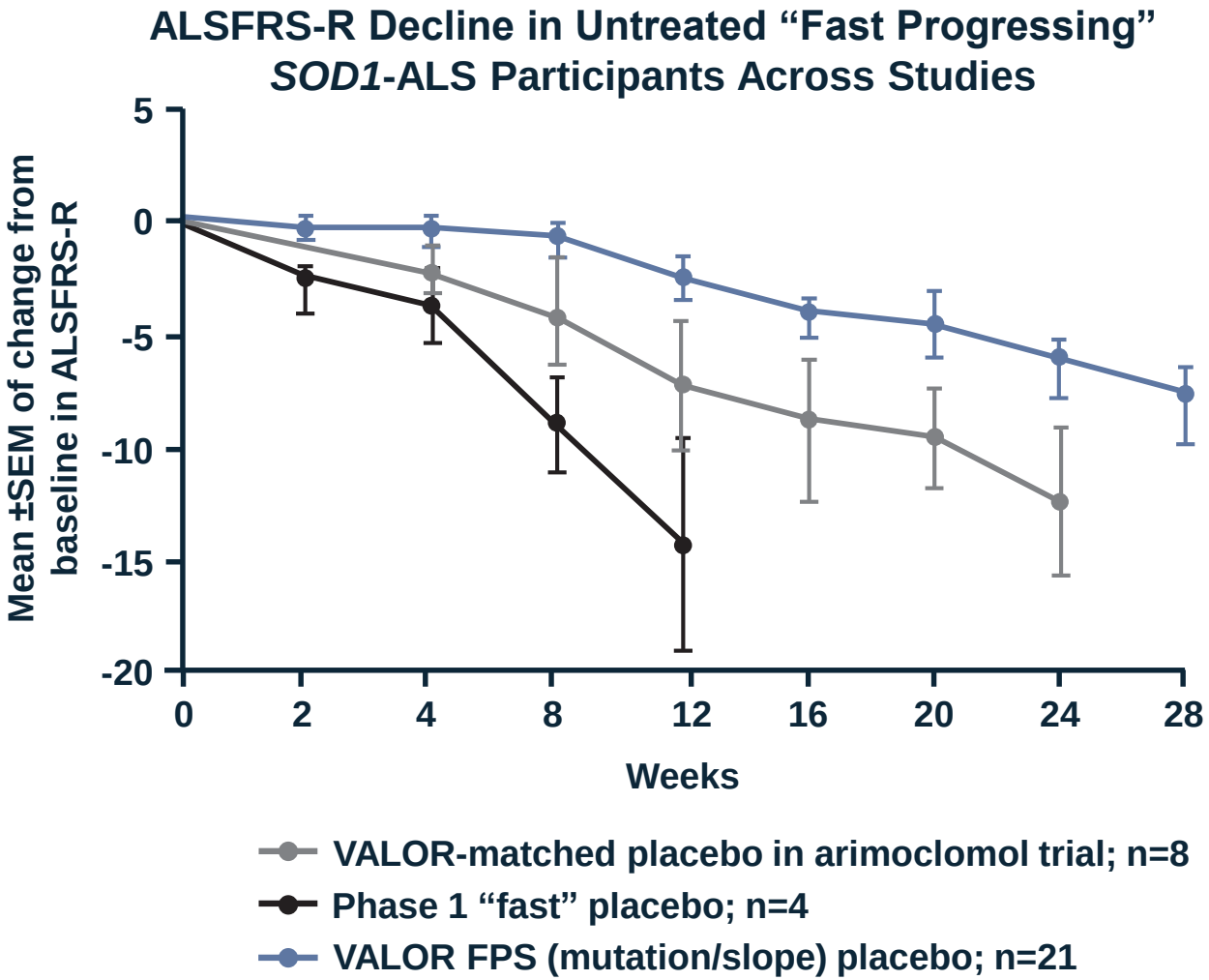
Baseline neurofilament levels can be used to control for disease heterogeneity

- Supported by robust ALS literature
- Superior to historical approaches to enrich with clinical features (diagnostic stage, disease duration, ALSFRS-R slope, mutation type, SVC)
- Incorporation of baseline NfL as a covariate more precisely controls for individual disease progression than categorical subgrouping of the population

ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS Functional Rating Scale-Revised; HHD, handheld dynamometry; NfL, neurofilament light; SVC, slow vital capacity.

Factors affecting the primary analysis

Duration

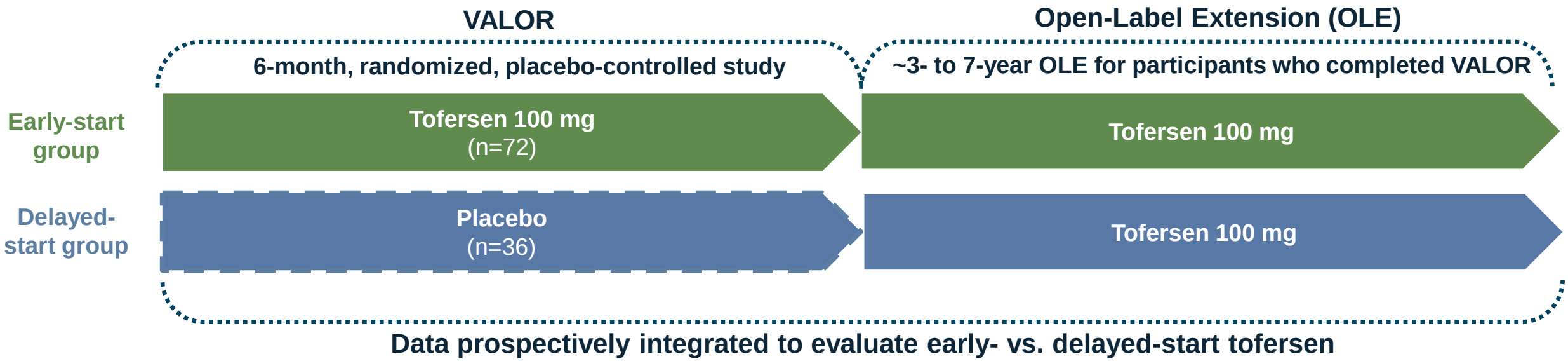


Longer study duration (> 6 months) needed to:

- Reliably detect a decline in the control arm
- Account for potential deaths unrelated to disease progression/study treatment
- Allow sufficient time for biological activity to translate to clinical benefit

ALSFRS-R, ALS Functional Rating Scale-Revised; FPS, faster progression subgroup; SOD1, superoxide dismutase-1.

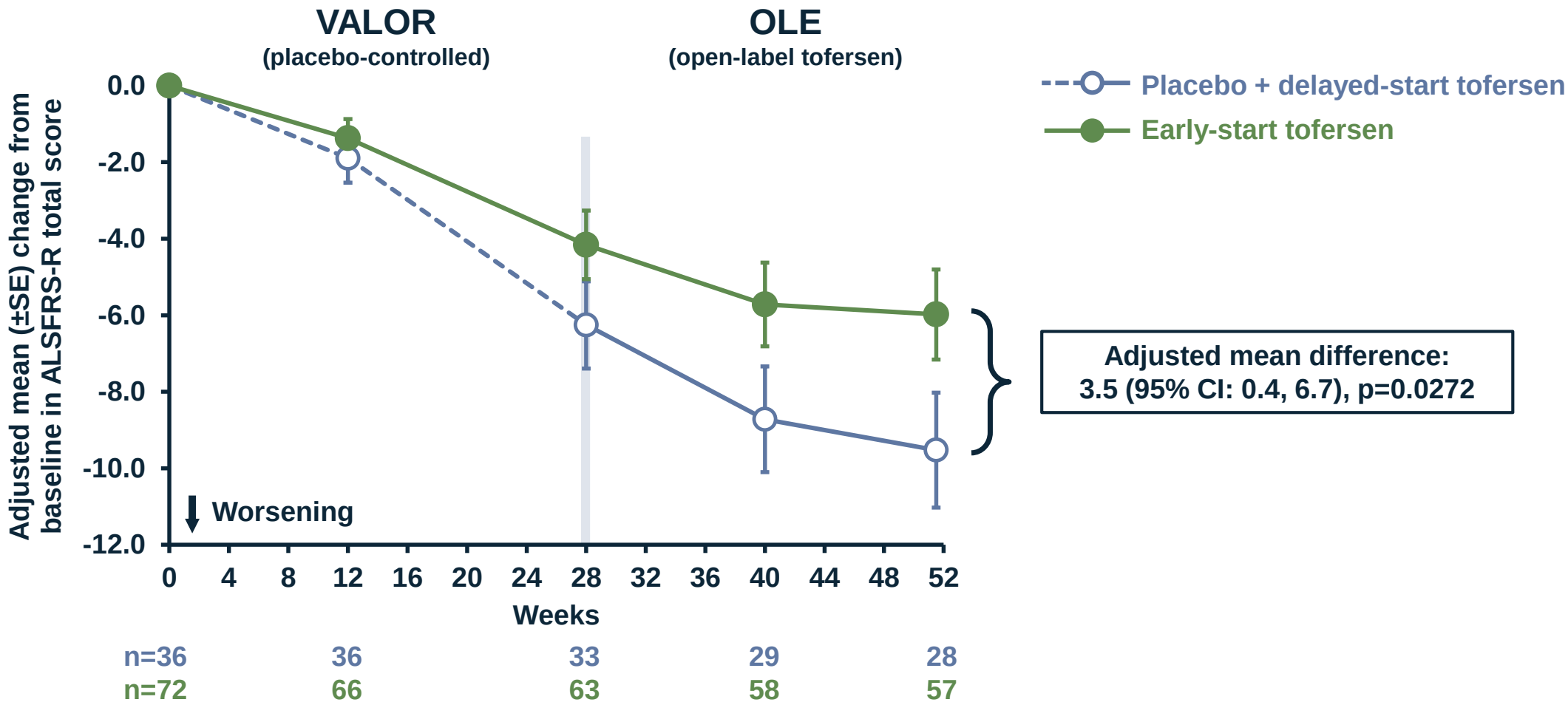
Integrated VALOR + OLE analyses



To preserve the integrity of ongoing data collection, participants, site staff, and the Biogen study team remain blinded to VALOR treatment assignments through completion of the OLE

Effect on clinical function (ALSFRS-R)

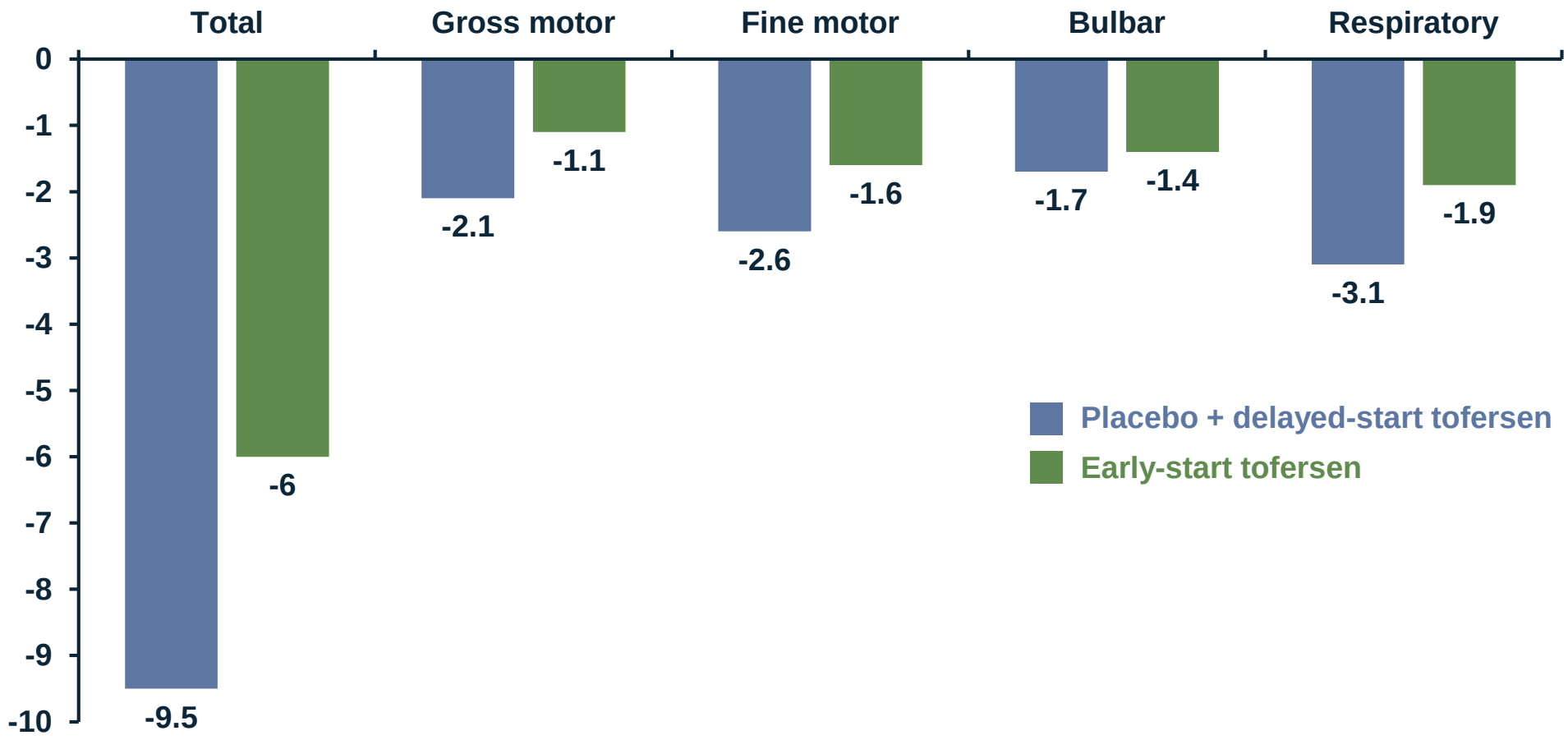
Combined VALOR + OLE; ITT population



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 ALSFRS-R domains

Combined VALOR + OLE; ITT population

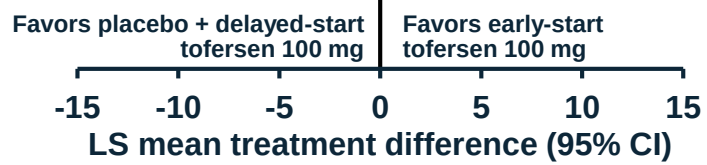


Adjusted mean difference (95% CI)	3.5 (0.4 to 6.7)	1.0 (0.1, 1.8)	1.0 (0.1, 2.0)	0.3 (–0.7, 1.3)	1.2 (–0.1, 2.6)

ALSFRS-R covariate forest plot

Combined VALOR + OLE; ITT population; Week 52

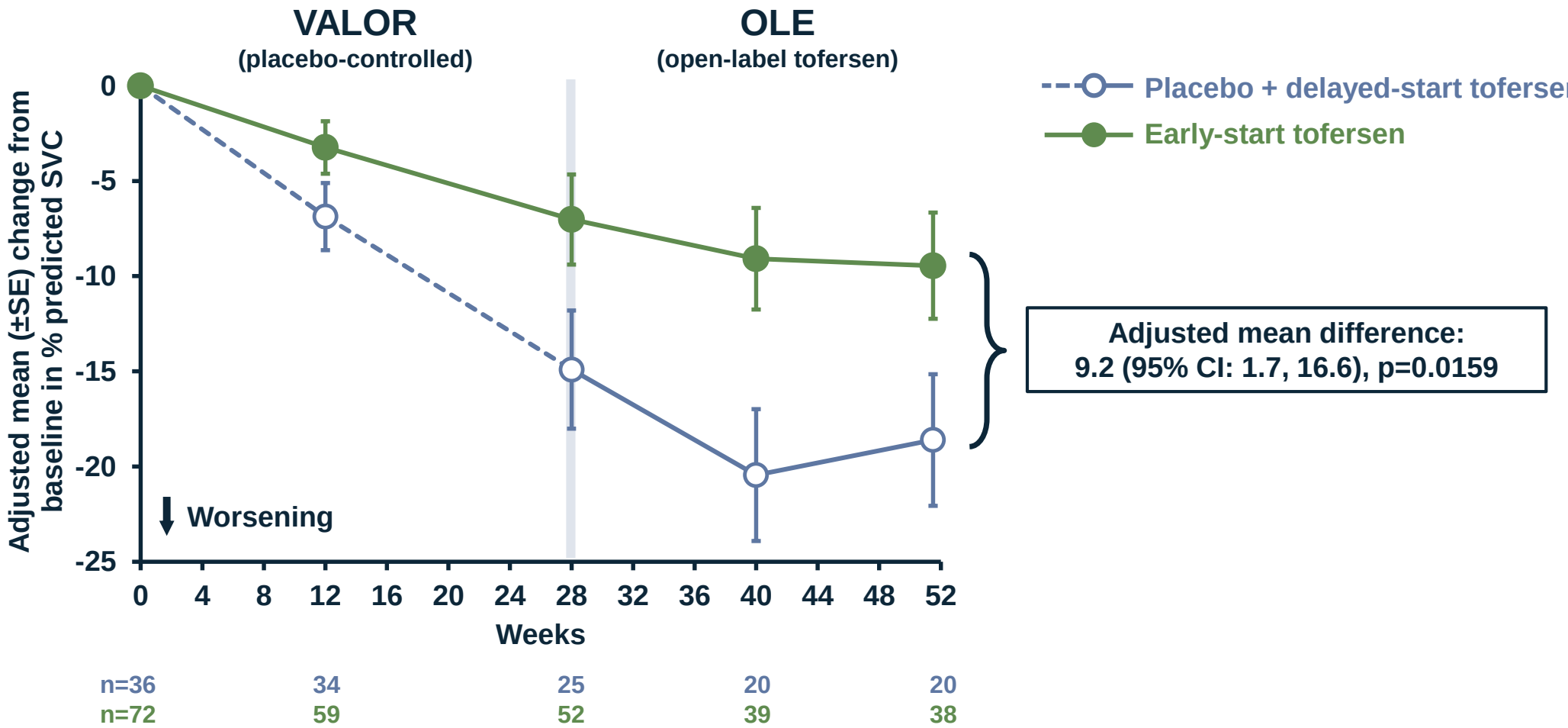
Population/ Subgroup	Covariate adjustment for baseline disease characteristics	Placebo+ delayed-start Tofersen, n	Early-start Tofersen, n	LSM Diff	95% CI	ANCOVA+MI p value
ITT	Baseline plasma NfL	36	72	3.5	(0.40, 6.69)	0.0272
	Disease duration	36	72	2.3	(-1.26, 5.82)	0.2073
	ALSFRS-R pre-randomization slope	36	72	2.2	(-1.49, 5.91)	0.2413
	ALSFRS-R pre-randomization slope + baseline plasma NfL	36	72	3.4	(0.30, 6.52)	0.0316
	Disease duration + baseline plasma NfL	36	72	3.2	(0.16, 6.34)	0.0394
	Unadjusted for baseline disease characteristics	36	72	2.5	(-1.31, 6.23)	0.2004
FPS (mutation/slope)	Baseline plasma NfL	21	39	3.9	(-1.50, 9.32)	0.1564
	Disease duration	21	39	2.6	(-2.89, 8.12)	0.3521
	Disease duration + baseline plasma NfL	21	39	3.6	(-1.70, 8.87)	0.1831
SPS (mutation/slope)	Baseline plasma NfL	15	33	3.0	(-0.05, 6.00)	0.0540
	Disease duration	15	33	2.6	(-0.69, 5.99)	0.1203
	Disease duration + baseline plasma NfL	15	33	3.0	(-0.02, 6.04)	0.0512
FPS (NF-based)	Baseline plasma NfL	16	38	6.5	(0.68,12.24)	0.0286
	Disease duration	16	38	5.7	(-0.36,11.76)	0.0655
	Disease duration + baseline plasma NfL	16	38	6.3	(0.53, 12.05)	0.0324
SPS (NF-based)	Baseline plasma NfL	20	34	1.7	(-0.88, 4.20)	0.2000
	Disease duration	20	34	1.2	(-1.66, 4.07)	0.4086
	Disease duration + baseline plasma NfL	20	34	1.4	(-1.13, 4.03)	0.2707



ALSFRS-R, ALS Functional Rating Scale-Revised; ANCOVA, analysis of covariance; ES, early-start tofersen 100 mg; FPS, faster progression subgroup; ITT, intent-to-treat; LSM, least square mean; MI, multiple imputation; NfL, neurofilament light; OLE, open label extension; P+DS, placebo + delayed-start tofersen 100 mg; SPS, slower progression subgroup.

Effect on respiratory strength (SVC)

Combined VALOR + OLE; ITT population

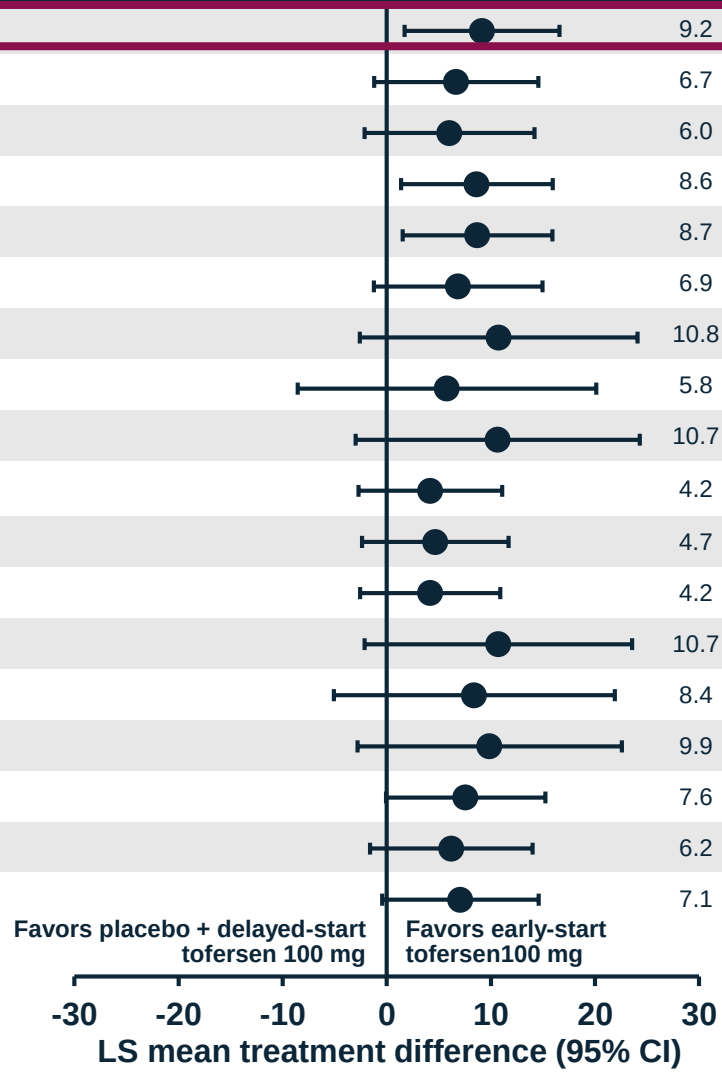


OLE, open-label extension; SVC, slow vital capacity.
Analysis is based on ANCOVA model in conjunction with multiple imputation for missing data. The model includes covariates for the corresponding baseline value, baseline plasma NfL, and use of riluzole or edaravone.

SVC covariate forest plot

Combined VALOR + OLE; Week 52

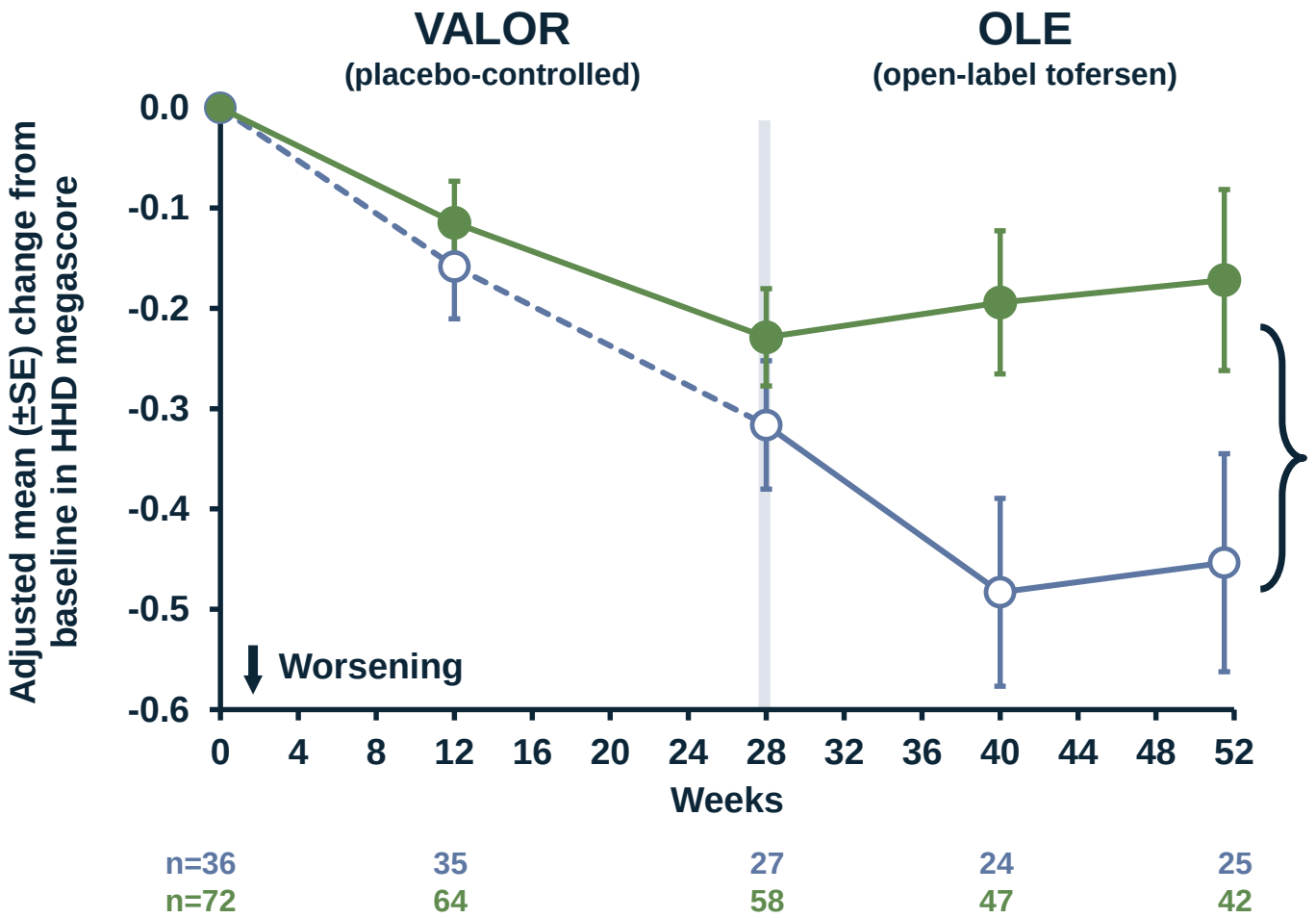
Population/ Subgroup	Covariate adjustment for baseline disease characteristics	Placebo+ delayed-start Tofersen, n	Early-start Tofersen, n	LSM Diff	95% CI	ANCOVA+ MI p value
ITT	Baseline plasma NfL	36	72	9.2	(1.72, 16.60)	0.0159
	Disease duration	36	72	6.7	(-1.21, 14.55)	0.0971
	ALSFRS-R pre-randomization slope	36	72	6.0	(-2.14, 14.19)	0.1483
	ALSFRS-R pre-randomization slope + baseline plasma NfL	36	72	8.6	(1.36, 15.94)	0.0201
	Disease duration + baseline plasma NfL	36	72	8.7	(1.52, 15.91)	0.0176
	Unadjusted for baseline disease characteristics	36	72	6.9	(-1.23, 14.96)	0.0965
FPS (mutation/slope)	Baseline plasma NfL	21	39	10.8	(-2.59, 24.10)	0.1139
	Disease duration	21	39	5.8	(-8.57, 20.11)	0.4297
	Disease duration + baseline plasma NfL	21	39	10.7	(-2.99, 24.31)	0.1257
SPS (mutation/slope)	Baseline plasma NfL	15	33	4.2	(-2.73, 11.08)	0.2354
	Disease duration	15	33	4.7	(-2.38, 11.71)	0.1940
	Disease duration + baseline plasma NfL	15	33	4.2	(-2.58, 10.91)	0.2256
FPS (NF-based)	Baseline plasma NfL	16	38	10.7	(-2.13, 23.56)	0.1019
	Disease duration	16	38	8.4	(-5.10, 21.90)	0.2223
	Disease duration + baseline plasma NfL	16	38	9.9	(-2.81, 22.58)	0.1269
SPS (NF-based)	Baseline plasma NfL	20	34	7.6	(-0.08, 15.23)	0.0525
	Disease duration	20	34	6.2	(-1.60. 14.02)	0.1192
	Disease duration + baseline plasma NfL	20	34	7.1	(-0.45, 14.60)	0.0652



ALSFRS-R, ALS Functional Rating Scale-Revised; ANCOVA, analysis of covariance; ES, early-start tofersen 100 mg; FPS, faster progression subgroup; ITT, intent-to-treat; LSM, least square mean; MI, multiple imputation; NfL, neurofilament light; OLE, open label extension; P+DS, placebo + delayed-start tofersen 100 mg; SPS, slower progression subgroup; SVC, slow vital capacity.

Effect on muscle strength (HHD megascore)

Combined VALOR + OLE; ITT population



Placebo + delayed-start tofersen

Early-start tofersen

Adjusted mean difference:
0.28 (95% CI: 0.05, 0.52)
p=0.0186

Improvement in HHD megascore from baseline to Week 52:

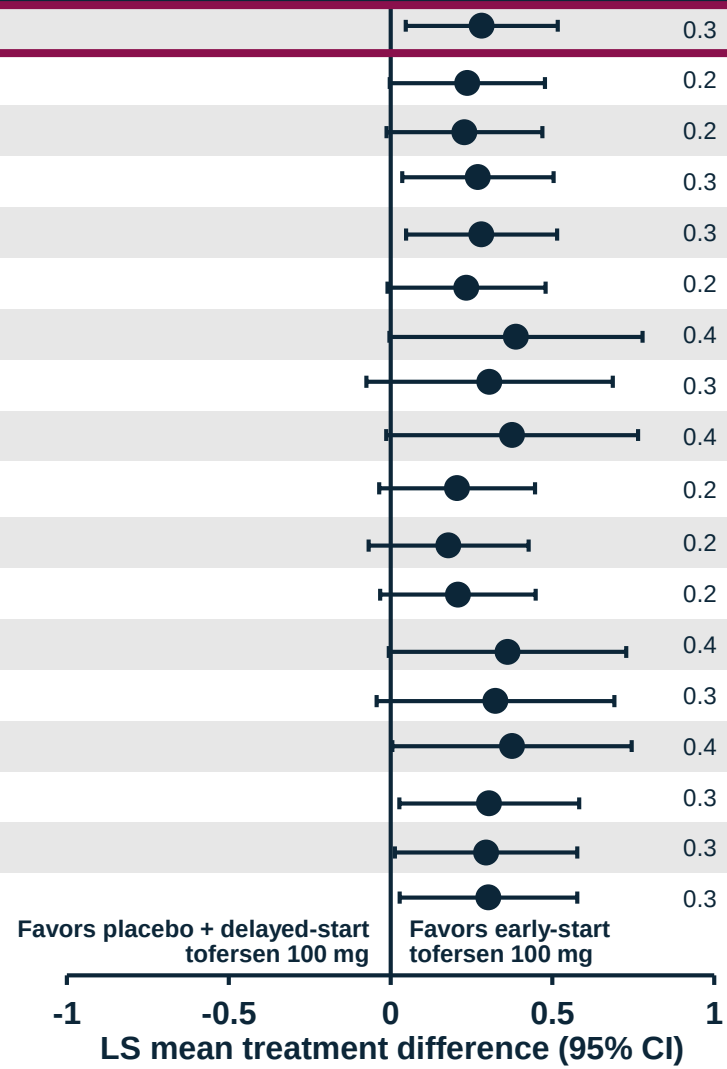
Delayed-start tofersen: 8.1%
Early-start tofersen: 26.9%
Difference: 18.8% (95% CI: 1.4, 36.2)

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.

HHD megascore covariate forest plot

Combined VALOR + OLE; Week 52

Population/ Subgroup	Covariate adjustment for baseline disease characteristics	Placebo+ delayed-start Tofersen, n	Early-start Tofersen, n	LSM Diff	95% CI	ANCOVA+ MI p value
ITT	Baseline plasma NfL	36	72	0.3	(0.05, 0.52)	0.0186
	Disease duration	36	72	0.2	(0.00, 0.48)	0.0529
	ALSFRS-R pre-randomization slope	36	72	0.2	(-0.01, 0.47)	0.0624
	ALSFRS-R pre-randomization slope + baseline plasma NfL	36	72	0.3	(0.04, 0.50)	0.0235
	Disease duration + baseline plasma NfL	36	72	0.3	(0.05, 0.51)	0.0183
	Unadjusted for baseline disease characteristics	36	72	0.2	(-0.01, 0.48)	0.0596
FPS (mutation/slope)	Baseline plasma NfL	21	39	0.4	(0.00, 0.78)	0.0522
	Disease duration	21	39	0.3	(-0.07, 0.69)	0.1152
	Disease duration + baseline plasma NfL	21	39	0.4	(-0.01, 0.76)	0.0586
SPS (mutation/slope)	Baseline plasma NfL	15	33	0.2	(-0.04, 0.45)	0.0946
	Disease duration	15	33	0.2	(-0.07, 0.43)	0.1545
	Disease duration + baseline plasma NfL	15	33	0.2	(-0.03, 0 45)	0.0894
FPS (NF-based)	Baseline plasma NfL	16	38	0.4	(-0.01, 0.73)	0.0534
	Disease duration	16	38	0.3	(-0.04, 0.69)	0.0833
	Disease duration + baseline plasma NfL	16	38	0.4	(0.01, 0.74)	0.0465
SPS (NF-based)	Baseline plasma NfL	20	34	0.3	(0.03, 0.58)	0.0313
	Disease duration	20	34	0.3	(0.01, 0.58)	0.0398
	Disease duration + baseline plasma NfL	20	34	0.3	(0.03, 0.58)	0.0306



ALSFRS-R, ALS Functional Rating Scale-Revised; ANCOVA, analysis of covariance; ES, early-start tofersen 100 mg; FPS, faster progression subgroup; ITT, intent-to-treat; LSM, least square mean; MI, multiple imputation; NfL, neurofilament light; OLE, open label extension; P+DS, placebo + delayed-start tofersen 100 mg; SPS, slower progression subgroup; SVC, slow vital capacity.

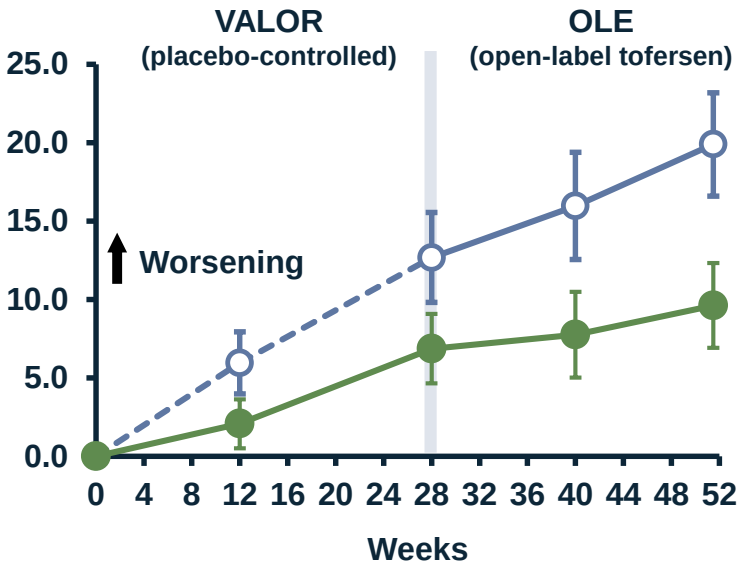
Effect on patient-reported outcome measures

Combined VALOR + OLE; ITT population

Placebo + delayed-start tofersen

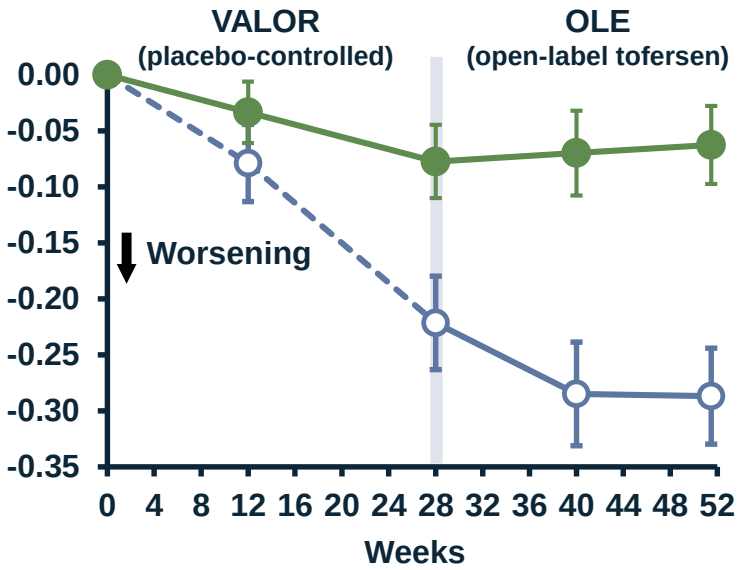
Early-start tofersen

Change in ALSAQ-5



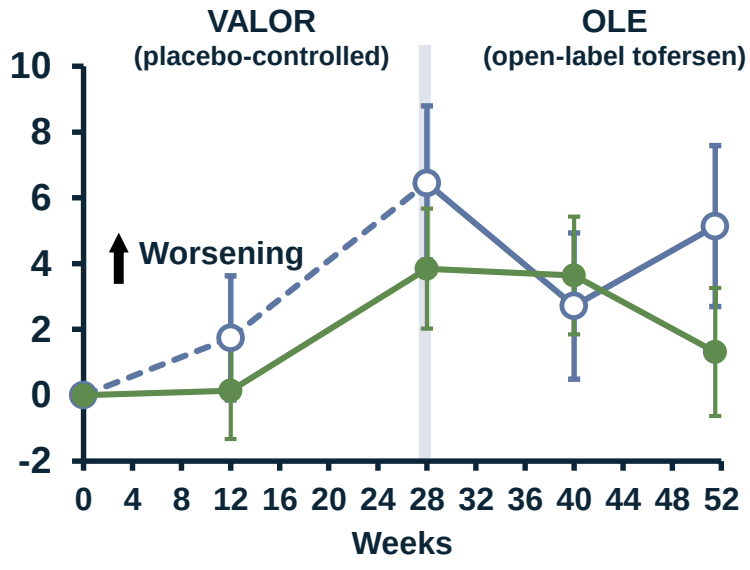
Difference: –10.3 (95% CI: –17.3, –3.2)
p=0.0044

Change in EQ-5D-5L Utility Score



Difference: 0.2 (95% CI: 0.13, 0.32)
p<0.0001

Change in Fatigue Severity Scale



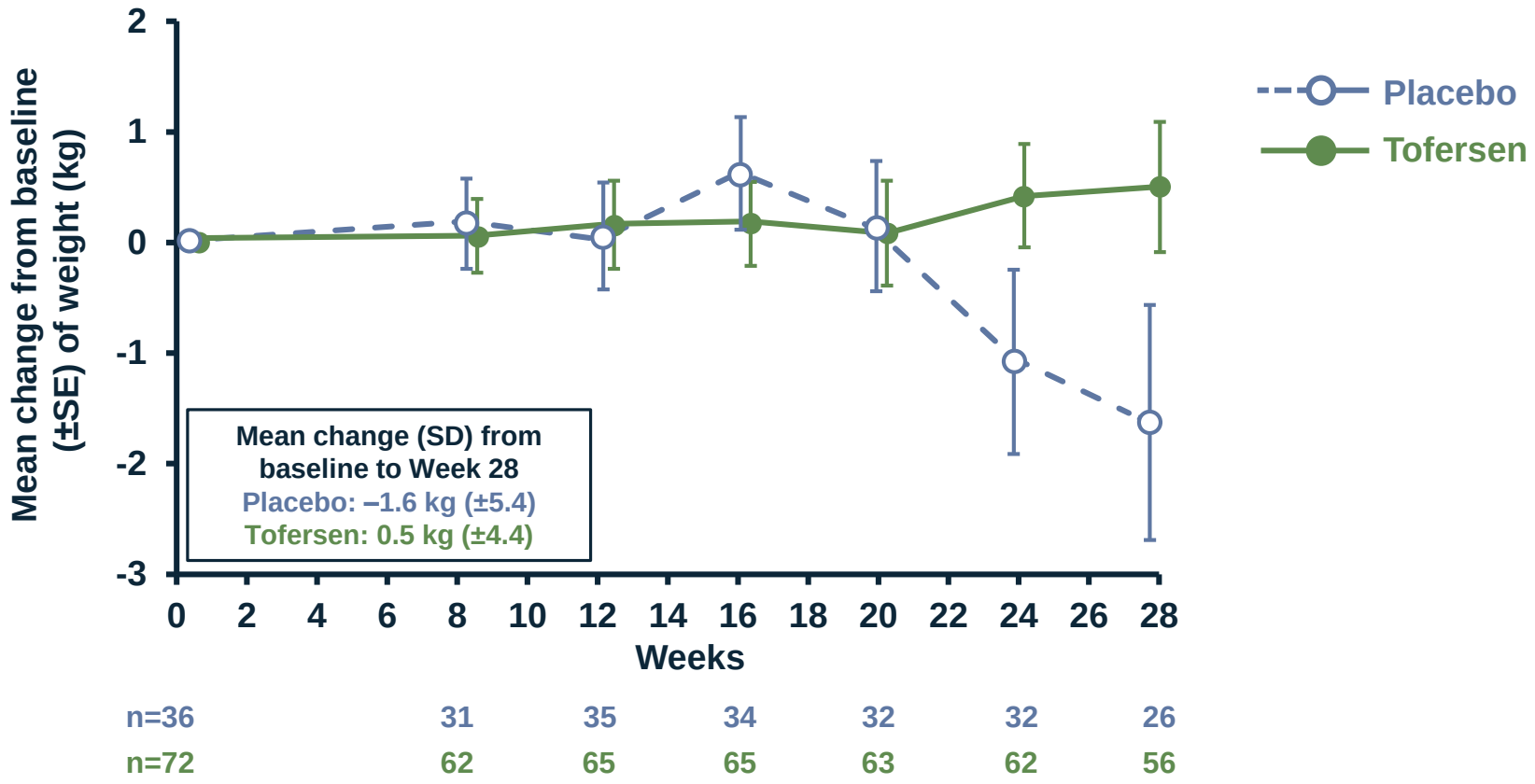
Difference: –3.8 (95% CI: –9.0, 1.38)
p=0.1493

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.

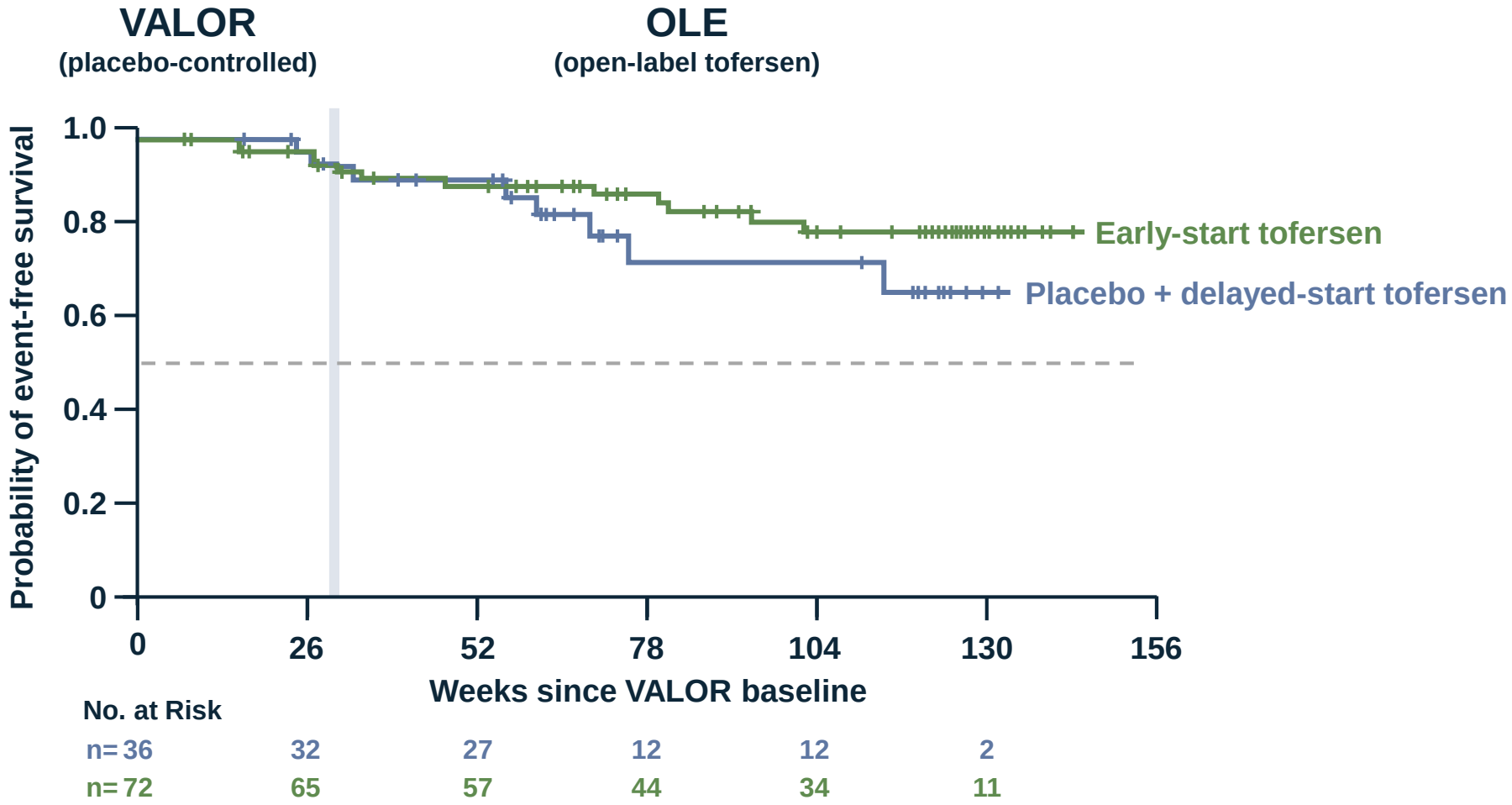
Effect on body weight

VALOR; ITT population



Time-to-event analysis for death or permanent ventilation

Combined VALOR + OLE; ITT population



OLE, open-label extension; PV, permanent ventilation.
Time to death or permanent ventilation is defined as the 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.

Time-to-event analyses

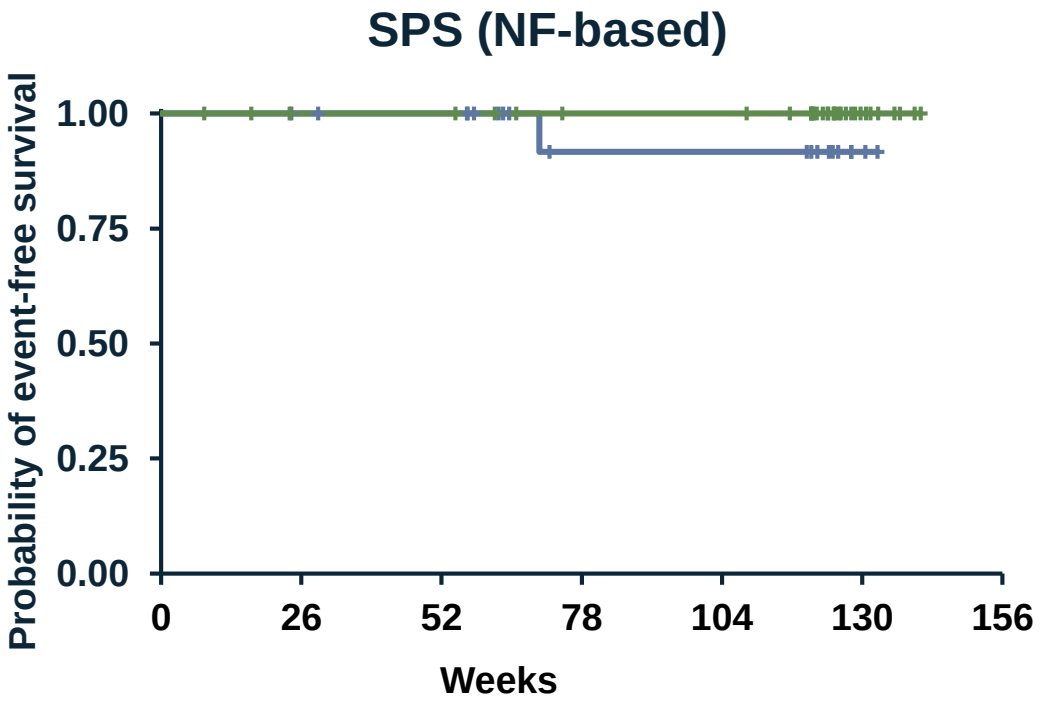
Combined VALOR + OLE; ITT population

Events	Early-start tofersen N=72	Placebo + delayed-start tofersen N=36	Hazard ratio (95% CI)	Log-rank p value	Cox regression p value
Death or permanent ventilation	12 (16.7%)	8 (22.2%)	**0.36** (0.137, 0.941)	0.0687	0.0373
Death	8 (11.1%)	6 (16.7%)	**0.27** (0.084, 0.890)	0.0879	0.0313
Death with additional post-withdrawal vital status data	12 (16.7%)	11 (30.6%)	**0.24** (0.096, 0.602)	0.0096	0.0023
Death, PV, or withdrawal due to disease progression	18 (25.0%)	13 (36.1%)	**0.38** (0.180, 0.821)	0.0217	0.0135

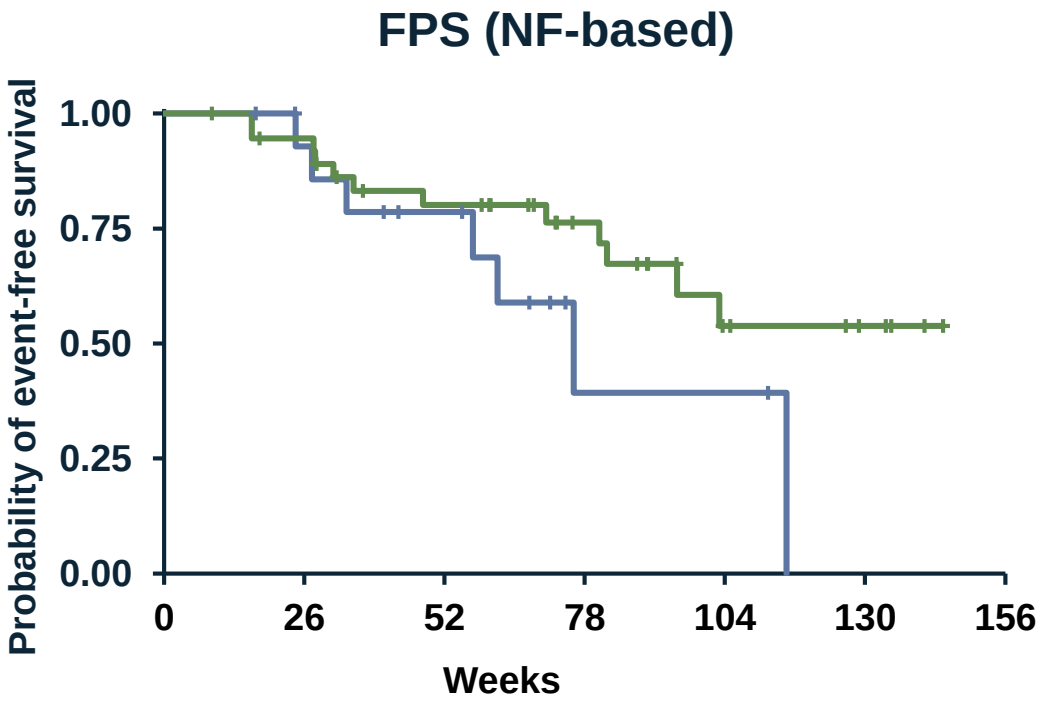
OLE, open-label extension; PV, permanent ventilation.
Time to death or permanent ventilation is defined as the time from first dose to death or PV (≥22 hours of mechanical ventilation per day for ≥21 consecutive days), whichever comes first. Participants who do not meet the endpoint definition are censored 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.

Time-to-event analysis for death or permanent ventilation

Combined VALOR + OLE; FPS and SPS (NF-based)



Placebo, n =	20	19	18	10	10	2	0
Tofersen, n =	34	31	31	27	27	7	0



Placebo, n =	16	13	9	2	2	0	0
Tofersen, n =	38	34	26	17	7	4	0

Time to event is 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 comes first. Subjects who do not meet the endpoint definition are censored at the subject's last known alive date.
Only events that were adjudicated by the Endpoint Adjudication Committee are included.
FPS, faster progression subgroup; ITT, intent-to-treat; KM, Kaplan-Meier; OLE, open-label extension; SPS, slower progression subgroup.

Disease duration in A5V carriers

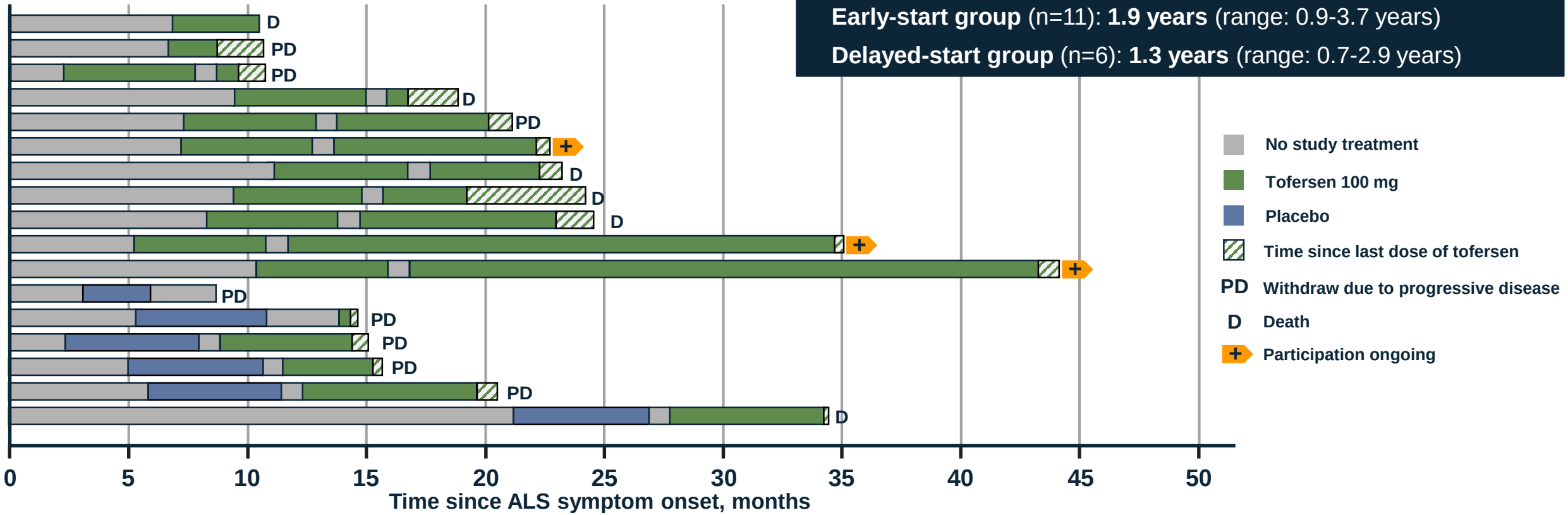
Combined VALOR + OLE; ITT population (data cutoff: 16 Jan 2022)

Median Disease Duration

Overall tofersen-treated (n=16): **1.7 years** (range: 0.9-3.7 years)

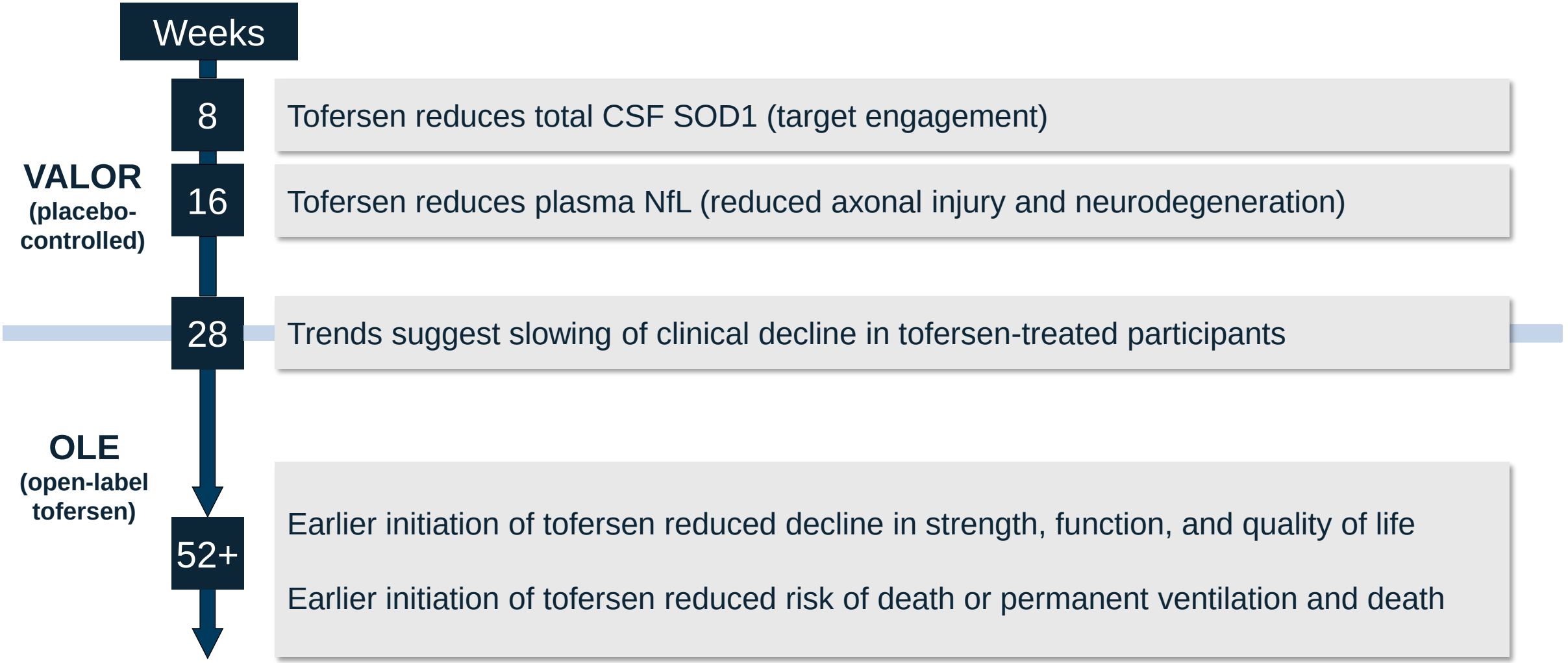
Early-start group (n=11): **1.9 years** (range: 0.9-3.7 years)

Delayed-start group (n=6): **1.3 years** (range: 0.7-2.9 years)

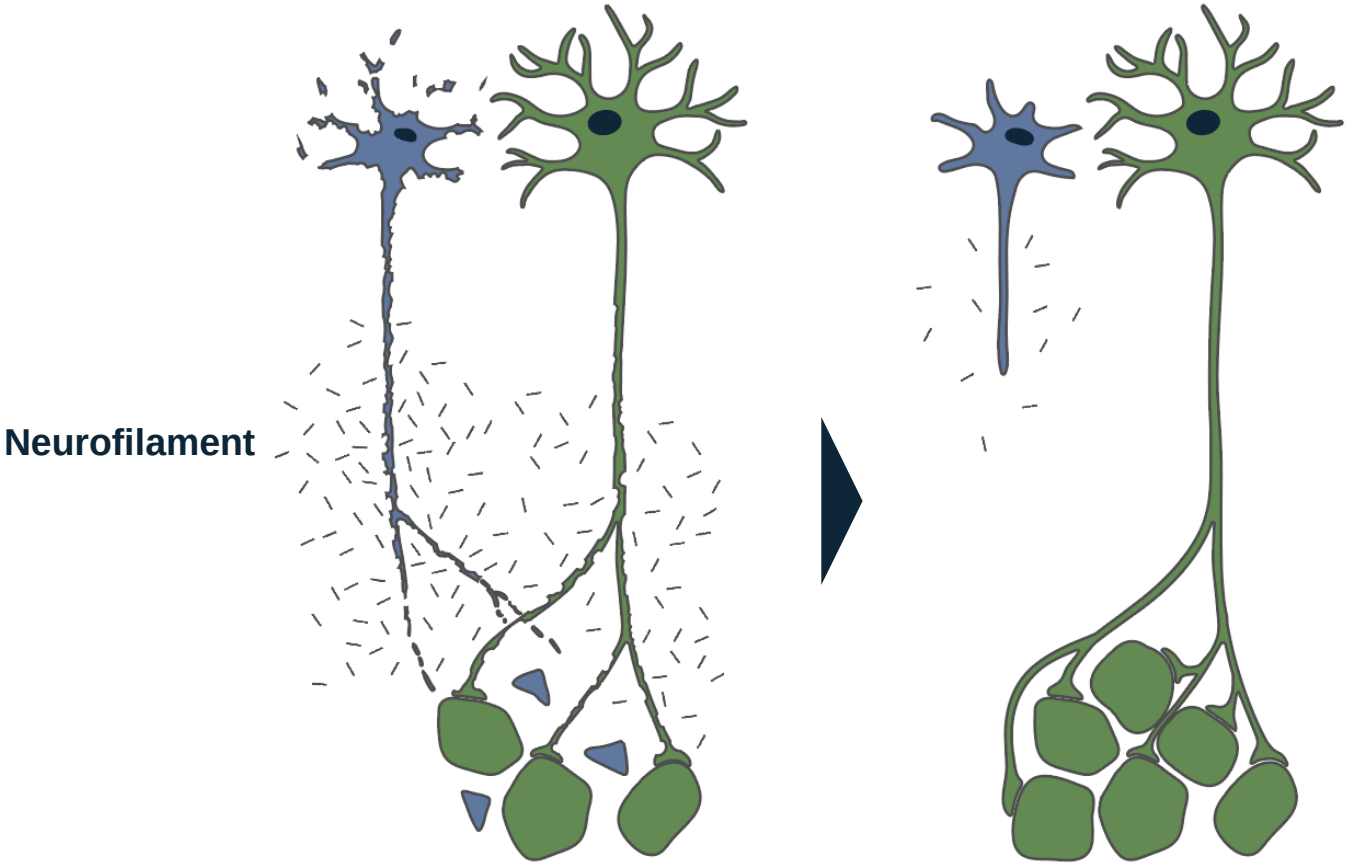


ITT, intent-to-treat; OLE, open-label extension.

Tofersen demonstrates evidence of biologic effect that precedes evidence of clinical benefit



Sequence of events is associated with strong biological plausibility

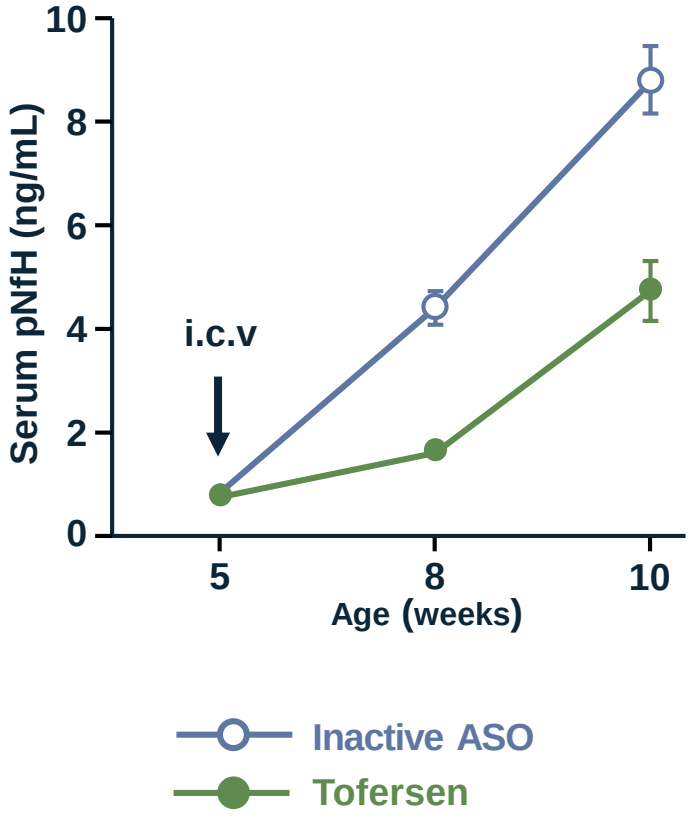


Utility of neurofilament in ALS trials

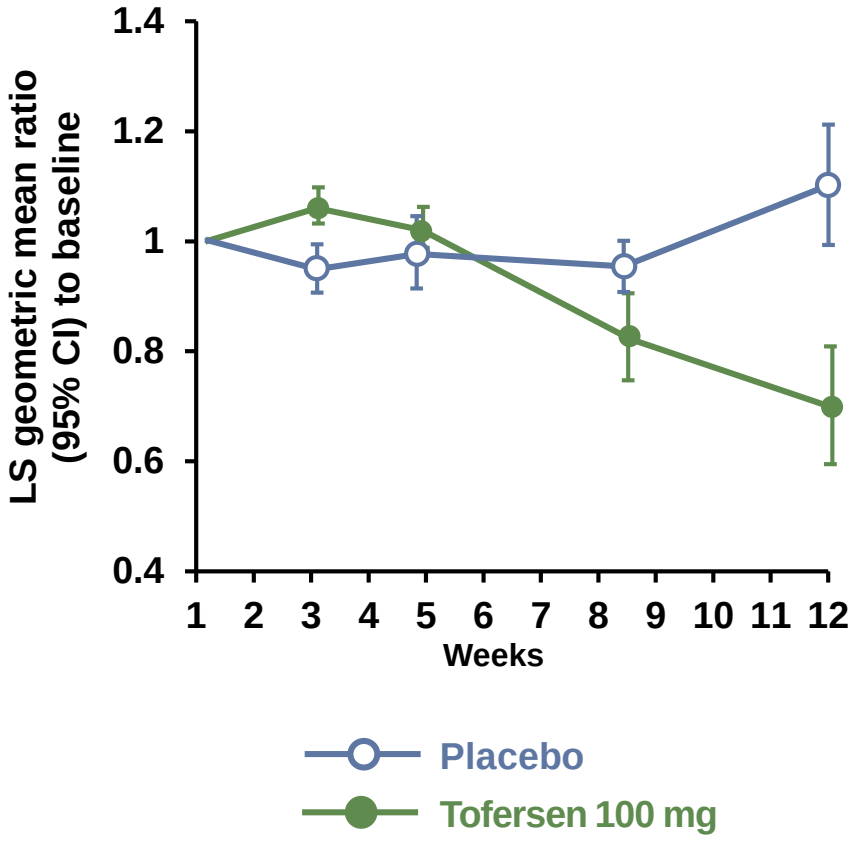
Clinical trial utility	**Identify presymptomatic at-risk carriers for prevention trials (e.g., ATLAS)**	**Control for disease heterogeneity in study populations (e.g., ensure treatment groups are balanced)**	**Assess for lowering of neurofilament as evidence of treatment effect and/or to predict clinical outcomes**
Type of biomarker	Susceptibility/risk biomarker	Prognostic biomarker of disease progression and survival	Biomarker of treatment response and/or a surrogate biomarker reasonably likely to predict clinical benefit

Reductions in neurofilament were consistently observed across preclinical and clinical studies

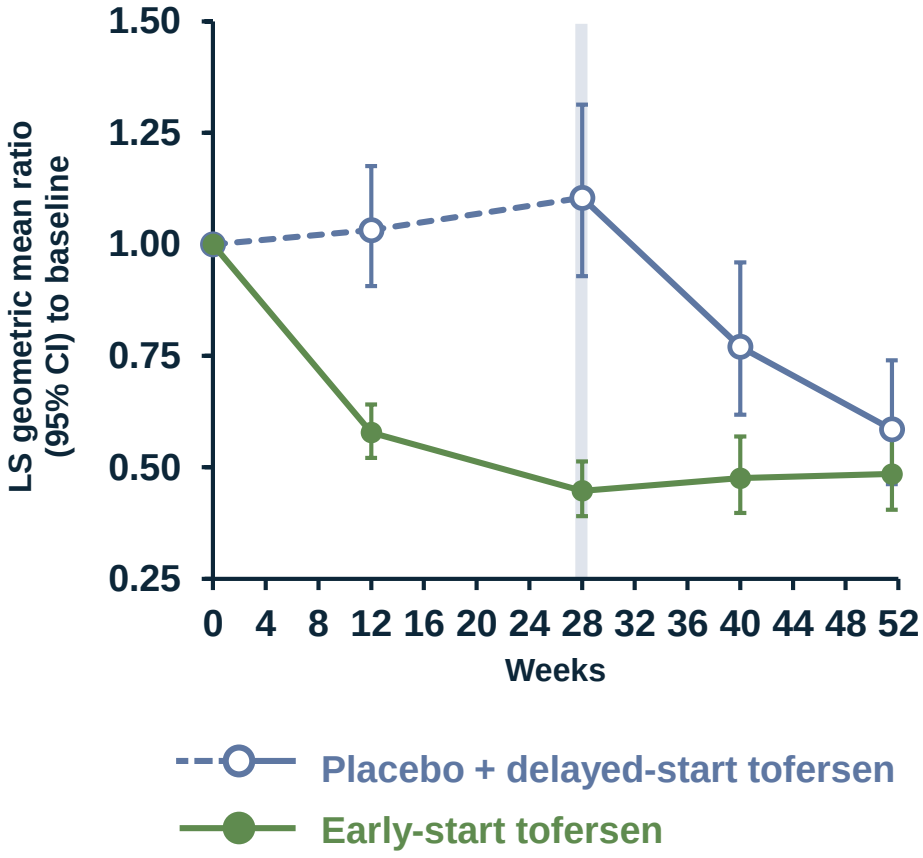
SOD1-G93A transgenic mice



Phase 1/2 Study

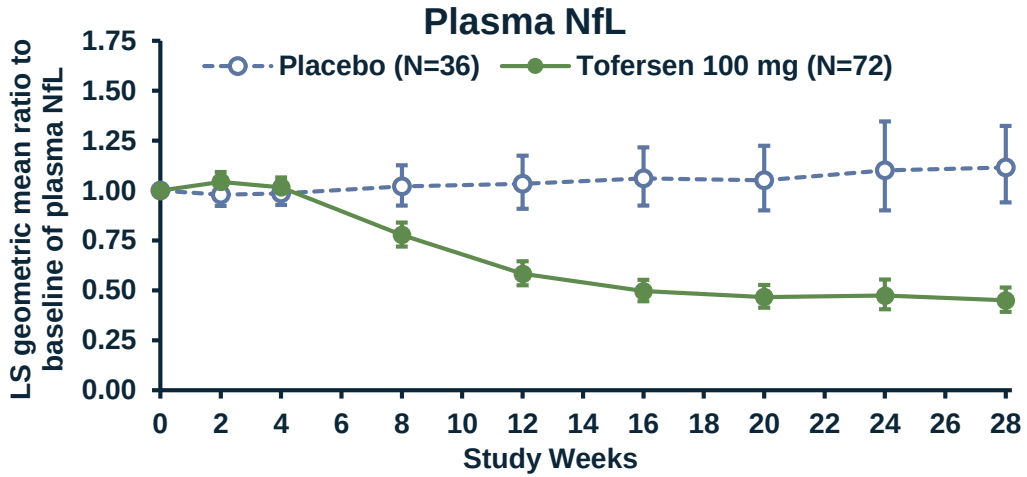


VALOR + OLE

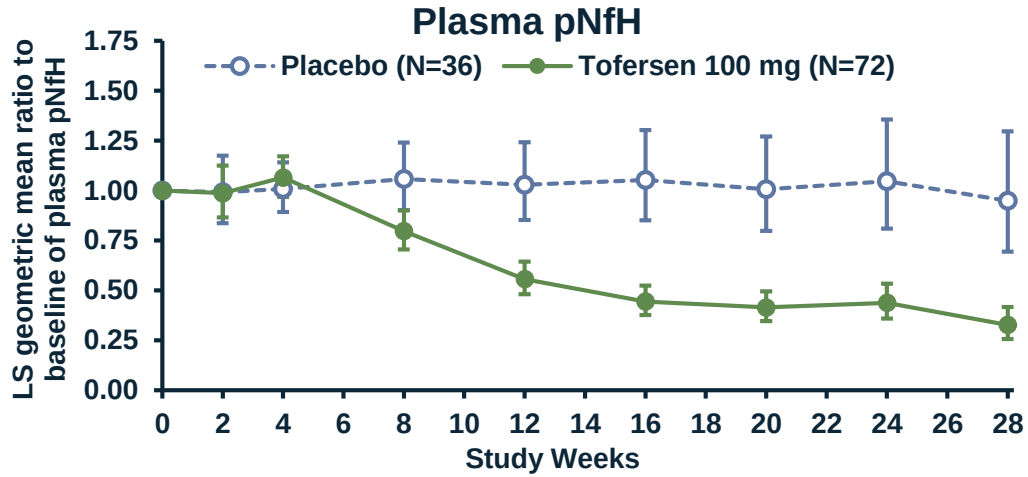


i.c.v., intracerebroventricular injection; NfL, neurofilament light chain; OLE, open-label extension.
Analysis is based on ANCOVA model in conjunction with multiple imputation for missing data; based on natural log transformed data. The model includes covariates for the corresponding baseline value i.e., log value, and use of riluzole or edaravone.

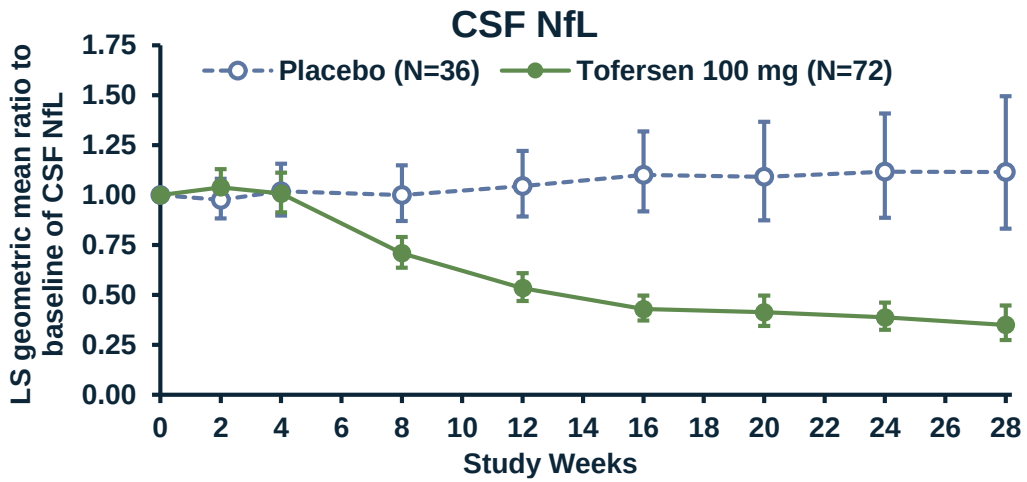
Consistent trends observed for NfL and pNfH in plasma and CSF



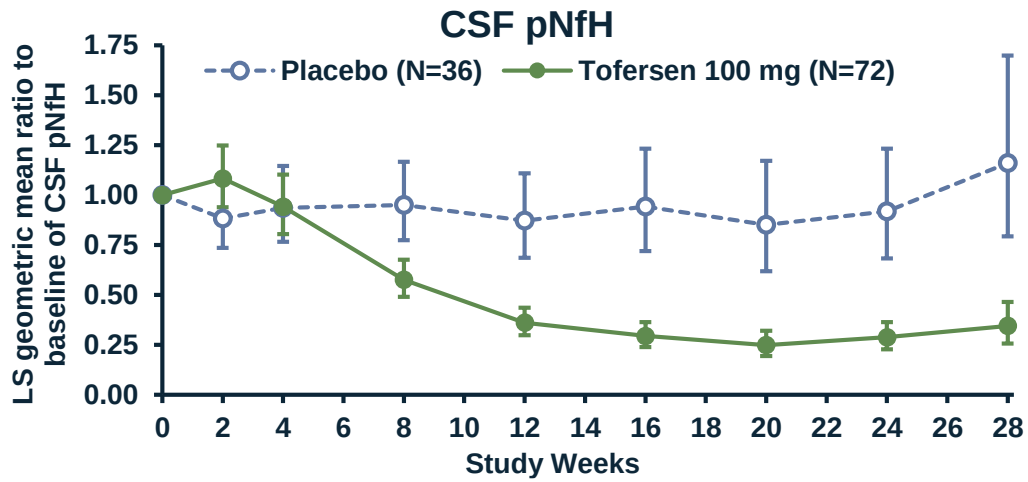
Placebo, n=	36	35	35	32	35	34	34	33	30
Tofersen 100 mg, n=	71	68	70	65	62	64	62	63	52



Placebo, n=	36	36	35	33	36	34	34	34	31
Tofersen 100 mg, n =	71	71	70	67	64	65	62	64	55



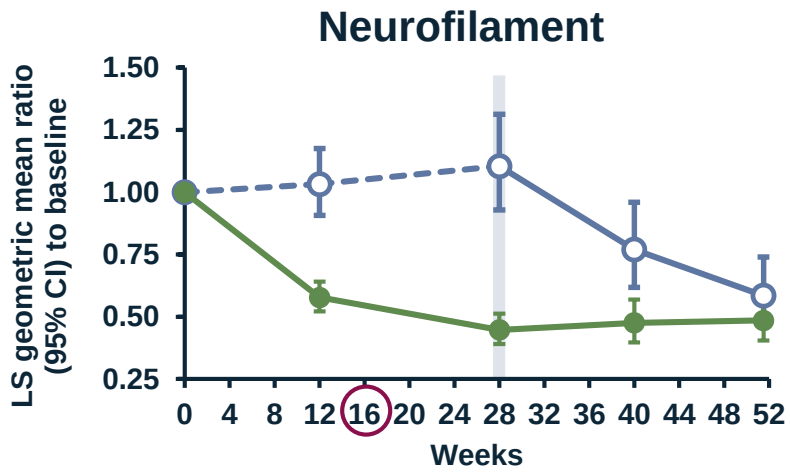
Placebo, n=	32	28	29	26	32	29	27	25	16
Tofersen 100 mg, n=	63	64	57	56	52	55	46	53	27

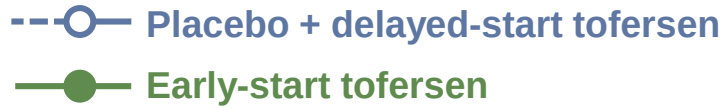


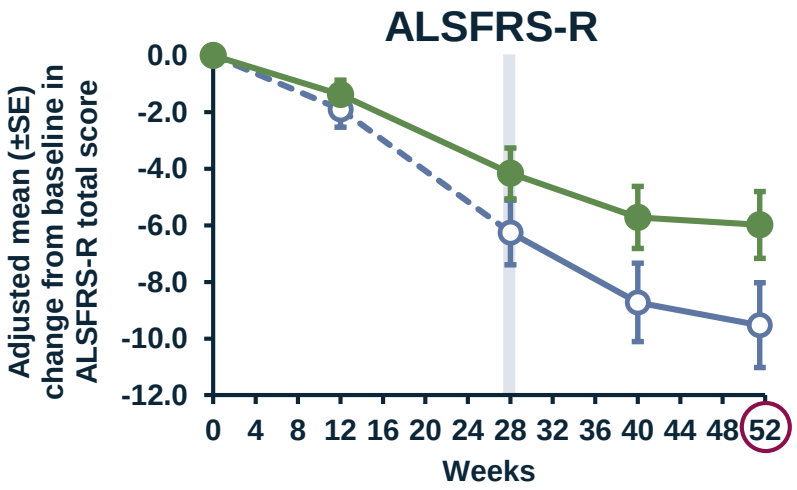
Placebo, n=	36	36	35	33	35	33	34	33	30
Tofersen 100 mg, n =	72	72	70	66	64	66	64	62	57

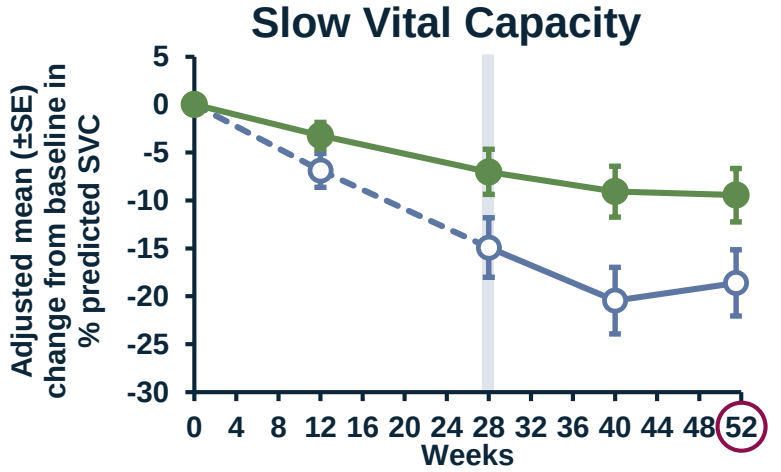
CSF, cerebrospinal fluid; NfL, neurofilament light; pNfH, phosphorylated neurofilament heavy chain.

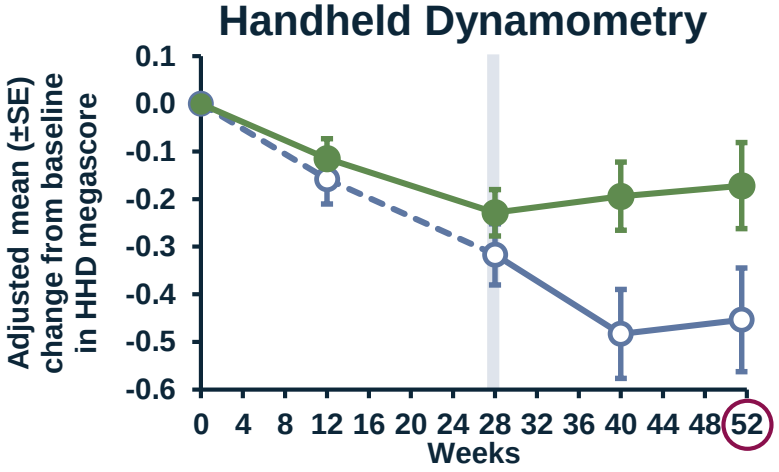
Reductions in NfL precede discernable clinical benefit







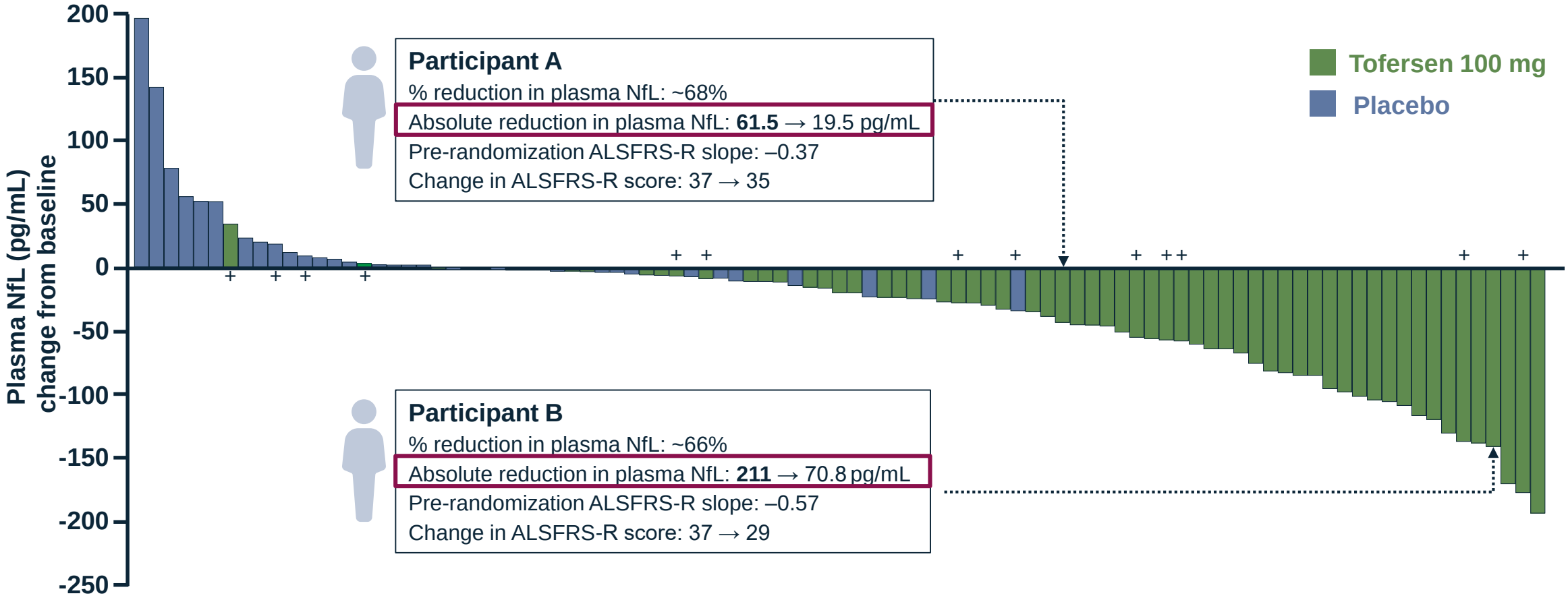




ALSFRS-R, ALS Functional Rating Scale-Revised; NfL, neurofilament light.

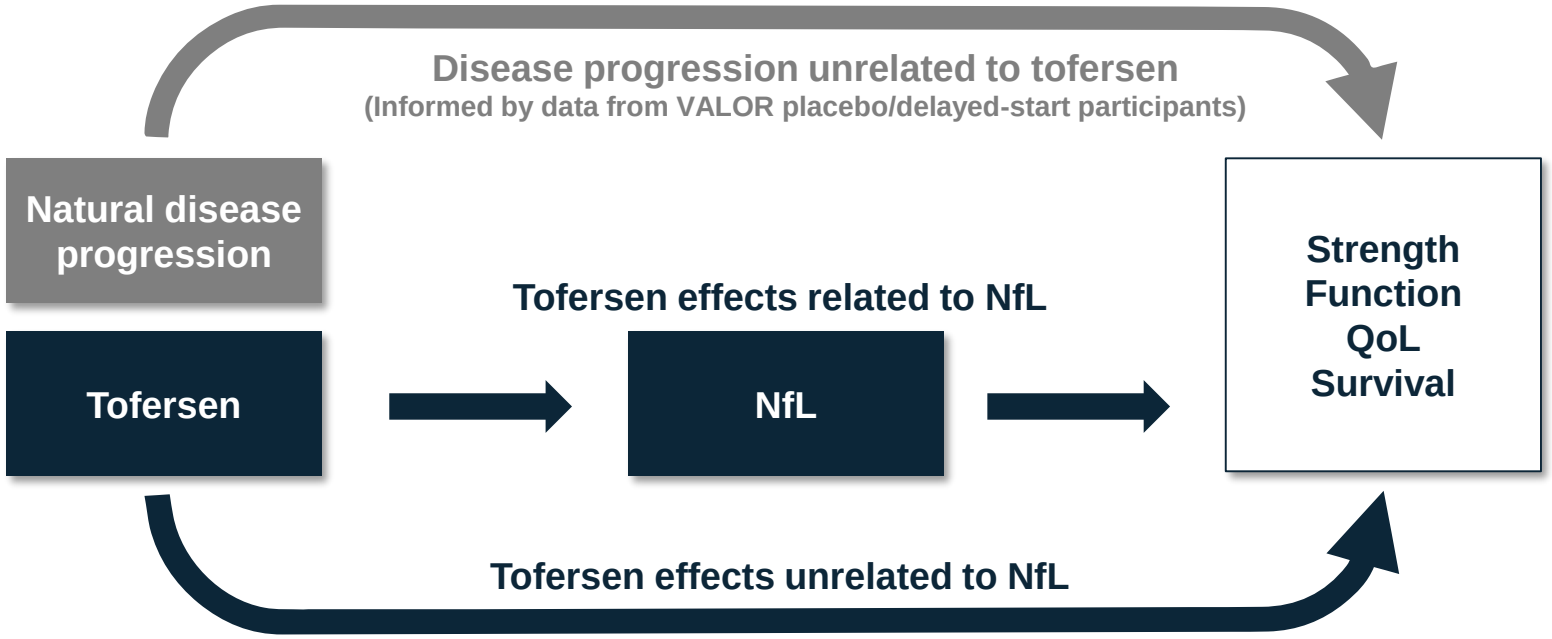
Individual changes in neurofilament over time in VALOR

Observed change change from baseline at Day 197 in plasma NfL
VALOR; ITT population (study completers)



Observed data are presented for only study completers with a valid NfL result at Day 169 or Day 197.
For completers with Day 197 data available, change from baseline at Day 197 is presented. For completers with missing Day 197 data, change from baseline at Day 169 is presented with +.
Values below limit of quantitation (BLQ) are set to half of lower limit of quantitation (LLOQ. 4.9 pg/mL) in calculations.

Model built to evaluate NF as a potential surrogate biomarker reasonably likely to predict clinical benefit



Model deconstructs the observed effect in a tofersen-treated participant into three components:

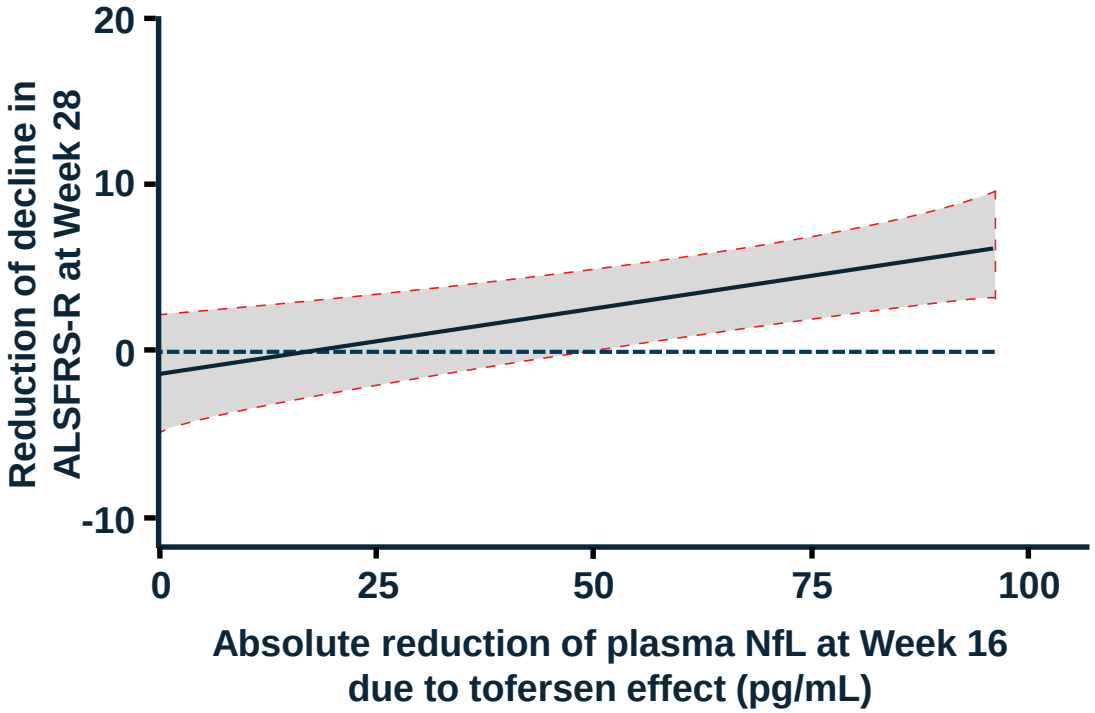
Change due to:

1. Natural disease progression
2. Effect of tofersen through the NfL pathway
3. Effect of tofersen through non-biomarker pathway/factors

NfL, neurofilament light; QoL, quality of life.

Model built to evaluate NF as a potential surrogate biomarker reasonably likely to predict clinical benefit

Tofersen-driven reductions in plasma NfL at Week 16 correlate with slowing of clinical decline in function, strength, QoL at Week 28



Predicted benefit on clinical outcomes (at Week 28) for each 10 pg/mL reduction of plasma NfL (at Week 16)*	
ALSFRS-R total score	0.77 (p=0.0038)
Percent-predicted SVC	1.45 (p=0.0706)
HHD overall megascore	0.029 (p=0.1303)
ALSAQ-5 total score	2.194 (p=0.0056)
EQ-5D-5L utility score	0.017 (p=0.0894)

*Example for a participant with a baseline plasma NfL level equivalent to the sample mean for ITT completers (96.78 pg/mL)

ALS, amyotrophic lateral sclerosis; ALSAQ-5, ALS Assessment Questionnaire; ALSFRS-R, ALS Functional Rating Scale-Revised; EQ-5D-5L, EuroQol 5 Dimension, 5 Level Questionnaire; HHD, handheld dynamometry; ITT, intent-to-treat; NfL, neurofilament light; QoL, quality of life; SVC, slow vital capacity.

Model built to evaluate NF as a potential surrogate biomarker reasonably likely to predict clinical benefit

Tofersen-driven reductions in plasma NfL at Week 16 correlate with a reduced risk of death-equivalent events over time

Survival endpoints	Tofersen effect through NfL lowering	Percent reduction in event risk for a 10 pg/mL reduction in NfL
Time to death	0.0175 (p=0.3690)	16.1%
Time to death or permanent ventilation	0.0224 (p=0.1119)	20.1%
Time to death, permanent ventilation, or withdrawal due to disease progression	0.0287 (p=0.0010)	24.9%
Time to death with additional vital status	0.0284 (p=0.0318)	24.7%

Table shows example for a participant with a baseline plasma NfL level equivalent to the sample mean for ITT completers (96.78 pg/mL).

Tofersen-driven reductions in plasma NfL are reasonably likely to predict clinical benefit in *SOD1*-ALS

Biological plausibility

In *SOD1*-ALS, toxic SOD1 protein leads to degeneration and death of motor neurons

Neurofilaments are released upon damage to the axons of motor neurons

Higher levels of neurofilament are associated with more rapid disease progression and shortened survival in ALS

Empirical evidence

By reducing production and accumulation of SOD1 protein, tofersen led to substantial reductions in plasma NfL, indicating a reduction in damage to motor neurons

These reductions correlated with evidence of clinical benefit over time (preserved function, strength, QoL, and reduced risk of death-equivalent events)

Long-term evidence generation plans

Proposed Confirmatory Study

Study 233AS303 (ATLAS)

Effects of tofersen when initiated in presymptomatic *SOD1* mutation carriers with elevated NfL

End of study: 2027*

Supportive Data

Study 233AS102 (OLE)

Long-term effects of tofersen in adults with *SOD1*-ALS

End of study: 2024

Real-World Evidence (RWE)

Effects of tofersen in the real-world setting via EAP + ALS disease registries

Descriptive analyses of disease duration by *SOD1* mutation type
Tofersen-treated (VALOR/OLE + registry) vs. untreated (literature, registries)

Cross-study comparison of the impact of timing of tofersen initiation on disease progression [ATLAS vs. VALOR vs. OLE]

*Timing estimated based on current study design and enrollment.

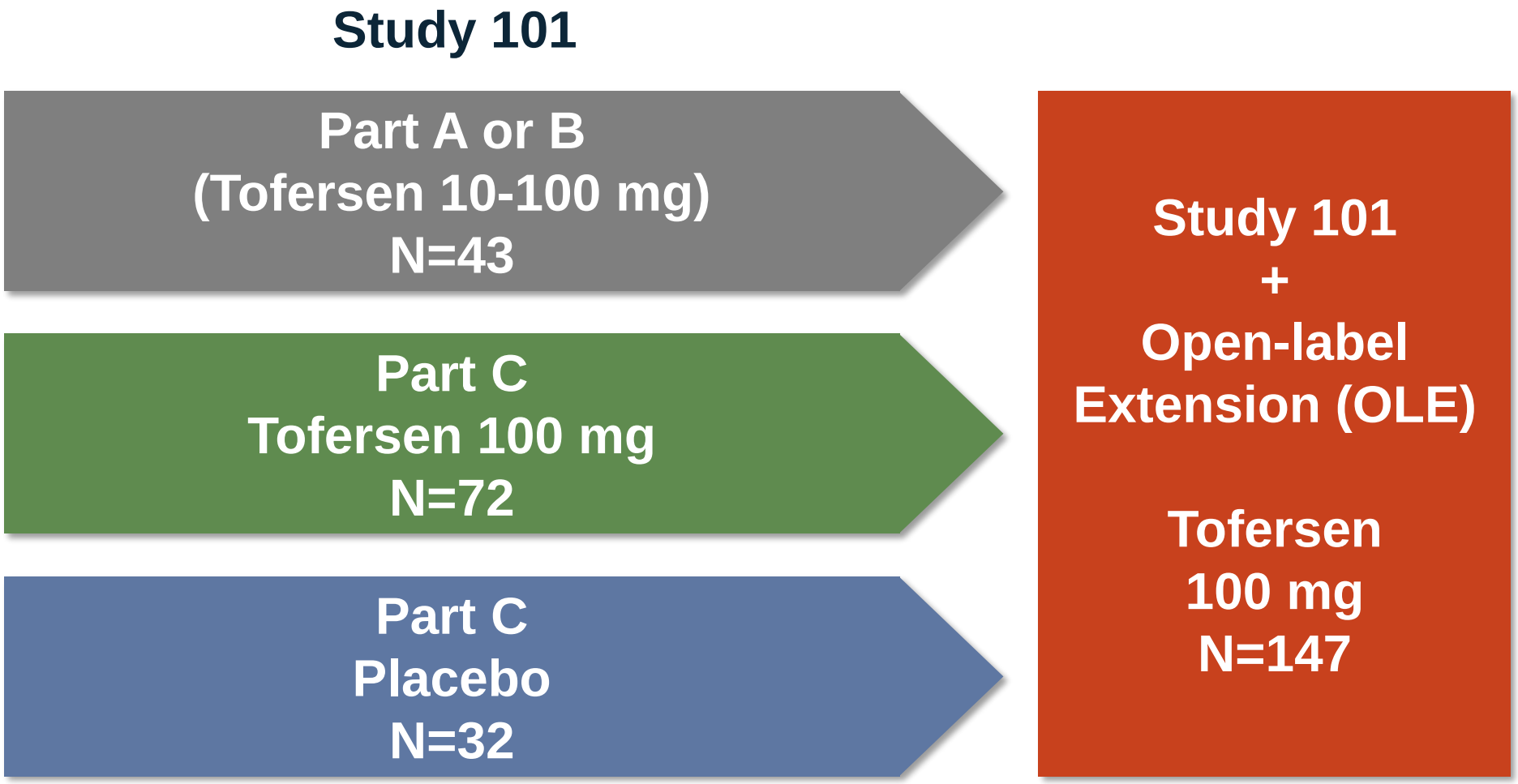
Safety

Laura Fanning, MD

Executive Medical Director, Global Medical Safety

Biogen

Pooling strategy to support integrated safety analysis



Extent of tofersen exposure

	VALOR	Study 101 and OLE Integrated
	Tofersen 100 mg N=72	Tofersen 100 mg N=147
Total duration of exposure, weeks		
Median	28.1	119.4
Min, max	8, 34	4, 212

Median of >2 years of exposure to tofersen 100 mg as of 15 July 2022

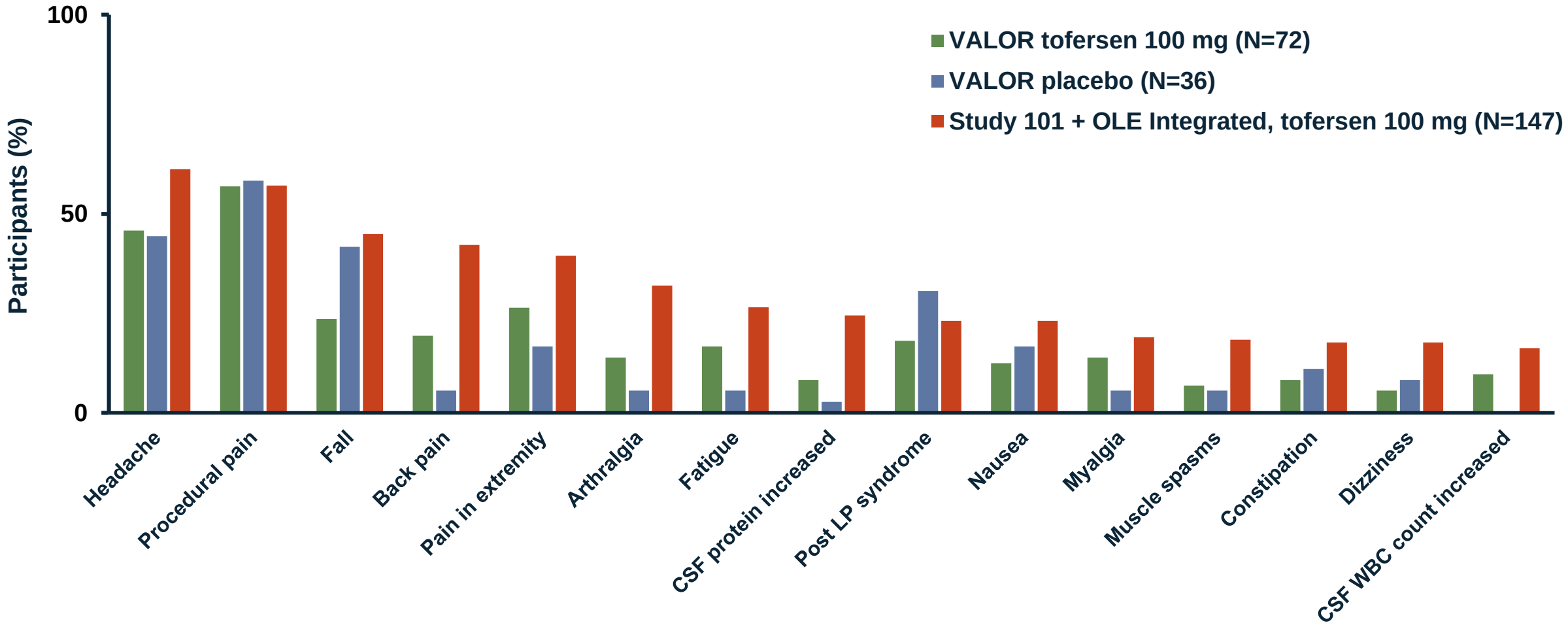
OLE, open-label extension.

Overview of safety

	Participants, n (%)		
	VALOR		Study 101 and OLE Integrated[a]
	Tofersen 100 mg N=72	Placebo N=36	Tofersen 100 mg N=147
≥1 AE	69 (95.8)	34 (94.4)	145 (98.6)
AEs related to lumbar puncture[b]	58 (80.6)	29 (80.6)	125 (85.0)
Grade ≥3 AEs	12 (16.7)	4 (11.1)	58 (39.4)
Serious AEs	13 (18.1)	5 (13.9)	59 (40.1)
AEs leading to drug discontinuation	4 (5.6)	0	26 (17.7)
AEs with fatal outcome	1 (1.4)	0	19 (12.9)

[a] An event in a placebo participant during Study 101 is only counted once; an event in a tofersen participant during Study 101 is counted in both the "VALOR/tofersen 100 mg" column, and again in the "Study 101 and OLE Integrated" column.
[b] Relatedness assessed by the investigator.
AE, adverse event; OLE, open-label extension.

Most common adverse events



LP, lumbar puncture; CSF, cerebrospinal fluid; WBC, white blood cell count.
Note: AEs presented by PTs according to MedDRA version 25.0.

CSF laboratory abnormalities

	Participants, n (%)		
	VALOR		Study 101 and OLE Integrated
	Tofersen 100 mg N=72	Placebo N=36	Tofersen 100 mg N=147
≥1 CSF WBC value >10×10^6/L	42/72 (58.3)	2/36 (5.6)	117/147 (79.6)
≥1 CSF WBC value >5×10^6/L	55/72 (76.4)	6/36 (16.7)	134/147 (91.2)
Proportion with shift to high CSF protein[a]	31/46 (67.4)	6/20 (30.0)	105/117 (89.7)

CSF lab abnormalities were common with tofersen and most were not considered adverse by investigators

[a] Shift to high includes normal to high, low to high, and unknown to high.
CSF, cerebrospinal fluid; OLE, open-label extension; WBC, white blood cell.

Most common lumbar puncture-related events (>5%)

	Participants, n (%)		
	VALOR		Study 101 and OLE Integrated
	Tofersen 100 mg N=72	Placebo N=36	Tofersen 100 mg N=147
Any AE related to lumbar puncture[a]	**58 (80.6)**	**29 (80.6)**	**125 (85.0)**
Procedural pain	40 (55.6)	21 (58.3)	83 (56.5)
Headache	22 (30.6)	12 (33.3)	64 (43.5)
Post lumbar puncture syndrome	13 (18.1)	11 (30.6)	34 (23.1)
Back pain	9 (12.5)	0	44 (29.9)
Pain in extremity	6 (8.3)	0	13 (8.8)
Nausea	4 (5.6)	3 (8.3)	13 (8.8)
CSF protein increased	3 (4.2)	0	11 (7.5)
Dizziness	2 (2.8)	1 (2.8)	11 (7.5)
CSF white blood cell count increased	4 (5.6)	0	9 (6.1)

[a] Relatedness assessed by investigator.
Note: AEs presented by PTs according to MedDRA version 25.0.
AE, adverse event; CSF, cerebrospinal fluid; OLE, open-label extension.

Serious adverse events (≥2%)

	Participants, n (%)		
	VALOR		Study 101 and OLE Integrated
	Tofersen 100 mg N=72	Placebo N=36	Tofersen 100 mg N=147
Any serious AE	**13 (18.1)**	**5 (13.9)**	**59 (40.1)**
Respiratory failure	1 (1.4)	0	16 (10.9)
Pneumonia aspiration	1 (1.4)	0	10 (6.8)
Dysphagia	0	0	7 (4.8)
Pulmonary embolism	3 (4.2)	1 (2.8)	6 (4.1)
Acute respiratory failure	1 (1.4)	0	5 (3.4)
Pneumonitis aspiration	2 (2.8)	0	4 (2.7)
Pneumonia	0	0	3 (2.0)
Intracranial pressure increased	0	0	3 (2.0)
Fall	0	0	3 (2.0)

Note: AEs presented by PTs according to MedDRA version 25.0.
AE, adverse event; OLE, open-label extension.

Adverse events leading to death

	Participants, n (%)		
	VALOR		Study 101 and OLE Integrated
	Tofersen 100 mg N=72	Placebo N=36	Tofersen 100 mg N=147
Any AE leading to death	**1 (1.4)**	**0**	**19 (12.9)**
Respiratory failure	0	0	11 (7.5)
Respiratory arrest	0	0	2 (1.4)
Amyotrophic lateral sclerosis	0	0	2 (1.4)
Cardiac arrest	0	0	1 (0.7)
Cardiac failure congestive	1 (1.4)	0	1 (0.7)
Euthanasia	0	0	1 (0.7)
Septic shock	0	0	1 (0.7)
Sudden death	0	0	1 (0.7)

Note: AEs presented by PTs according to MedDRA version 25.0.
AE, adverse event; OLE, open-label extension.

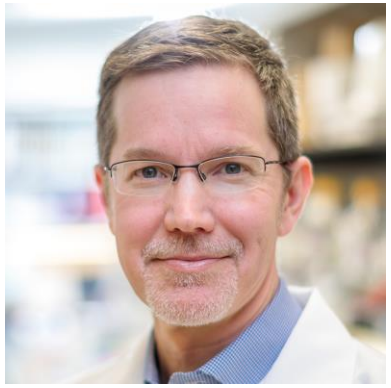
Serious neurologic events

	Participants, n (%)		
	VALOR		Study 101 and OLE Integrated
	Tofersen 100 mg N=72	Placebo N=36	Tofersen 100 mg N=147
Serious neurologic events	**4 (5.6)**	**0**	**10 (6.8)**
Intracranial pressure increased	0	0	3 (2.0)
Papilledema	0	0	1 (0.7)
Myelitis	1 (1.4)	0	2 (1.4)
Lumbar radiculopathy	1 (1.4)	0	1 (0.7)
Myelitis transverse	1 (1.4)	0	1 (0.7)
Neurosarcoidosis[a]	0	0	1 (0.7)
Radiculopathy	0	0	1 (0.7)
Meningitis aseptic	0	0	1 (0.7)
Meningitis chemical	1 (1.4)	0	1 (0.7)

[a] Verbatim term: Neurosarcoid transverse myelitis.
Note: AEs presented by PTs according to MedDRA version 25.0.
OLE, open-label extension.

Summary of safety

- Tofersen was generally well tolerated with an acceptable safety profile
- Longer duration of exposure (up to >3 years) was not associated with new safety concerns
- Adverse events, including lumbar puncture events, were generally mild to moderate in severity and not treatment limiting
- Serious neurologic events (myelitis/radiculitis, papilledema, aseptic meningitis) were manageable with standard of care



Clinical Perspective

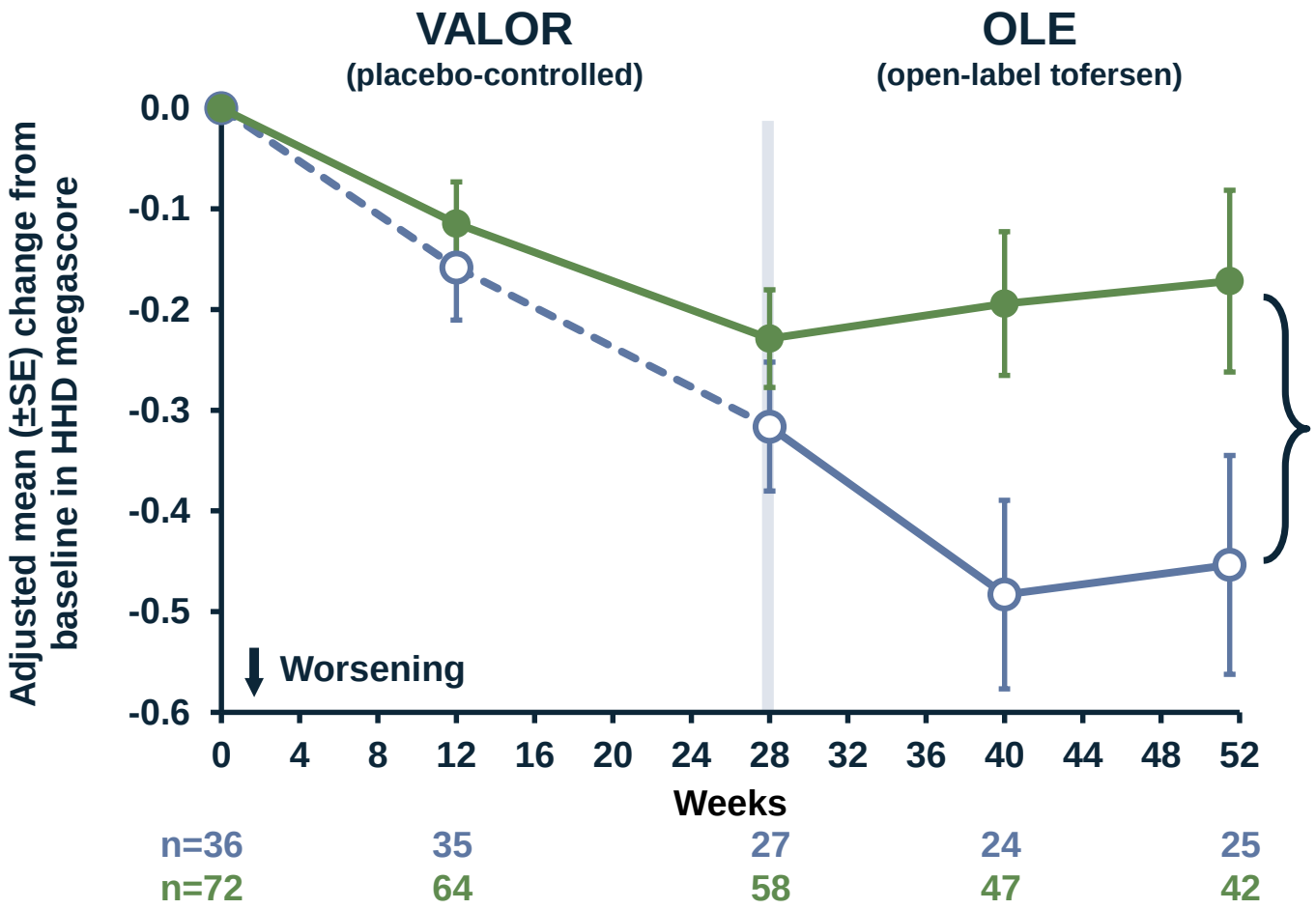
Timothy M. Miller, MD, PhD

David Clayson Professor of Neurology

Washington University in St. Louis

Early-start tofersen slowed loss of muscle strength

Combined VALOR + OLE; ITT population



Placebo + delayed-start tofersen

Early-start tofersen

Adjusted mean difference:
0.28 (95% CI: 0.05, 0.52)
p=0.0186

Improvement in HHD megascore from baseline to Week 52:

Delayed-start tofersen: 8.1%

Early-start tofersen: 26.9%

Difference: 18.8% (95% CI: 1.4, 36.2)

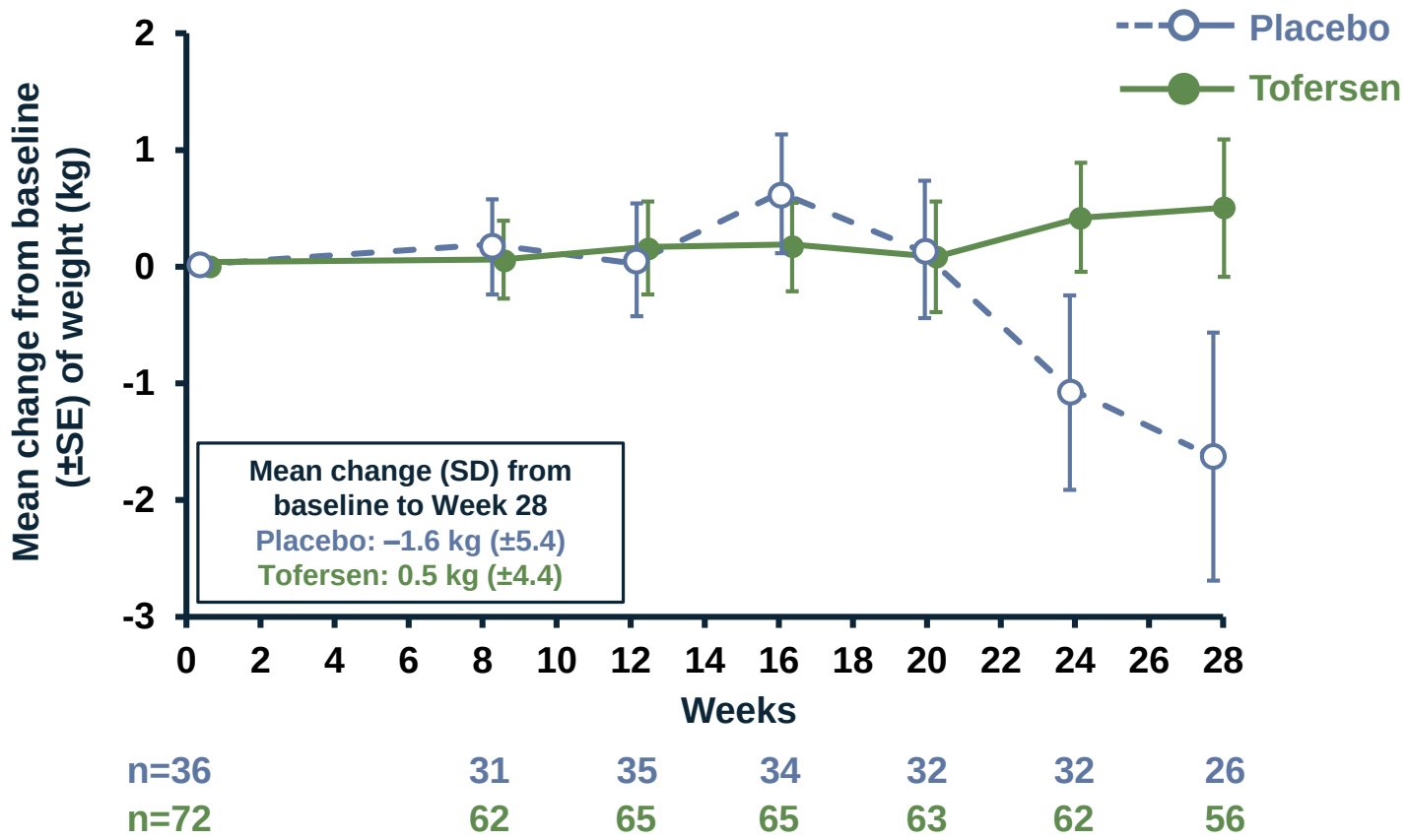
HHD, handheld dynamometry; ITT, intent-to-treat; OLE, open-label extension.

Improvements in people living with ALS are very rare

- In 2 decades of treating people living with ALS, I have not seen improvements
- In over 900 participants in the dexpramipexole study, ~4.4% of participants showed “improvement” in strength over 1 year
- With tofersen, 27% of the early-start participants showed improvement over the same time frame
- While clearly not everyone had a dramatic improvement, the fact that one quarter improved is remarkable

Tofersen participants experienced stabilization of weight in a disease associated with progressive weight loss

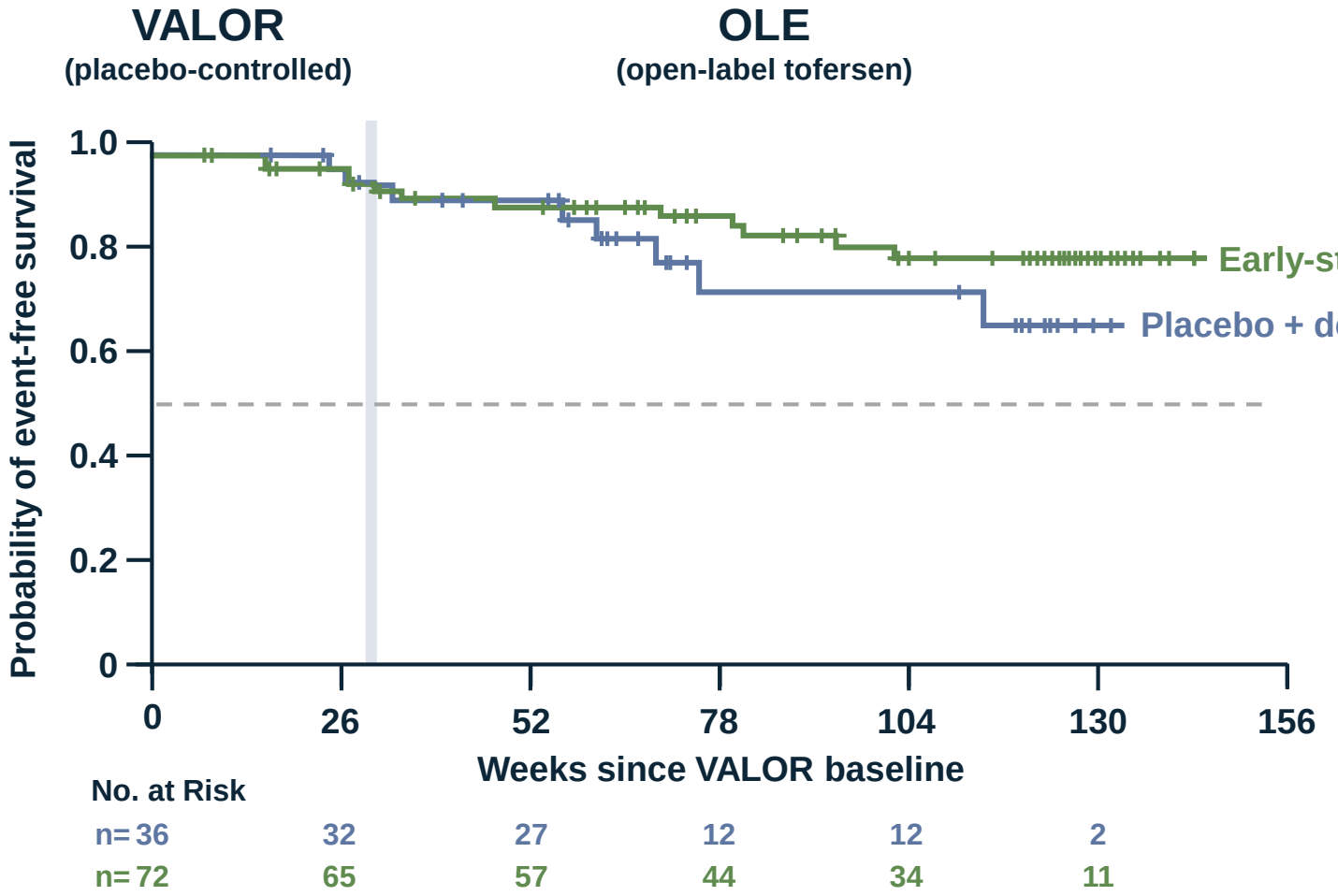
VALOR; ITT population



ITT, intent-to-treat.

Early-start tofersen was associated with reduced risk of death or permanent ventilation

Combined VALOR + OLE; ITT population



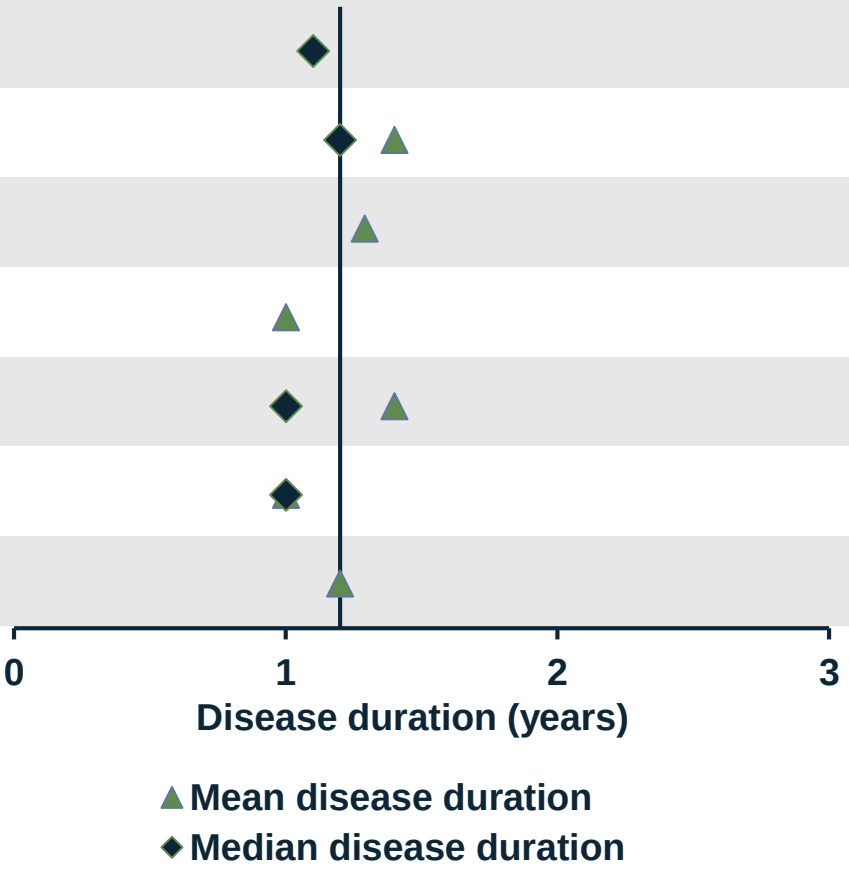
	Death or permanent ventilation n (%)	Hazard ratio (95% CI)
Placebo + delayed-start tofersen N=36	8 (22.2%)	0.36 (0.137, 0.941)
Early-start tofersen N=72	12 (16.7%)	

ITT, intent-to-treat; OLE, open-label extension; PV, permanent ventilation.
Time to death or permanent ventilation is defined as the 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.

Median disease duration in A5V mutation carriers is consistently at or below 1.2 years

A5V (A4V, p.A5V) carriers

	Median disease duration ≤1.2 years	Mean (SD)	Median	n
Opie-Martin et al. 2022		N/A	1.1*	205
Bali et al. 2017		1.40 (0.7)	1.2*	51
Broom et al. 2008		1.29	N/A	79
Cudkowicz et al. 1998		1.00 (0.5)	N/A	8
Cudkowicz et al. 1997		1.40 (0.9)	1.0*	84
Juneja et al. 1997		1.00 (0.4)	1.0*	75
Rosen et al. 1994		1.20 (0.8)	N/A	24



The forest plot reflects identified literature with at least 5 A5V carriers. Unless denoted by * the descriptive statistics are based on raw data for disease duration since symptom onset. * denotes that the median survival was estimated from the Kaplan-Meier curve.

Early-start tofersen was associated with prolonged survival in A5V carriers

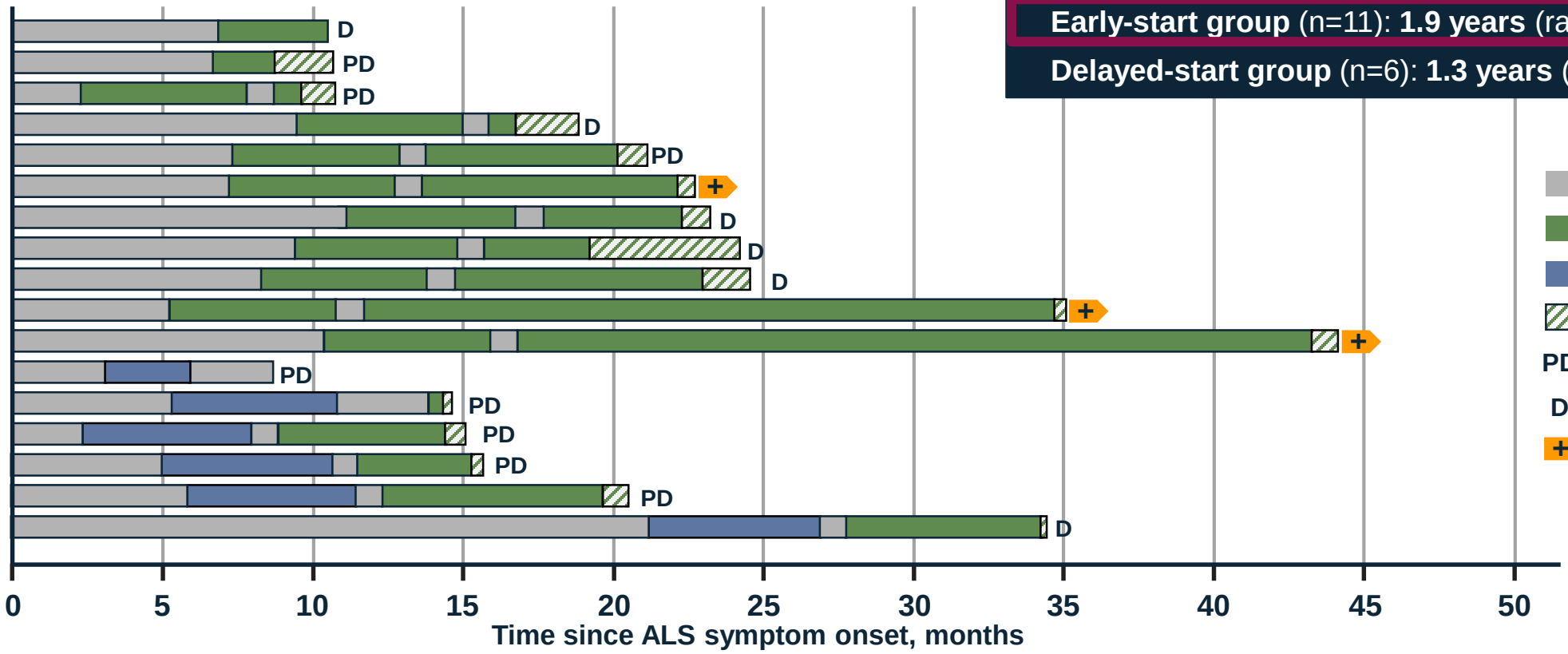
Combined VALOR + OLE; ITT population (data cutoff: 16 Jan 2022)

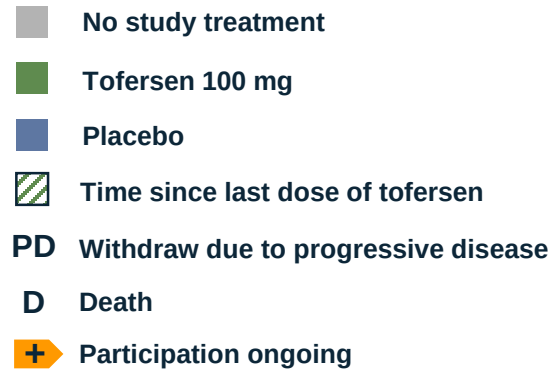
Median Disease Duration

Overall tofersen-treated (n=16): **1.7 years** (range: 0.9-3.7 years)

Early-start group (n=11): **1.9 years** (range: 0.9-3.7 years)

Delayed-start group (n=6): **1.3 years** (range: 0.7-2.9 years)





50% increase in median survival compared to expected natural history

ITT, intent-to-treat; OLE, open-label extension.

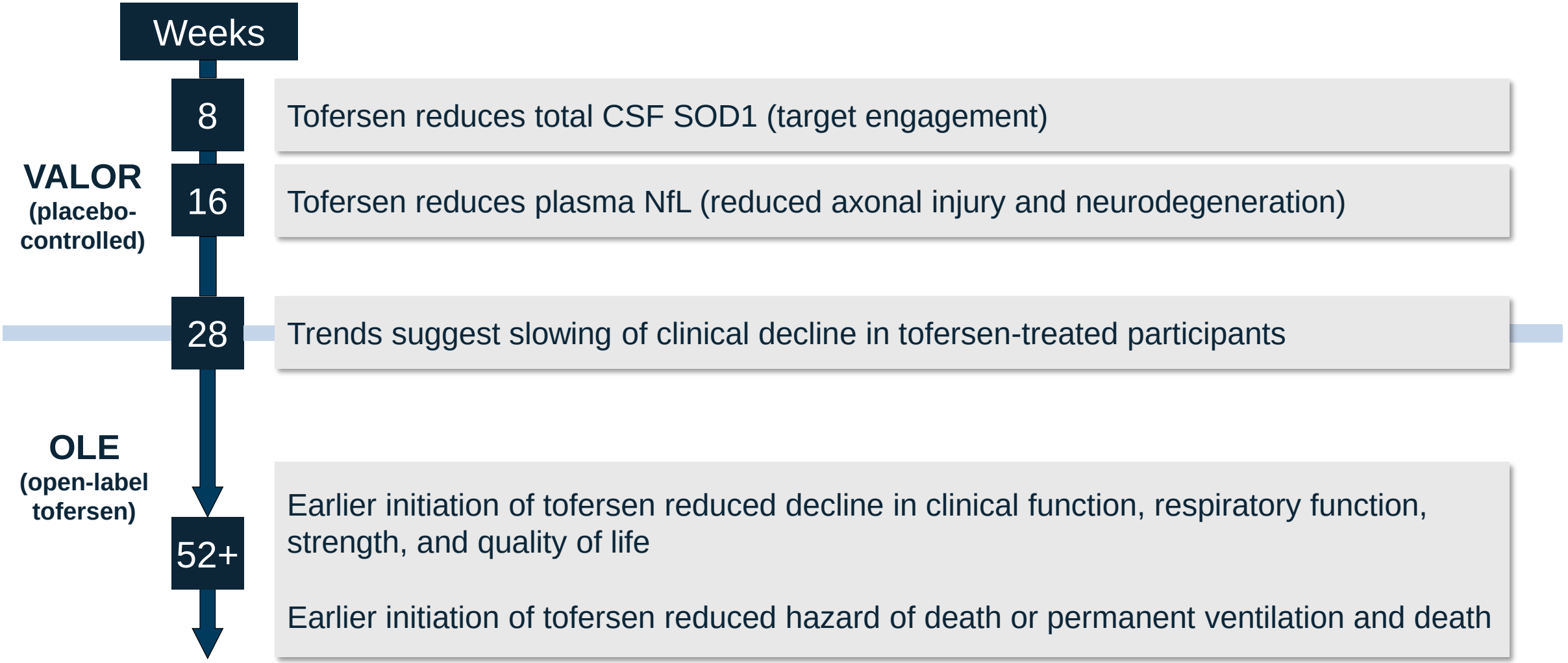
Serious neurological events were observed in participants who received tofersen

Study 101 + 102 ISS, safety population

	Participants, n (%)		
	VALOR		Study 101 and OLE Integrated
	Tofersen 100 mg N=72	Placebo N=36	Tofersen 100 mg N=147
Serious neurologic events	**4 (5.6)**	**0**	**10 (6.8)**
Intracranial pressure increased	0	0	3 (2.0)
Papilledema	0	0	1 (0.7)
Myelitis	1 (1.4)	0	2 (1.4)
Lumbar radiculopathy	1 (1.4)	0	1 (0.7)
Myelitis transverse	1 (1.4)	0	1 (0.7)
Neurosarcoidosis	0	0	1 (0.7)
Radiculopathy	0	0	1 (0.7)
Meningitis aseptic	0	0	1 (0.7)
Meningitis chemical	1 (1.4)	0	1 (0.7)

ISS, Integrated Summary of Safety; OLE, open-label extension.

Tofersen demonstrates evidence of biologic effect that precedes evidence of clinical benefit



CSF, cerebrospinal fluid; NfL, neurofilament light; OLE, open-label extension; SOD1, superoxide dismutase-1.

Individual cases support evidence of clinical benefit

Case 1

Phase 1 participant with no worsening over several years

Case 2

Phase 3 participant with decline in VALOR, followed by stabilization and ultimately improvement in the OLE

Case 3

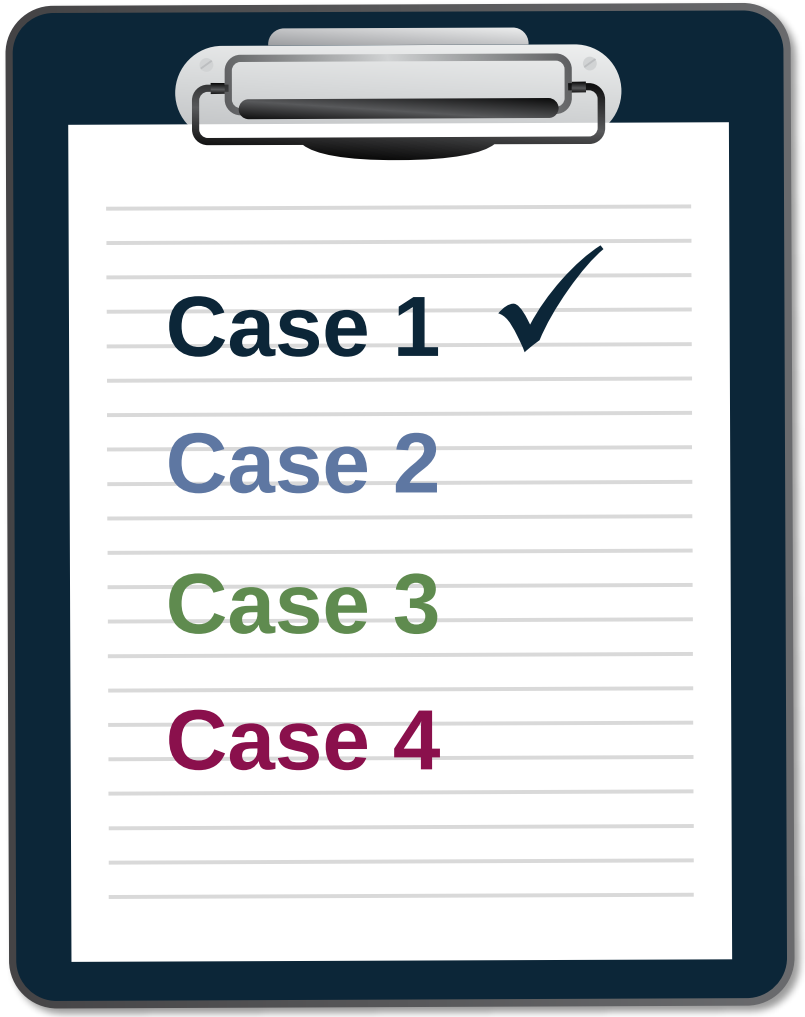
Expanded access participant with reductions of NfL and improvement of strength & function

Case 4

Expanded access participant with reductions of NfL and improvement of strength & function

NfL, neurofilament light; OLE, open-label extension.
Unpublished data, Washington University Neuromuscular Clinic.

Case 1: Phase 1 participant with no worsening over several years



At trial entry:

- Entered the Phase 1/2 trial in 2017
- Mildly symptomatic, mainly with falls
- *SOD1*-ALS has taken many in his family with typical survival ranging from 5-10 years

ALS, amyotrophic lateral sclerosis; SOD1, superoxide dismutase-1.

Case 1: Phase 1 participant with no worsening over several years

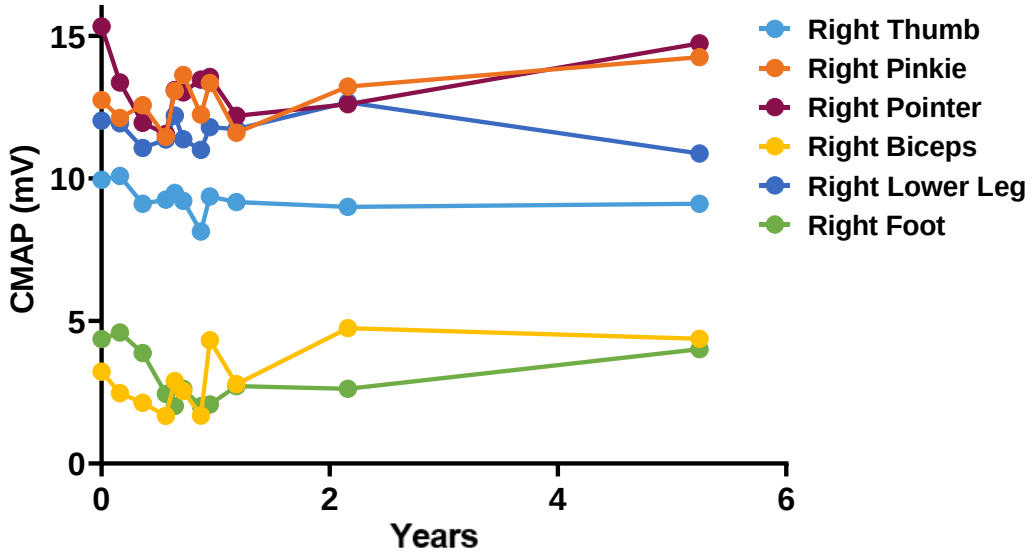
Clinical status in 2023

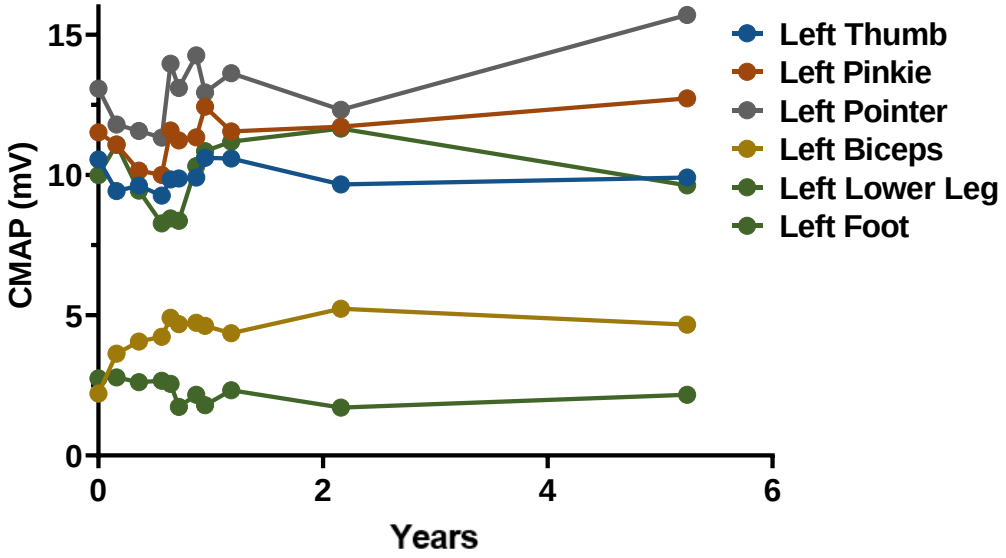
Participant is stronger with fewer falls

- CMAP is stable

On EMG (compared to 2017): stable to improved, no evidence of worsening

- Arms:
  - 3/3 muscles showed evidence of improvement
- Legs:
  - 1 muscle normal in 2017 remains normal
  - 1 muscle with mild improvement but still clearly abnormal
  - 1 muscle with improvement

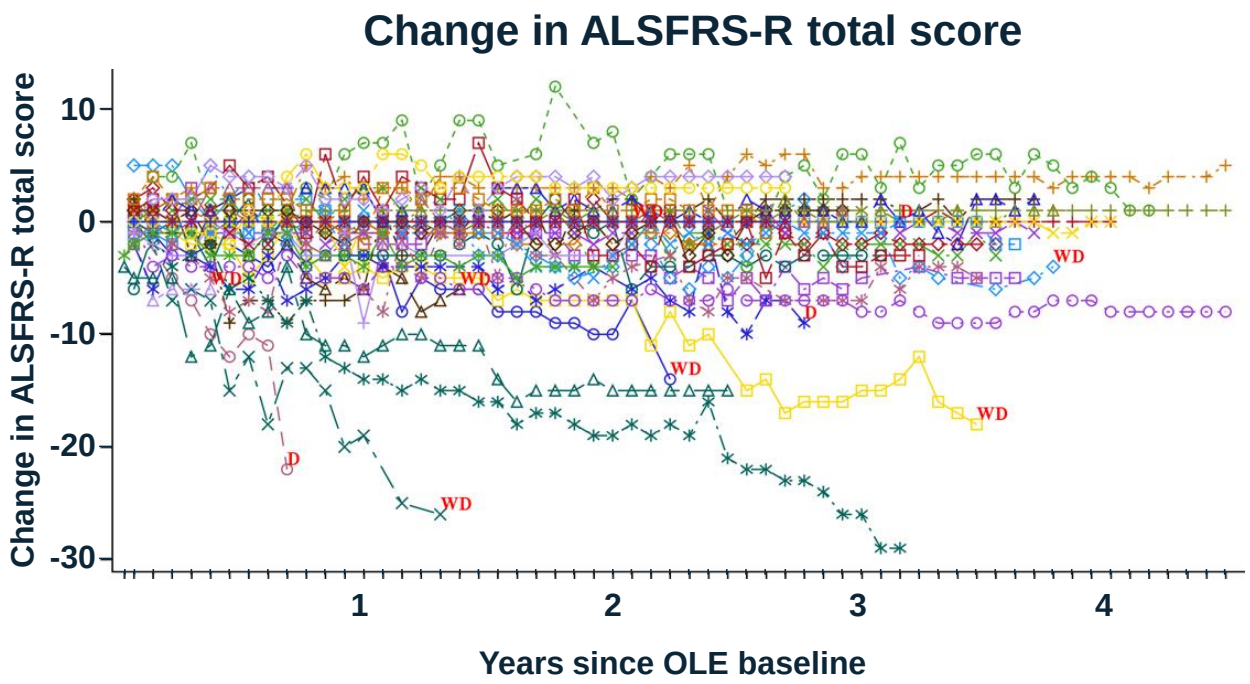


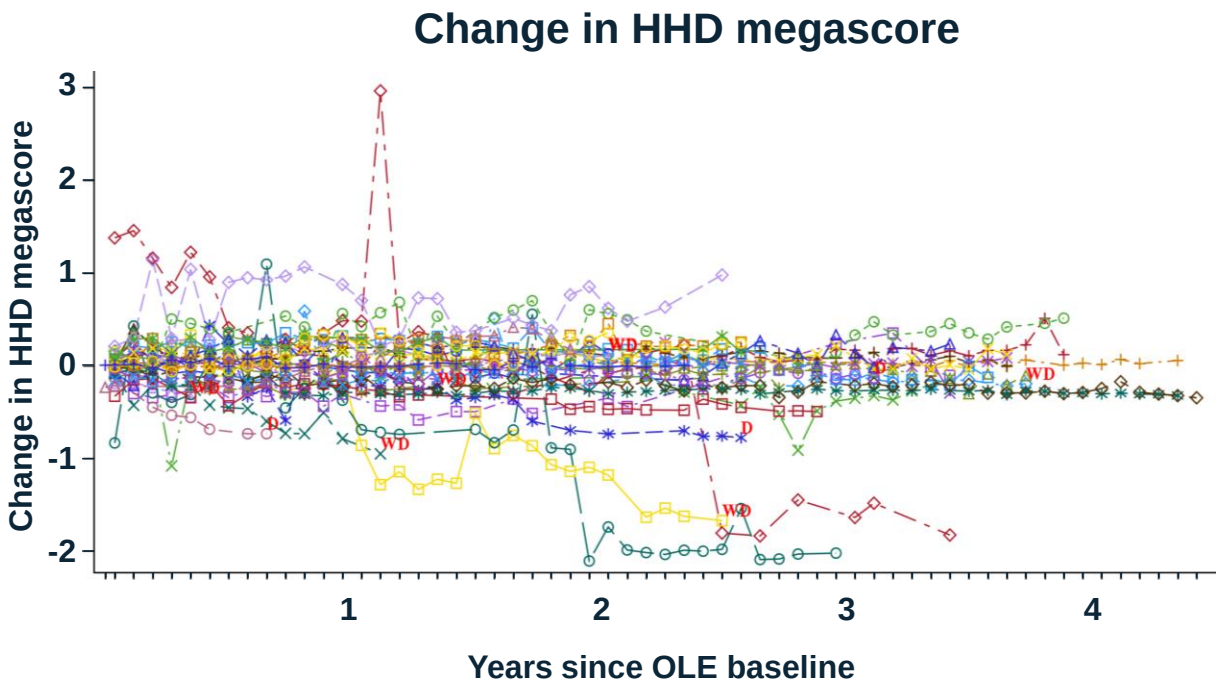


CMAP, compound muscle action potential; EMG, electromyography.

Longer-term follow-up in Phase 1 participants who received at least 1 dose of tofersen 100 mg in the OLE

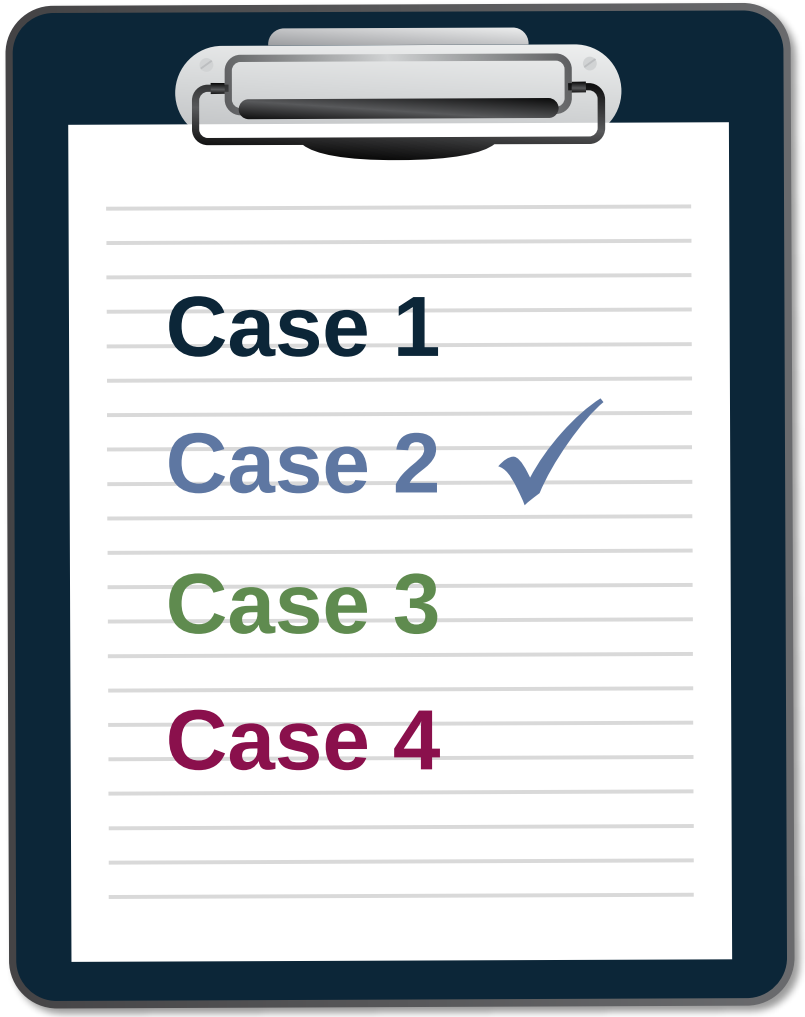
- 40 participants (59%) received at least 1 dose of tofersen 100 mg in the OLE
  - Participants had variable dosing histories and washout periods (16 weeks – 2 years) between studies





ALSFRS-R, ALS Functional Rating Scale-Revised; D, death; HHD, handheld dynamometry; OLE, open-label extension; WD, withdraw from study.
Data as of 16 Jan 2022 cut off OLE.

Case 2: Phase 3 participant with decline in VALOR, followed by stabilization and ultimately improvement in the OLE

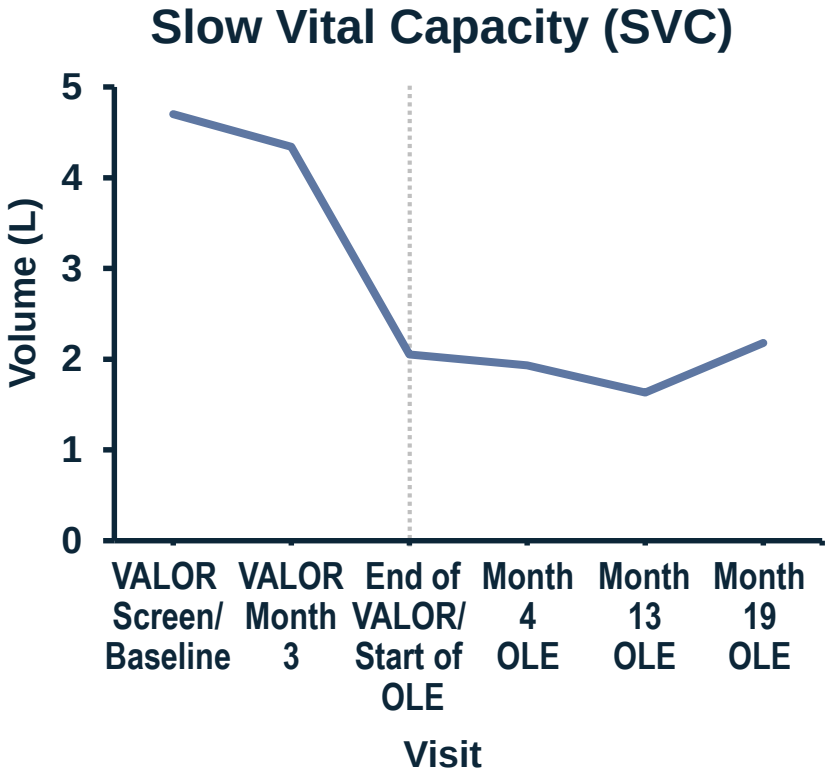


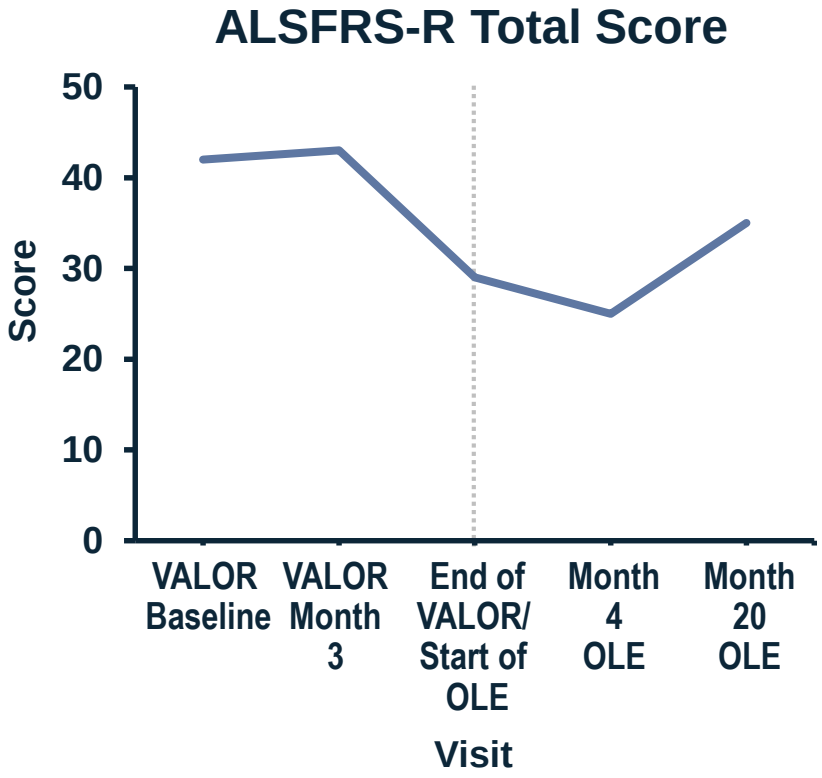
At trial entry:

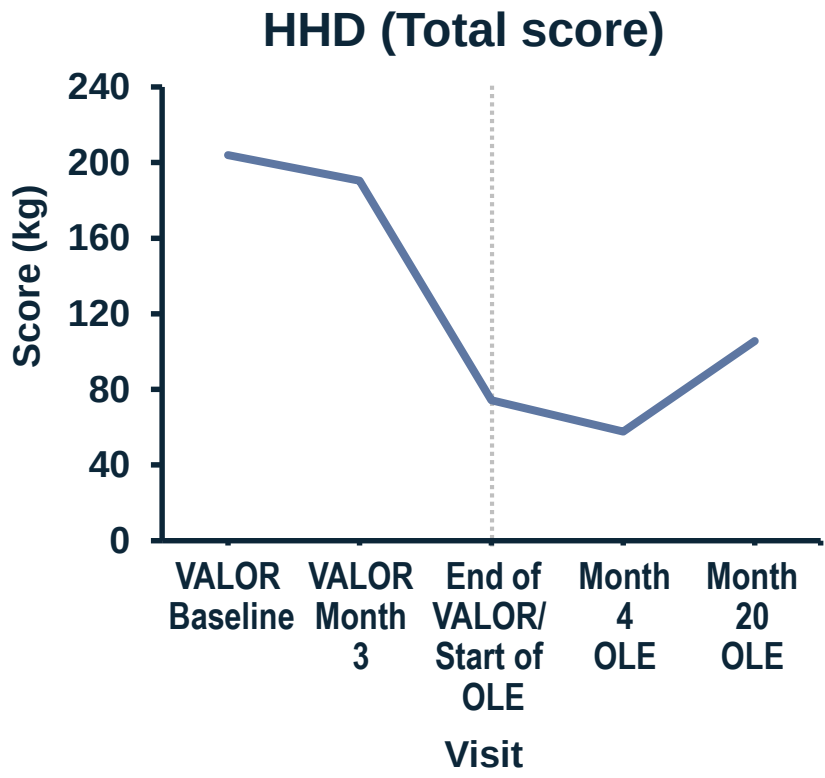
- Entered VALOR in late 2020
- Baseline plasma NfL: ~63 pg/mL

NfL, neurofilament light; OLE, open-label extension.

Case 2: Phase 3 participant with decline in VALOR, followed by stabilization and ultimately improvement in the OLE





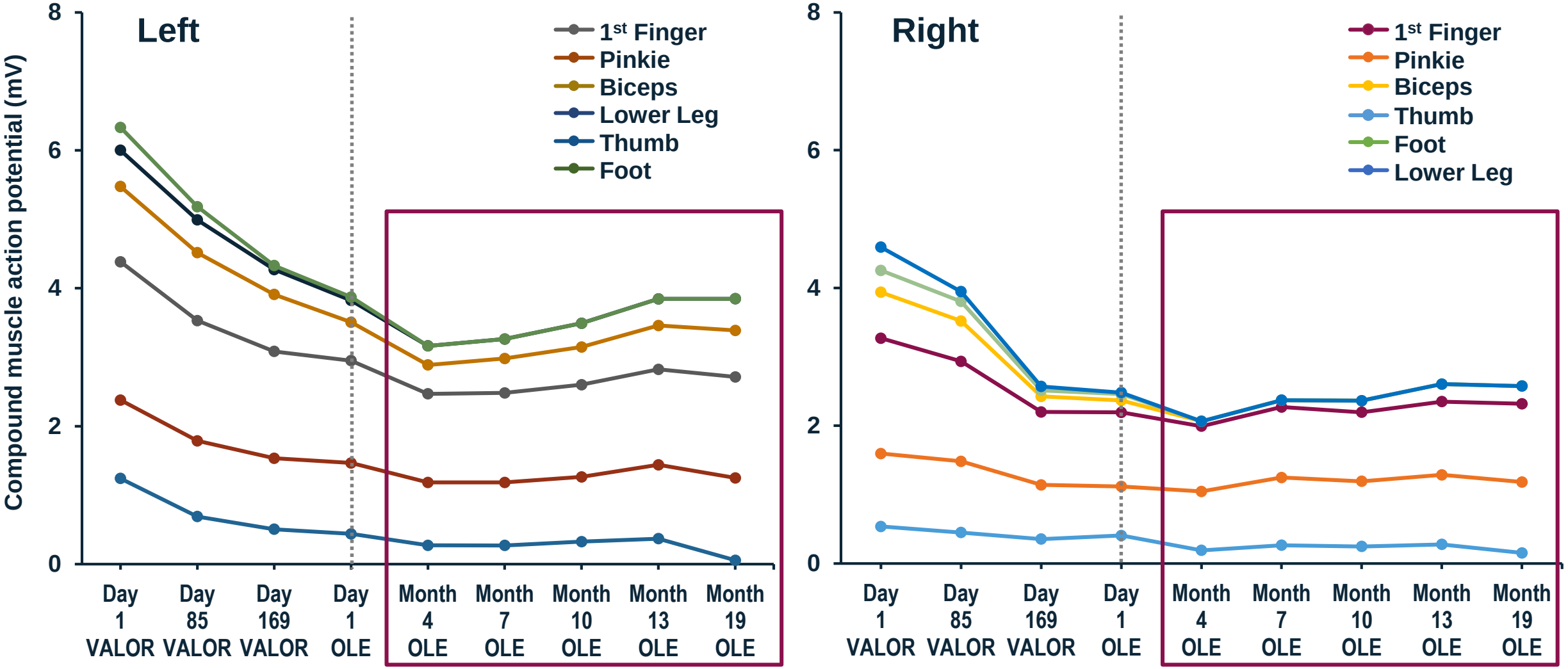


Clinical status in 2023

Participant can now use right arm to pour from a full gallon of distilled water, lifts arm easily above head, muscles with nearly full strength in arms; feels much better, no shortness of breath with talking; in rehab to re-learn walking

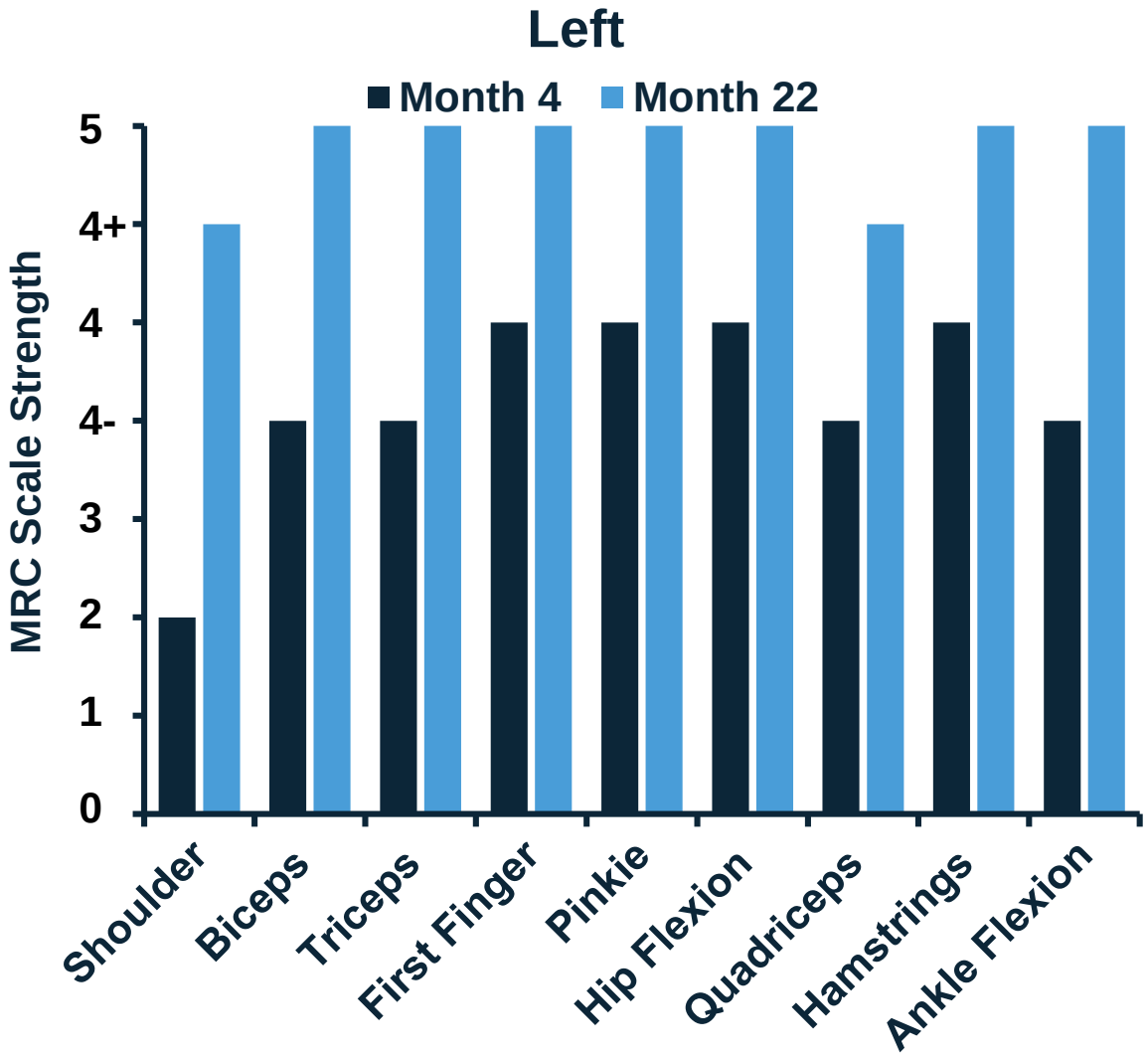
ALSFRS-R, ALS Functional Rating Scale-Revised; HHD, handheld dynamometry; OLE, open-label extension.

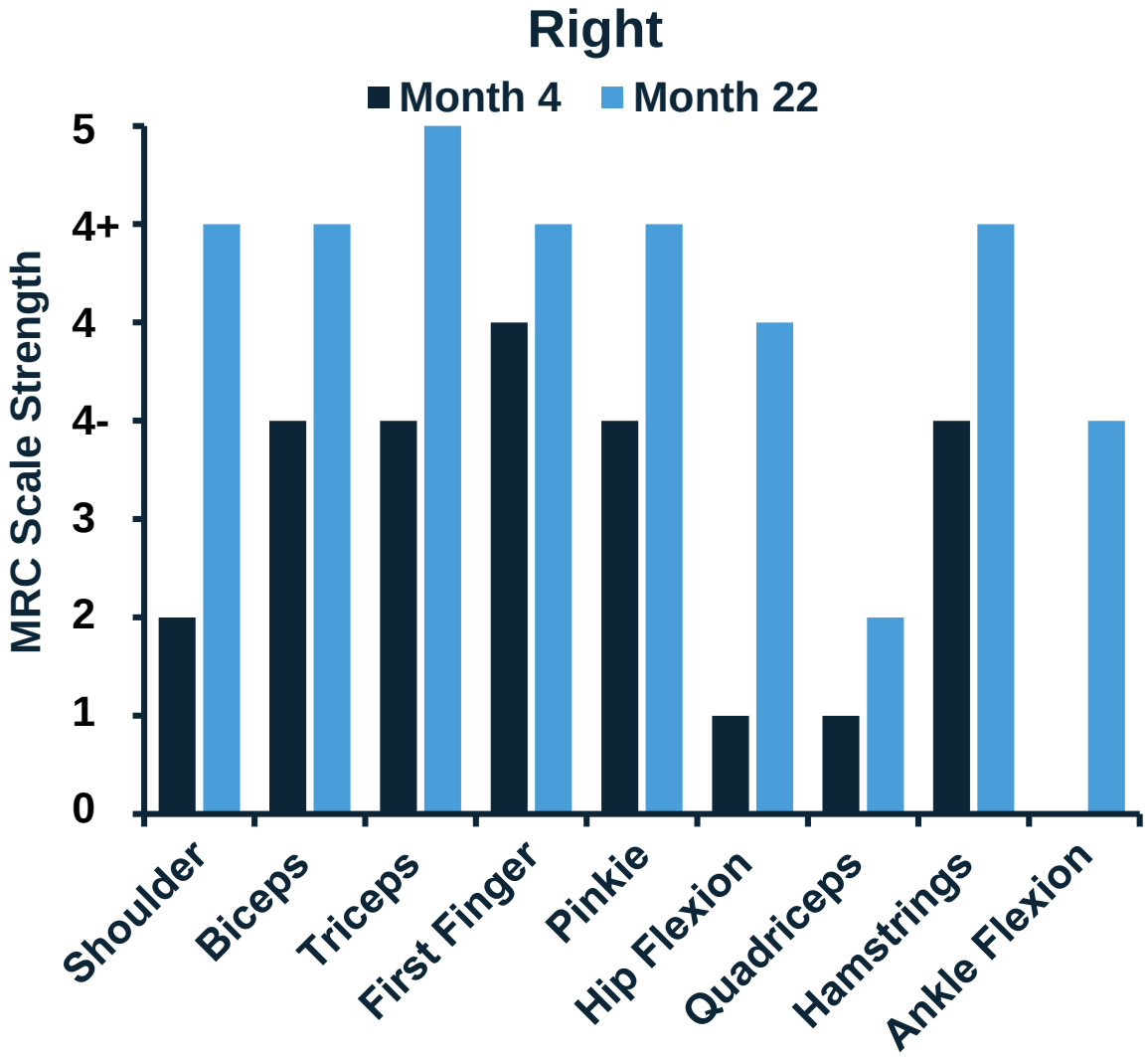
Case 2: Phase 3 participant with decline in VALOR, followed by stabilization and ultimately improvement in the OLE



OLE, open-label extension.

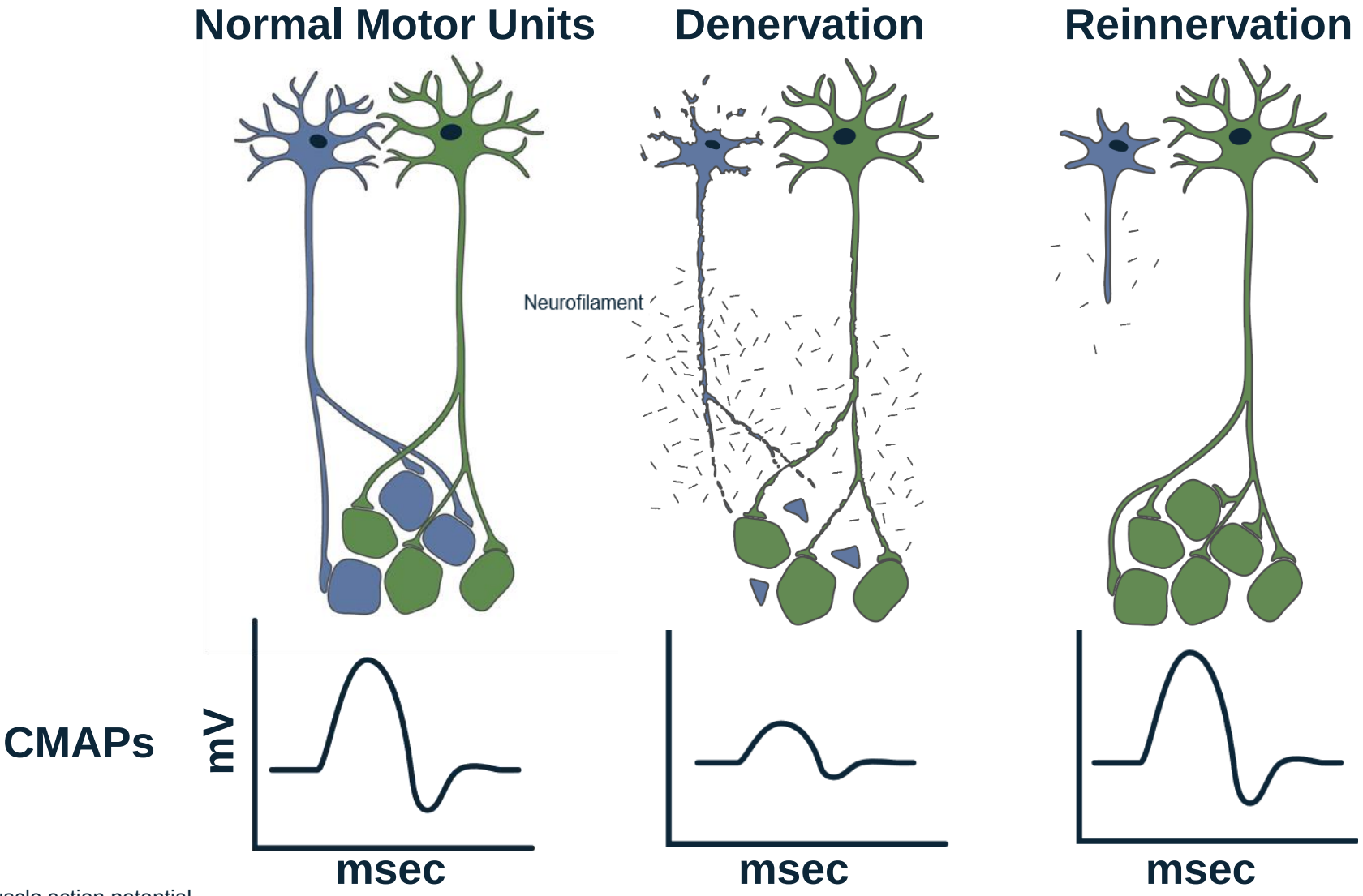
Case 2: Phase 3 participant with decline in VALOR, followed by stabilization and ultimately improvement in the OLE





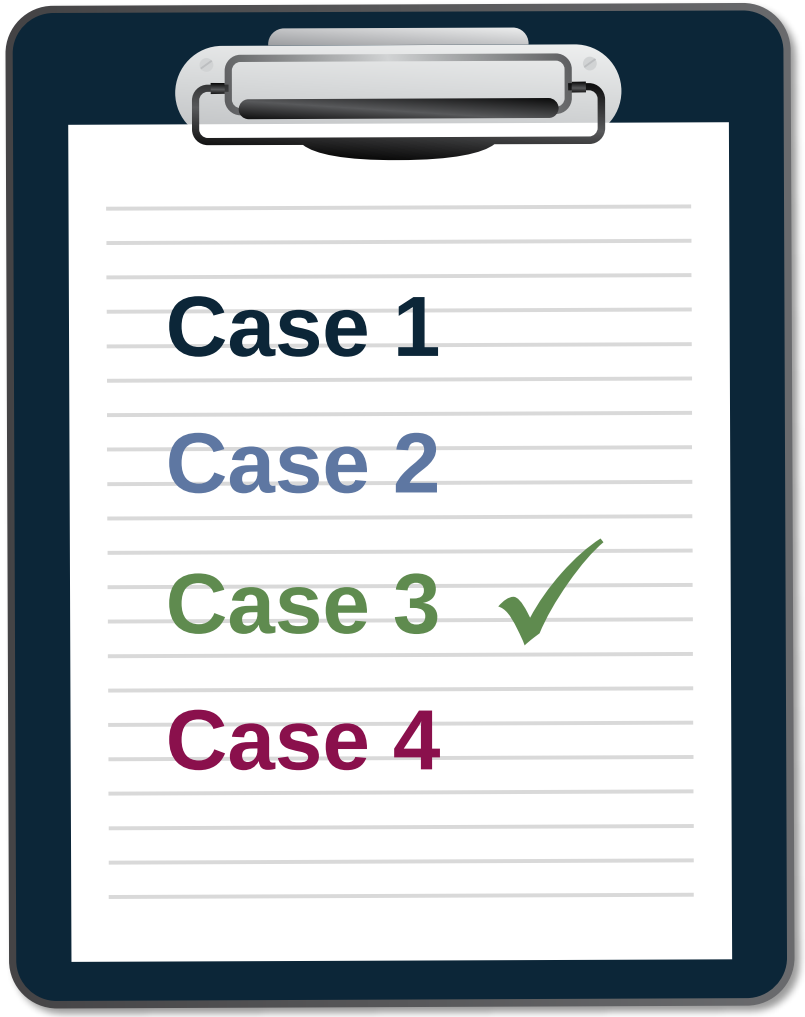
MRC, Medical Research Council; OLE, open-label extension.

Reinnervation may account for increases in CMAP and strength



CMAP, compound muscle action potential.

Case 3: Expanded access participant with reductions of NfL and improvement of strength and function



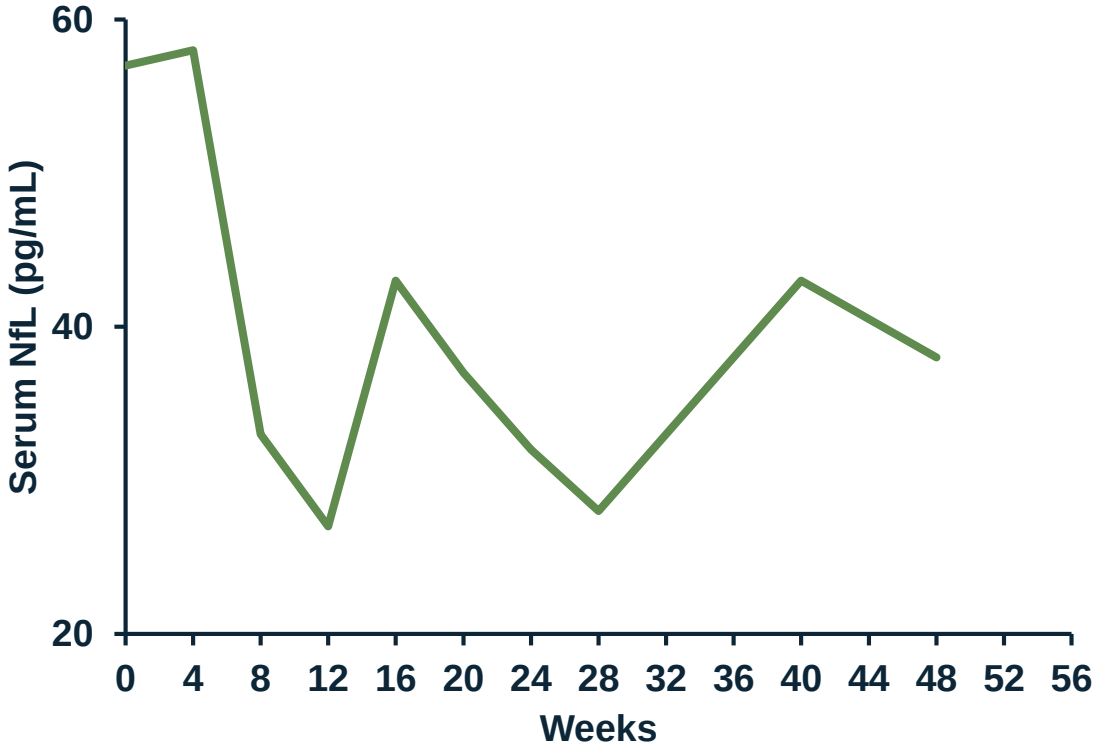
At EAP entry:

- Entered the EAP in 2022
- Serum NfL level: ~57 pg/mL
- Able to walk but with some falls and difficulty with some tasks using arms

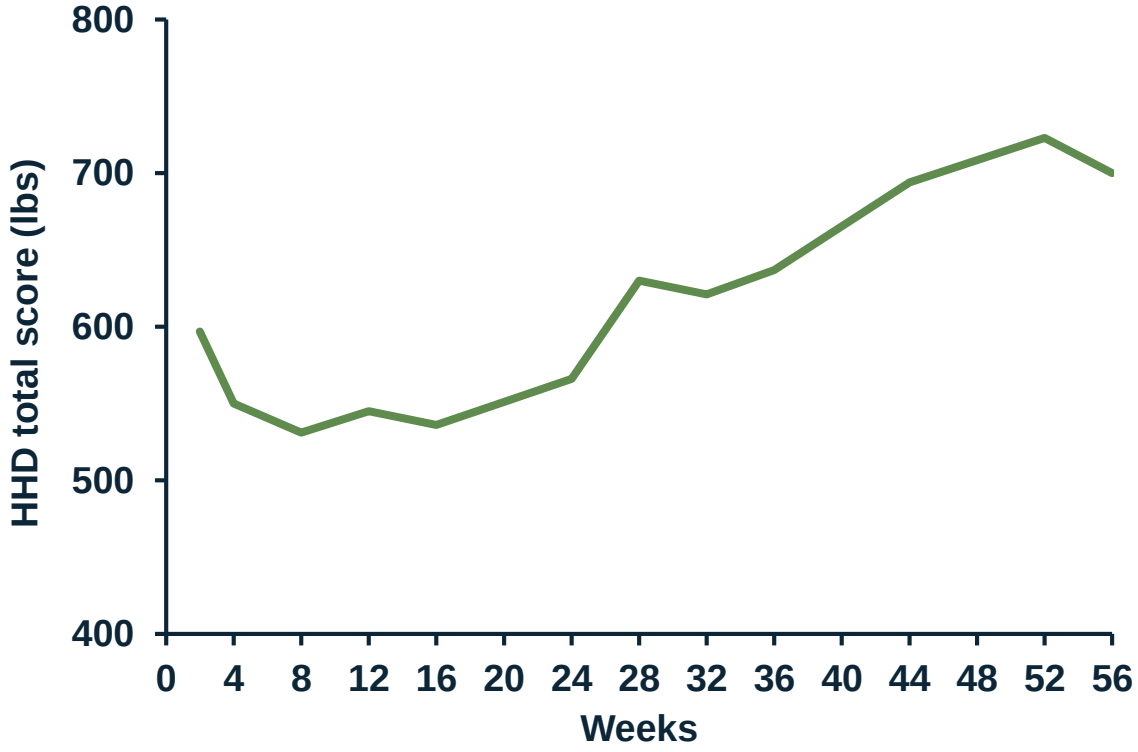
EAP, Expanded Access Program; NfL, neurofilament light.

Case 3: Expanded access participant with reductions of NfL and improvement of strength and function

Change in serum NfL



Change in HHD total score

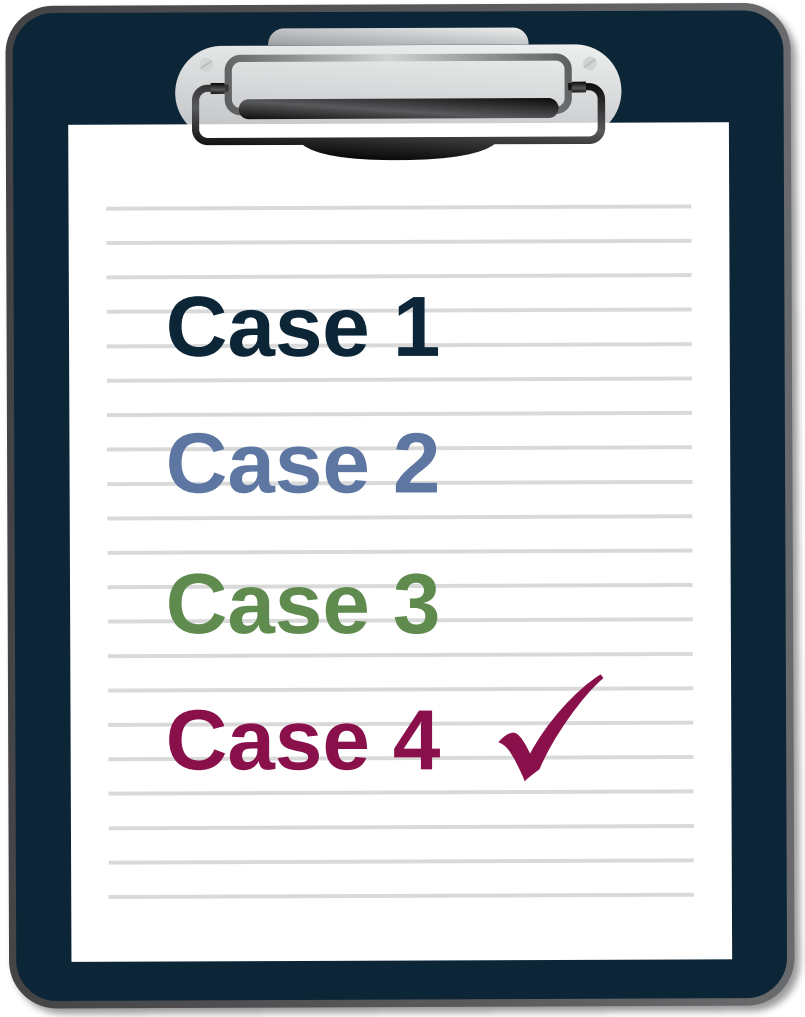


Status since initiating tofersen:

Robust reductions in NfL; improvement in strength; fewer falls; able to push off more easily to get out of chair

HHD, handheld dynamometry; NfL, neurofilament light.

Case 4: Expanded access participant with reductions of NfL and improvement of strength and function

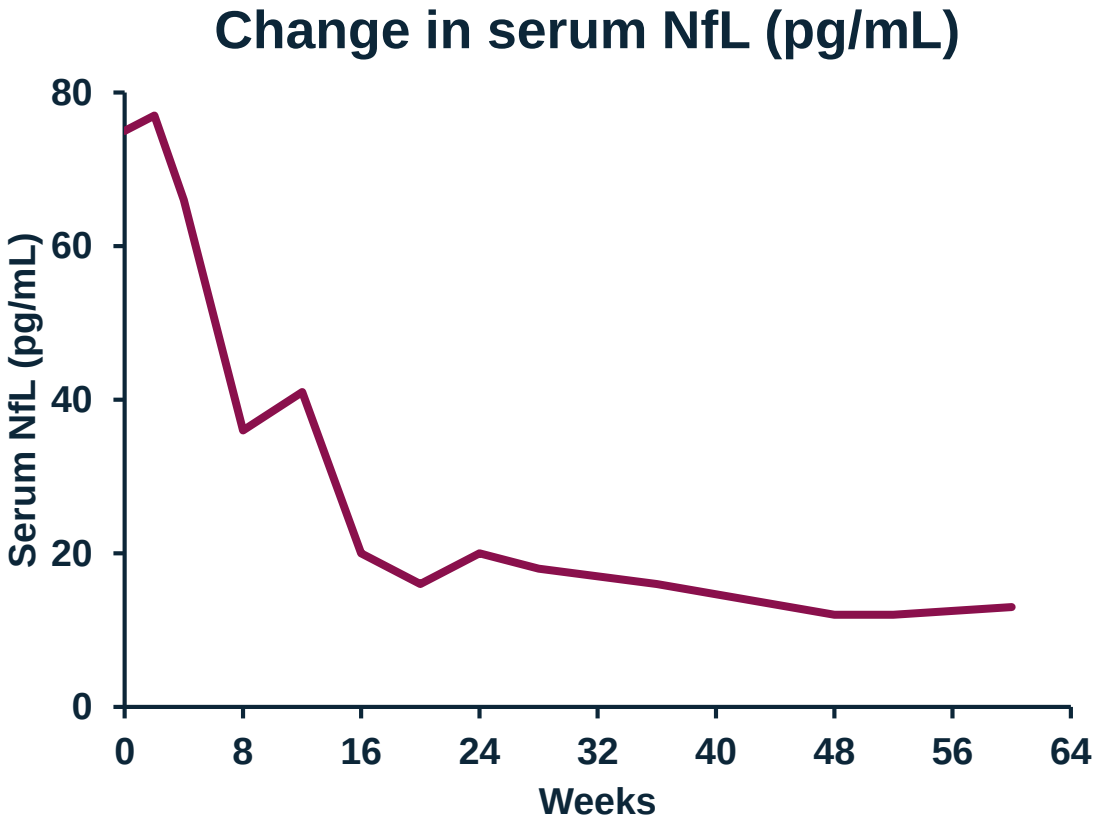


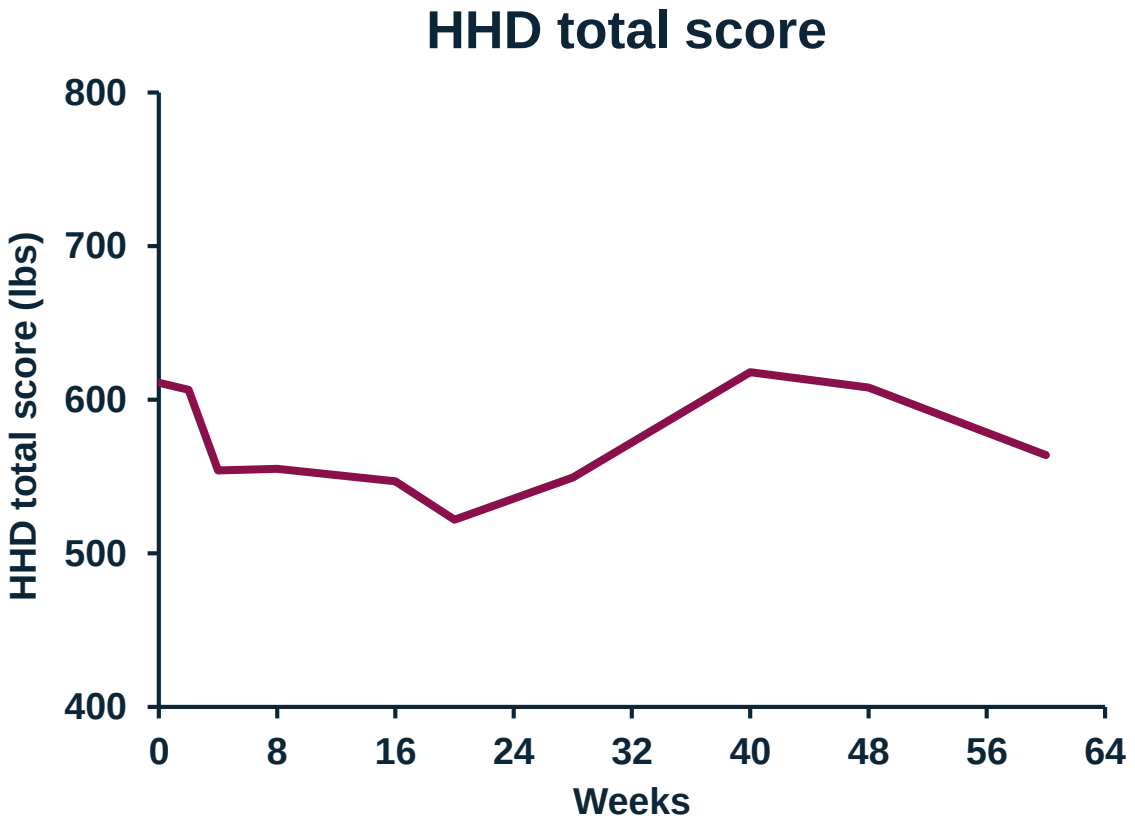
At EAP entry:

- Entered the EAP in 2021
- Young man (<35 years old) with relatively new diagnosis of ALS and a *SOD1* mutation known to be relatively rapid
- Serum NfL level: ~78 pg/mL
- Preserved function (45/48 ALSFRS-R) but losing strength

ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS Functional Rating Scale-Revised; EAP, Expanded Access Program; NfL, neurofilament light; SOD1, superoxide dismutase-1.

Case 4: Expanded access participant with reductions of NfL and improvement of strength and function





Status since initiating tofersen:

Robust reductions in NfL; improvement in strength and function

HHD, handheld dynamometry; NfL, neurofilament light.

Case 4: Expanded access participant with reductions of NfL and improvement of strength and function

Functional Assessment	Initial PT Evaluation	PT Evaluation at 52 Weeks
Berg Balance Scale	**24 / 56**	**25 / 56**
Timed Up and Go (using rollator) *Meaningful change: ~2.1 seconds*	**17 seconds**	**12.5 seconds**
10-meter walk test *Meaningful change speed is about 0.15 m/s*	**0.37 m/s**	**0.92 m/s**

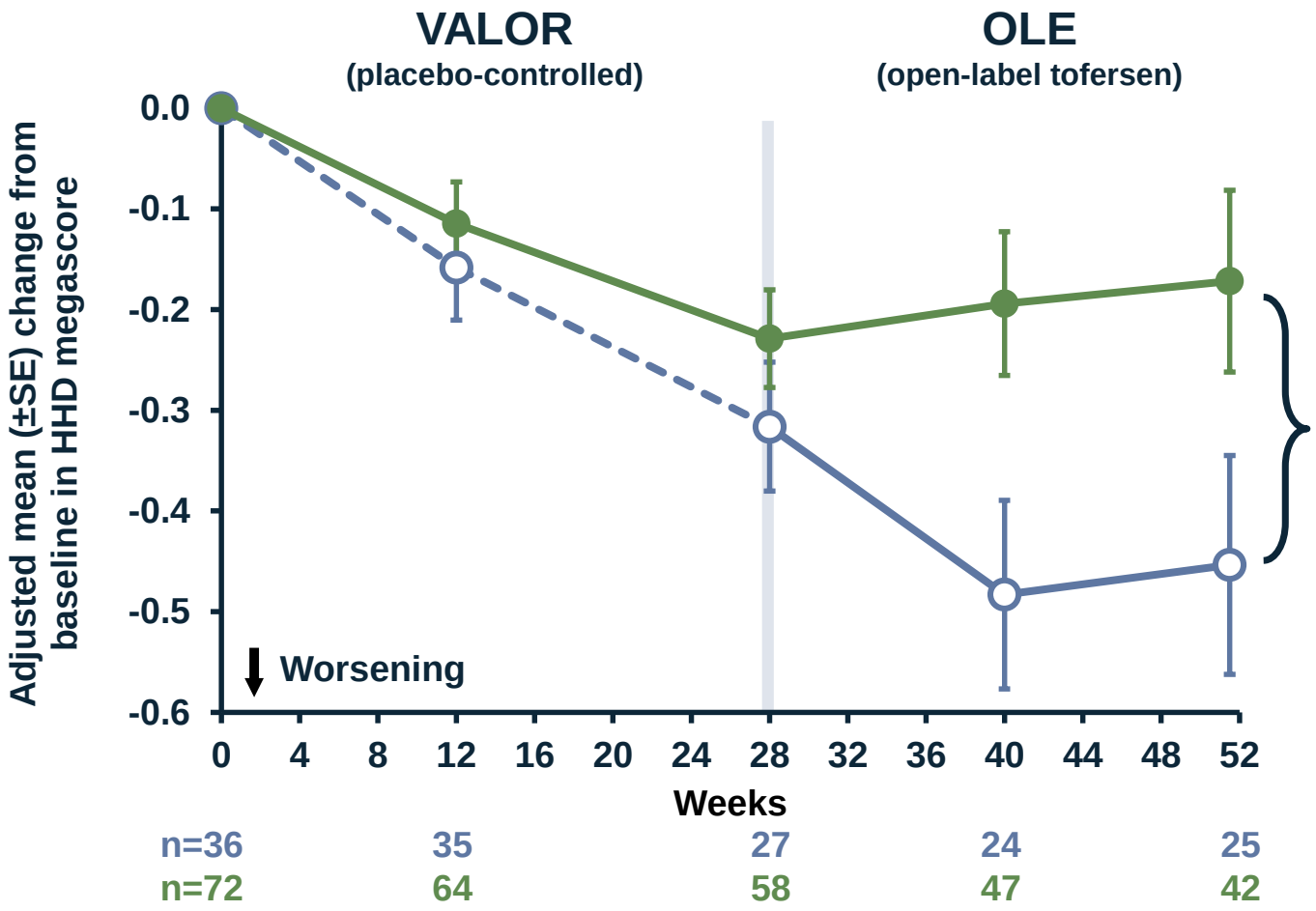
Status since initiating tofersen:

Robust reductions in NfL; improvement in strength and function

NfL, neurofilament light.

Early-start tofersen slowed loss of muscle strength

Combined VALOR + OLE; ITT population



Placebo + delayed-start tofersen

Early-start tofersen

Adjusted mean difference:
0.28 (95% CI: 0.05, 0.52)
p=0.0186

Improvement in HHD megascore from baseline to Week 52:

Delayed-start tofersen: 8.1%

Early-start tofersen: 26.9%

Difference: 18.8% (95% CI: 1.4, 36.2)

HHD, handheld dynamometry; ITT, intent-to-treat; 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.

Reports from global colleagues are equally impressive

TRICALS

The consensus view of TRICALS neurologists is that Tofersen shows clear benefit for people with ALS due to *SOD1*mutation, especially if given early in the disease course, and support should be given for licensing in this group of patients.

CANADA TODAY

‘Really remarkable’ drug helps motor neuron diseases

Layla Nelson · September 21, 2022

“In my 30 years as an ALS physician, this is the first study where I have personally seen people stop progressing AND….some of them recover function. The dramatic effect also on NfL is a huge step forward for the field.”

Dr. Merit Cudkowicz; Massachusetts General Hospital

“This is the first-time participating patients have reported an improvement in their motor function – ‘I can walk without my poles. I can climb my garden steps, which I haven’t been able to do for two years. I can write my Christmas cards this year, which I couldn’t do last year.’”

Prof Dame Pamela Shaw; Neuroscience Institute in Sheffield

THE TIMES OF ISRAEL

‘New era of treatment’: Israelis among first to receive ‘game-changing’ ALS medicine

Tofersen, which is injected into the spine like an epidural, is giving new hope to two patients at Tel Aviv Sourasky Medical Center

By NATHAN JEFFAY
15 December 2022, 11:49 am

Current therapies do not address *SOD1*-ALS pathophysiology

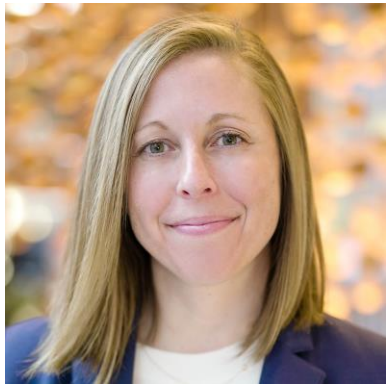
1995	2011	2017	2022
Rilutek® (riluzole)	**Nuedexta® (dextromethorphan hydrobromide and quinidine sulfate)**	**Radicava® (edaravone)**	**Relyvrio™ (sodium phenylbutyrate and taurursodiol)**
Indicated for the treatment of ALS	Indicated for the treatment of pseudobulbar affect (PBA)	Indicated for the treatment of ALS	Indicated for the treatment of ALS

None designed to target underlying disease pathology of *SOD1*-ALS

Based on initial US approvals. www.fda.gov.

Perspective on use of tofersen in clinical practice

- *SOD1*-ALS is serious, progressive, and ultimately fatal with significant unmet medical need
- Adverse events warrant consideration (serious neurologic events, LP-related events), but in the context of the disease and the effects demonstrated, the potential benefits outweigh the potential risks
- A reduction of neurofilament indicates slowing of the neurodegenerative disease process
- Tofersen has demonstrated potential for stabilization or improvement of clinical function, strength, and quality of life
- Case report data and individual stories of improved strength and function are consistent, remarkable, and unprecedented
- We recognize and appreciate the many people who made this possible
- Urgent need to make tofersen available to people living with *SOD1*-ALS



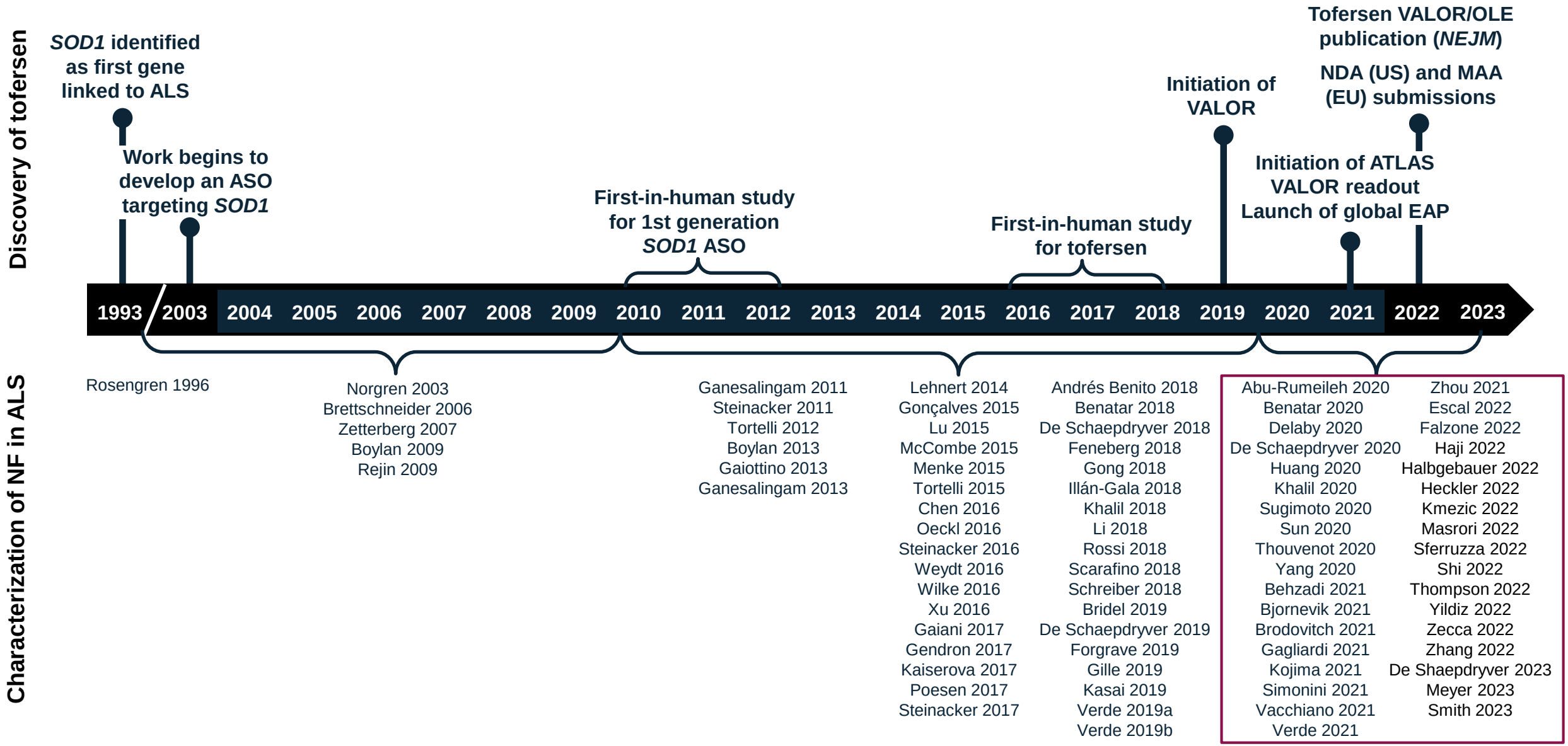
Conclusion

Stephanie Fradette, PharmD

Clinical Development Lead and ALS Portfolio Head

Biogen

Tofersen development program reflects the progression of scientific knowledge



Support for the approval of tofersen for *SOD1*-ALS

SOD1-ALS is a serious, life-threatening disease with critical unmet medical need

Tofersen has a substantial effect on neurofilament, a surrogate endpoint that is reasonably likely to predict clinical benefit

Tofersen has a clinically significant impact on disease progression

Serious neurologic events warrant awareness and consideration, but are manageable in the context of *SOD1*-ALS

ATLAS is an ongoing, adequately-controlled study to confirm clinical benefit

To our study participants, their families, and their caregivers…

To our study investigators and site staff…

To the patient advocacy organizations and clinical trial consortia…

To the entire ALS community…

Thank You