Lessons learned from development of a genetically targeted therapy for SOD1 ALS

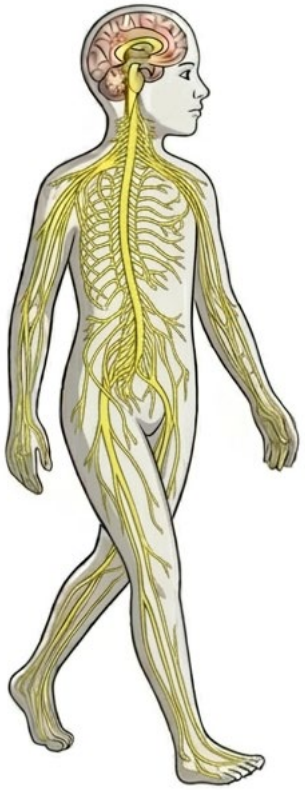
Precision Medicine in Neuroscience: Tools, Translation, and Implementation
National Academy of Medicine
March 4, 5th, 2026

Toby Ferguson, MD, PhD

Disclosures

I am a current employee of Alnylam Pharmaceuticals and past employee of Biogen and Voyager Therapeutics.

ALS is a fatal disease characterized by loss of motor neurons and muscle weakness



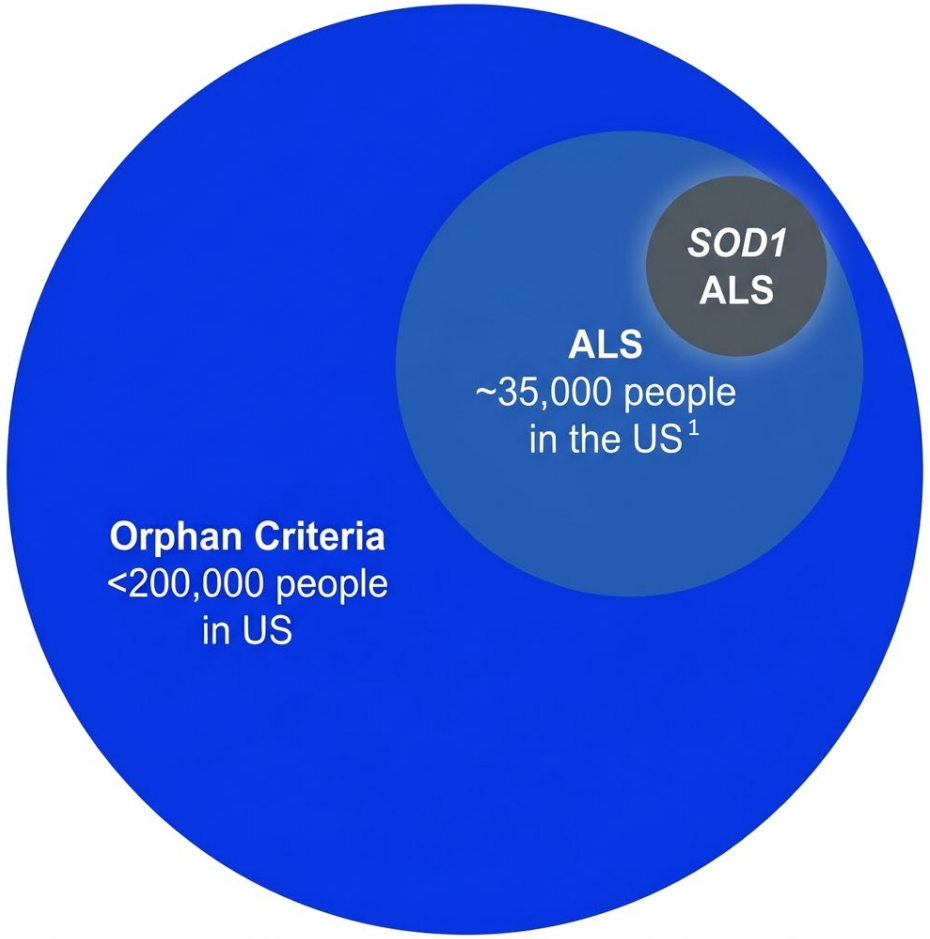
ALS is a progressive disease with no natural history of sustained plateaus or improvement

Weakness leads to difficulty breathing, swallowing, and moving

ALS is uniformly fatal typically from respiratory failure 3-5 years from symptom onset

Al-Chalabi and Hardiman Nature Reviews Neurology 2013

SOD1 ALS is rare but genetic testing facilitates a trial in the SOD1 population



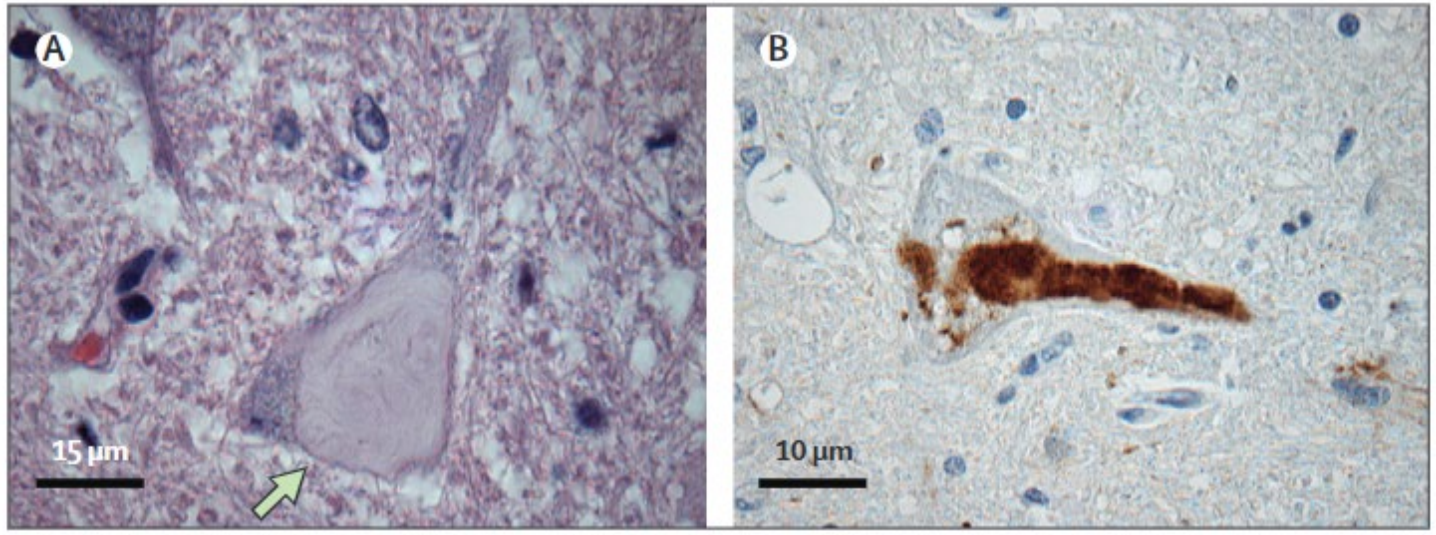
- SOD1 discovered as first genetic cause of ALS (1993), genetic testing now widely available
- SOD1 ALS is rare
  - ~300-600 US
  - ~1,000 Europe
  - ~500 Japan

[1] CDC National ALS Registry 2026

Mutations of SOD1 lead to production of a toxic protein species

Knockdown of SOD1 is appropriate therapeutic approach

Mutant SOD1 accumulates in motor neurons



Loss of enzyme activity not linked to disease

Normal enzymatic activity:

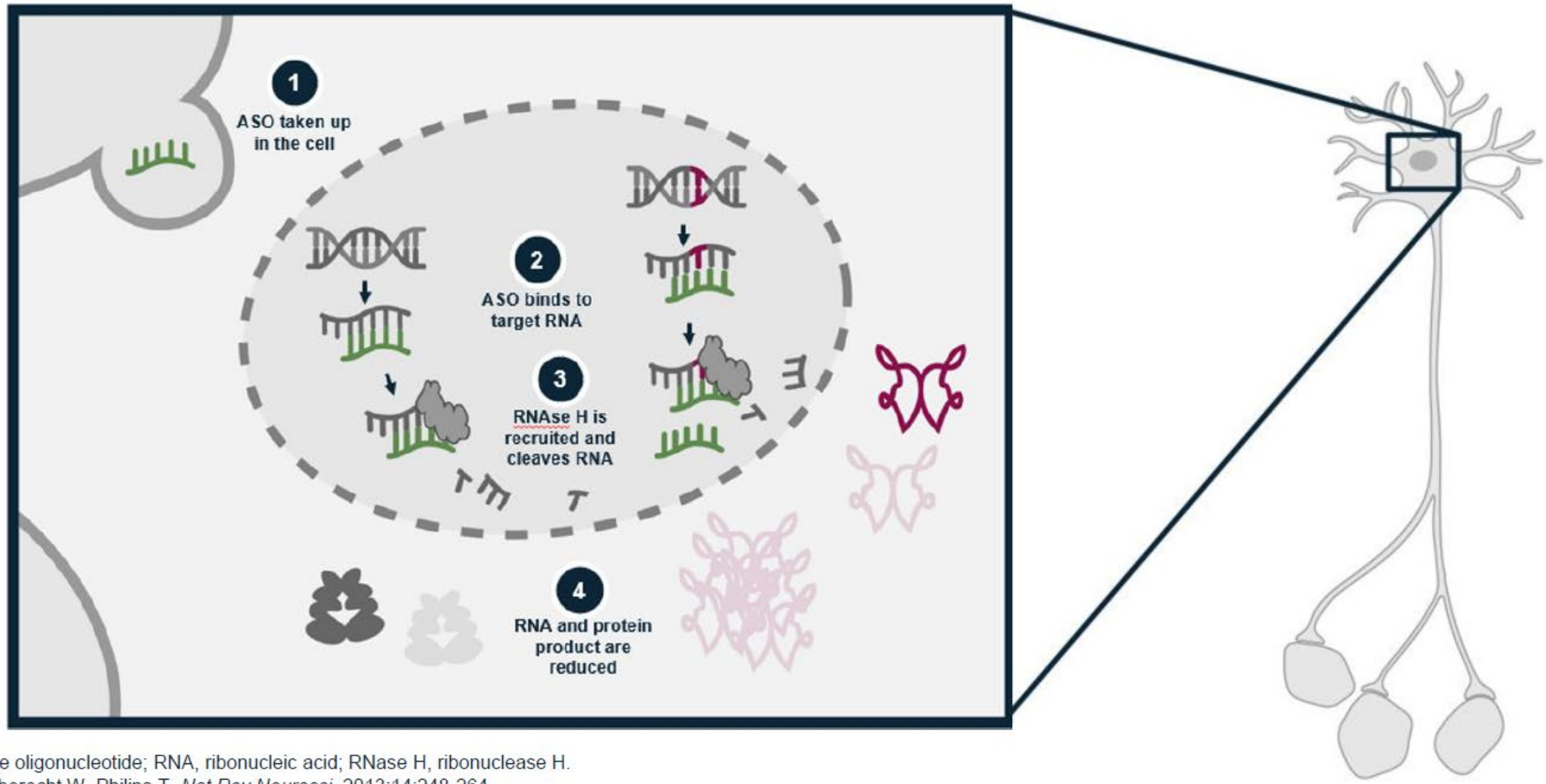
- Cys7Ser, Glu41Gly, Leu85Phe, Asp91Ala, Asp110Thr, Leu118Val, Glu134Ala

No enzymatic activity:

- His47Arg, Gly86Arg, Cys112Tyr, Leu127*, Gly128*

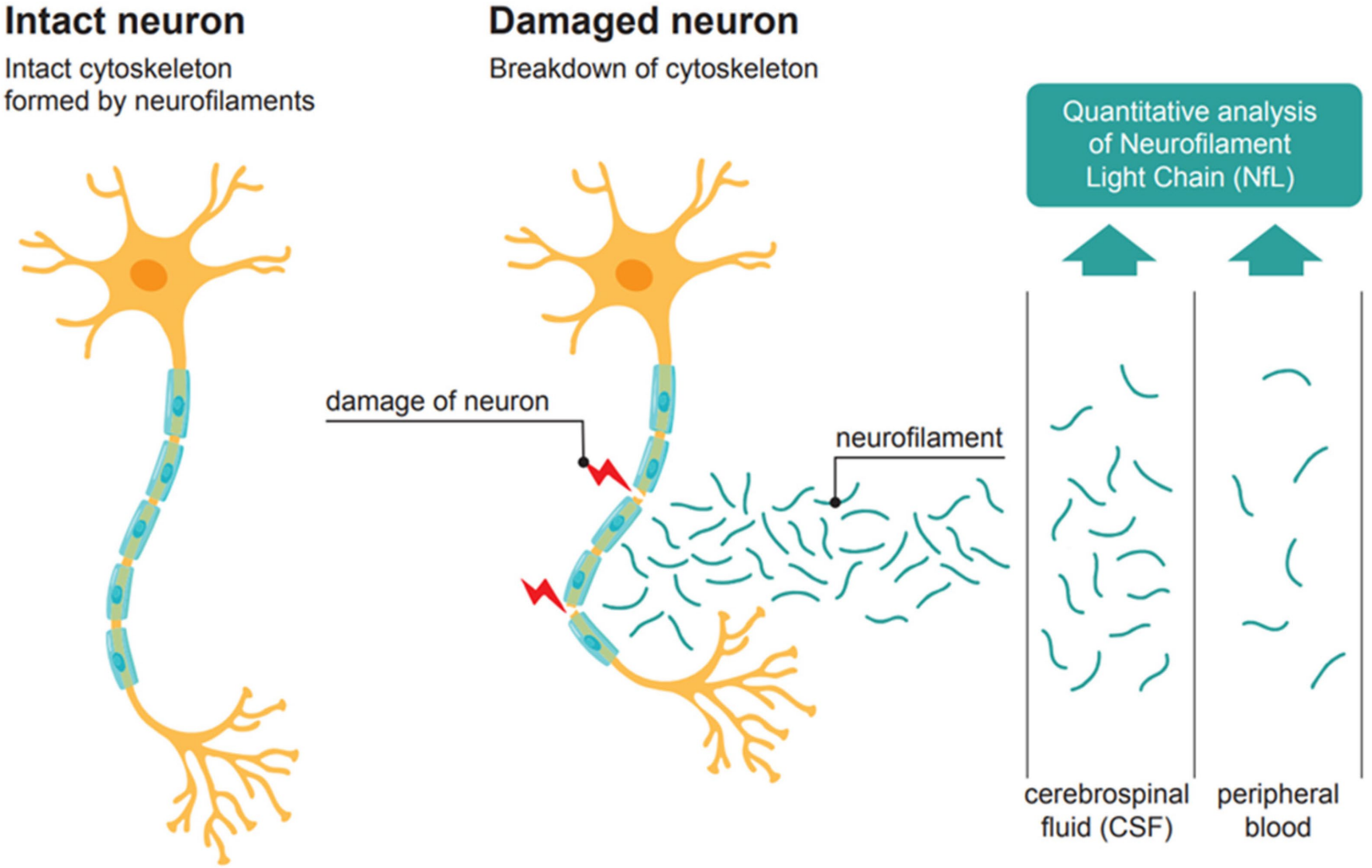
Benatar et al., 2025

Tofersen is an ASO that targets knockdown of SOD1 mRNA



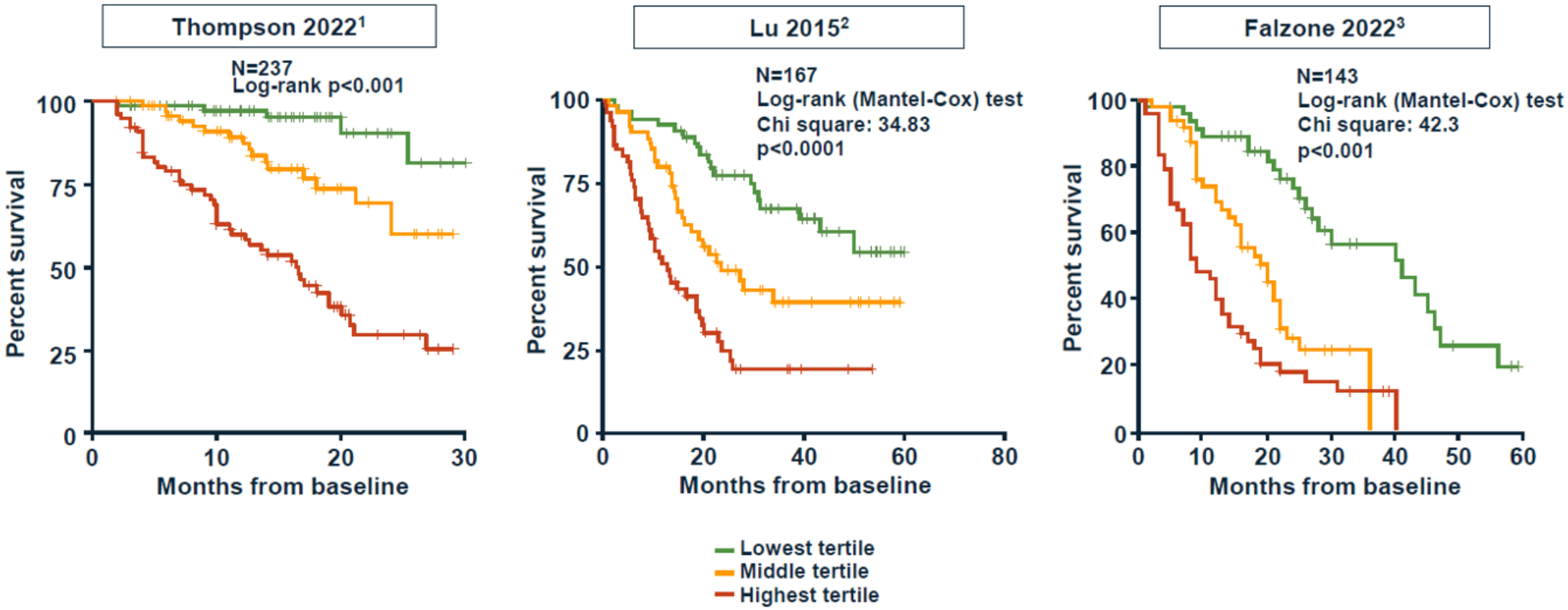
ASO, antisense oligonucleotide; RNA, ribonucleic acid; RNase H, ribonuclease H.
Based on Robberecht W, Philips T. *Nat Rev Neurosci*. 2013;14:248-264.

Neurofilaments are a marker of motor neuron integrity and injury



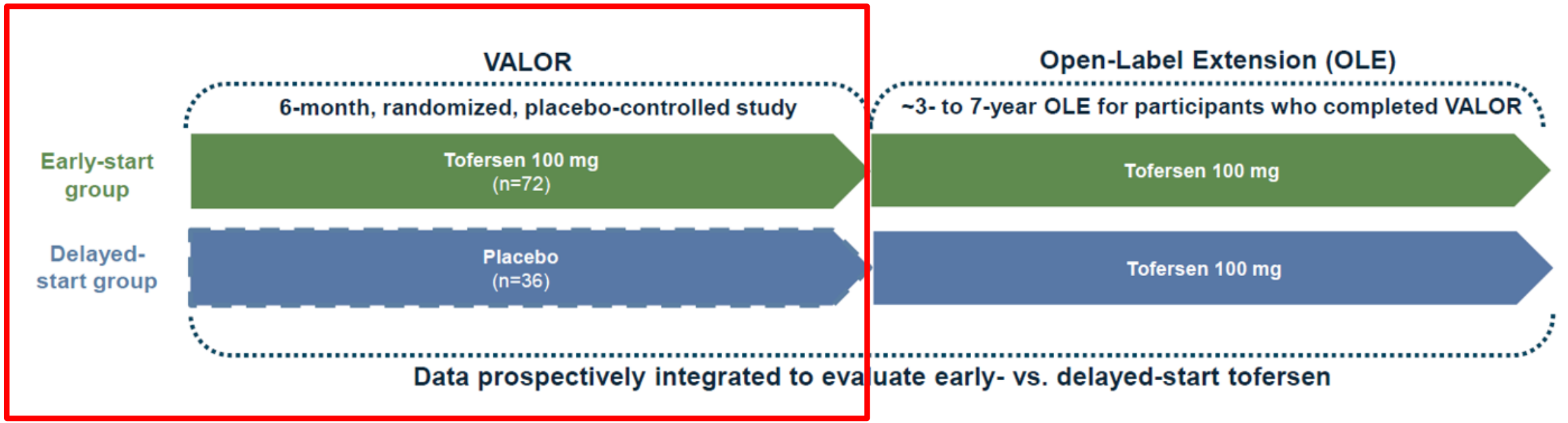
Wellman et al., 2024

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.

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

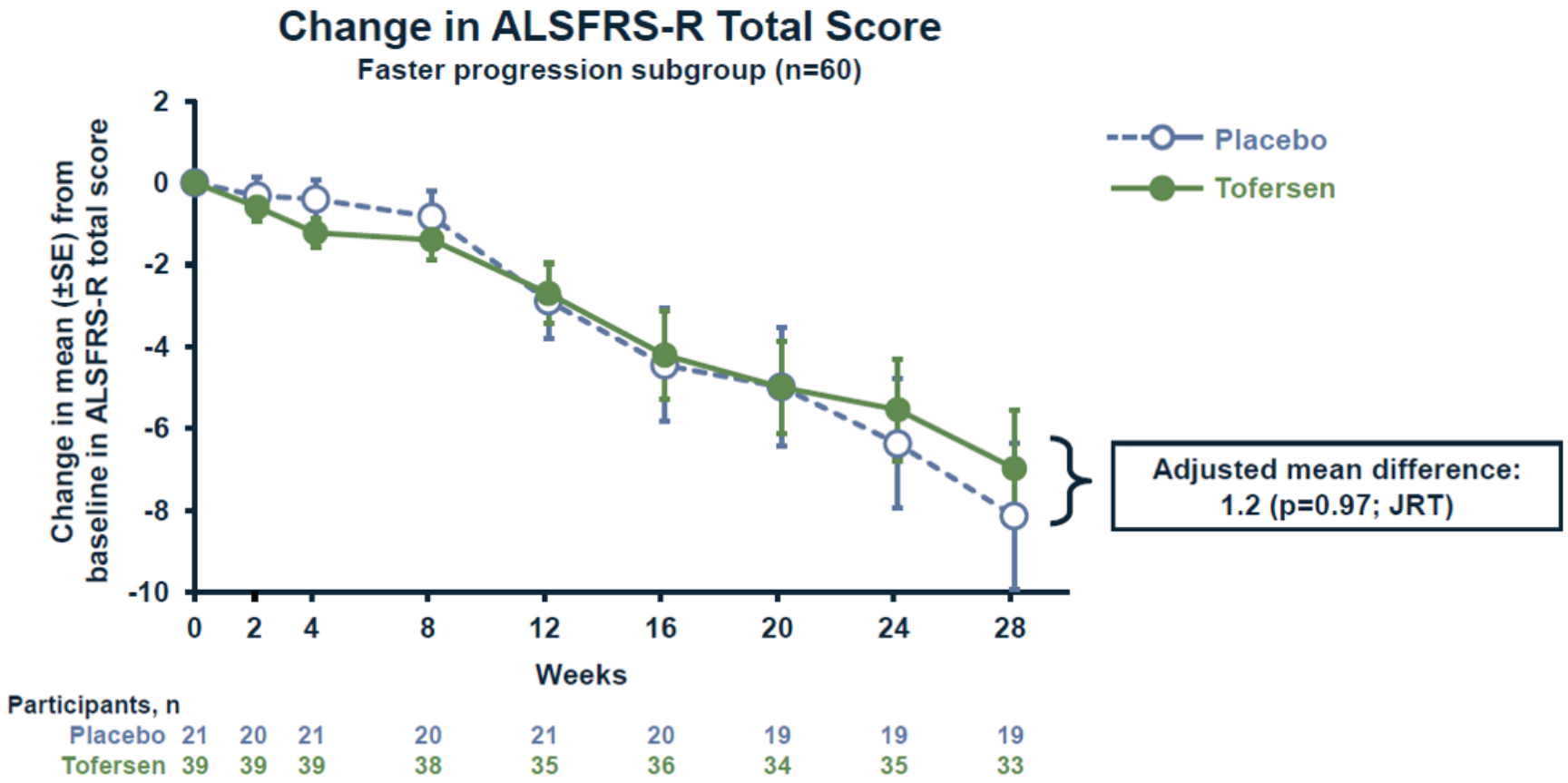
- ALSFRS-R total score

Secondary endpoints (in order of testing)

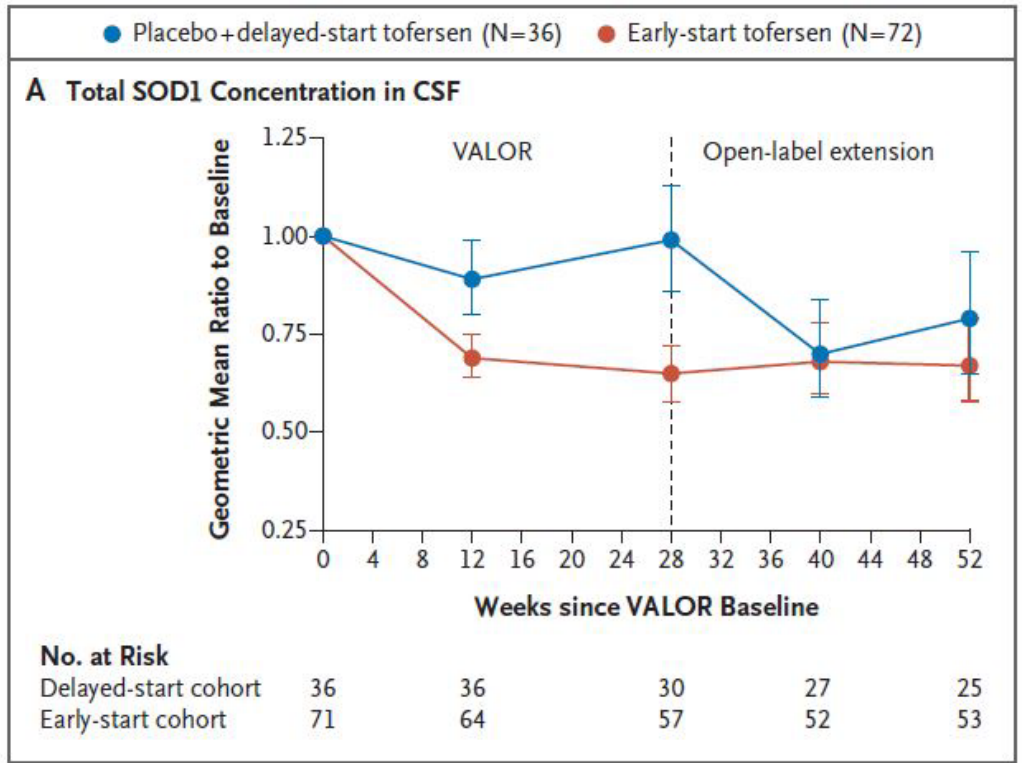
- Total SOD1 protein
- Plasma NfL
- Percent-predicted slow vital capacity (SVC)
- HHD megascore
- Ventilation assistance-free survival
- Overall survival

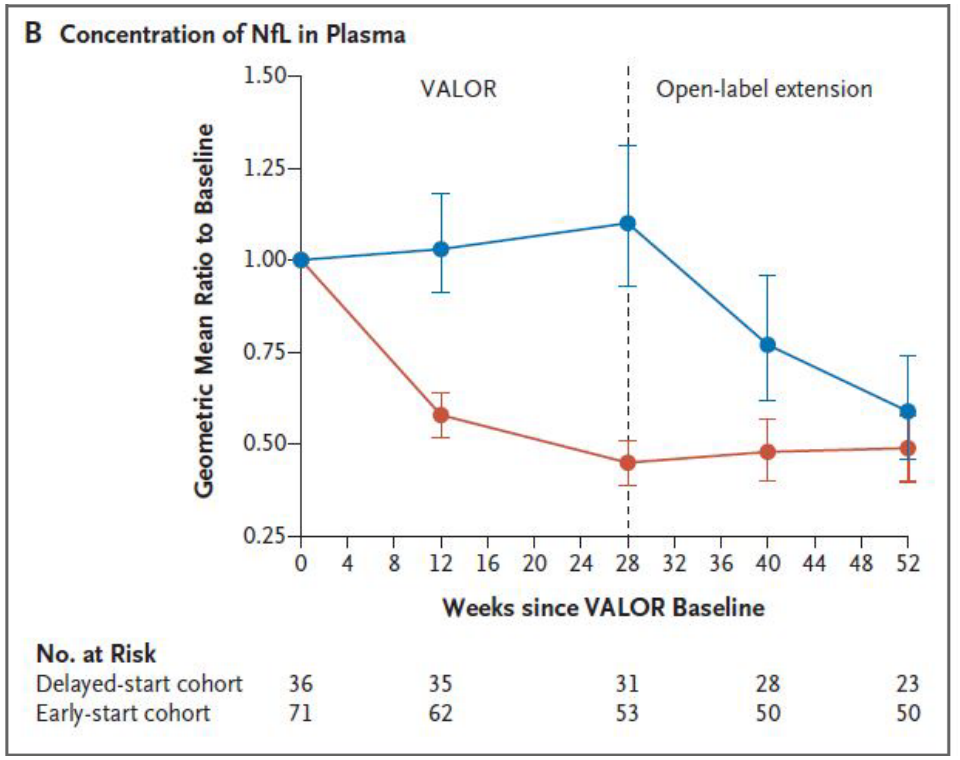
Statistical significance was not achieved on the primary endpoint in VALOR

VALOR, FPS (mutation/slope)



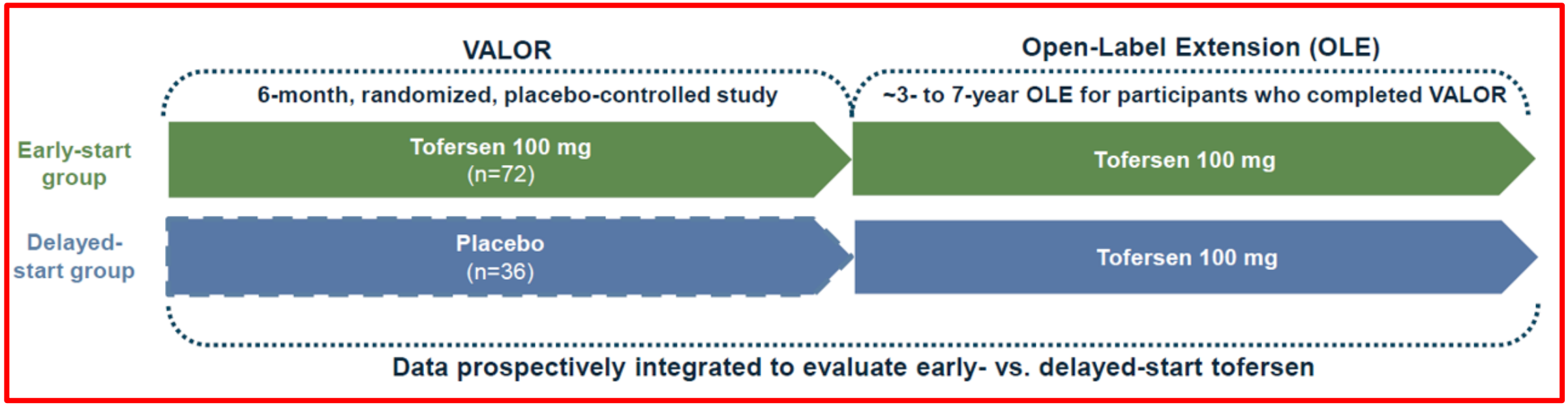
Tofersen reduces CSF SOD1 and plasma neurofilament





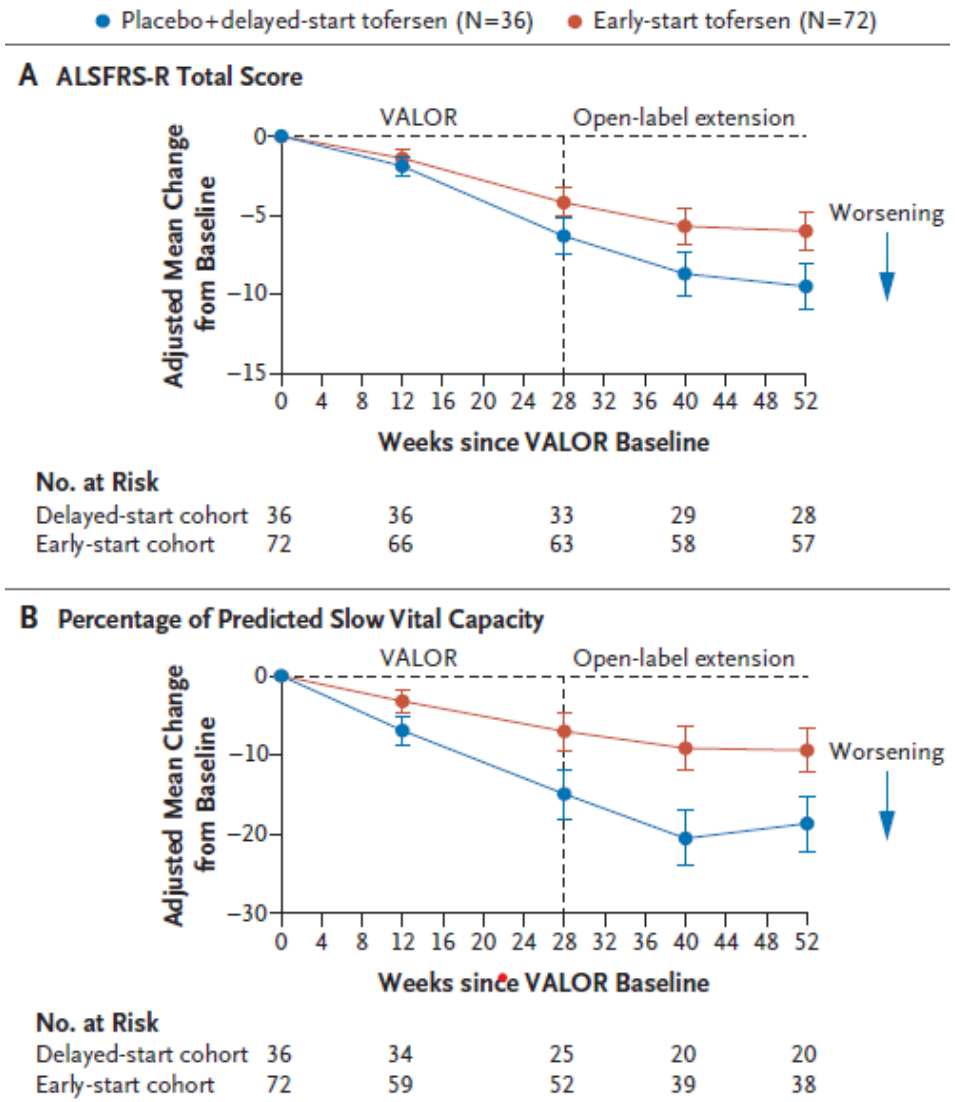
Miller TM et al. NEJM 2022

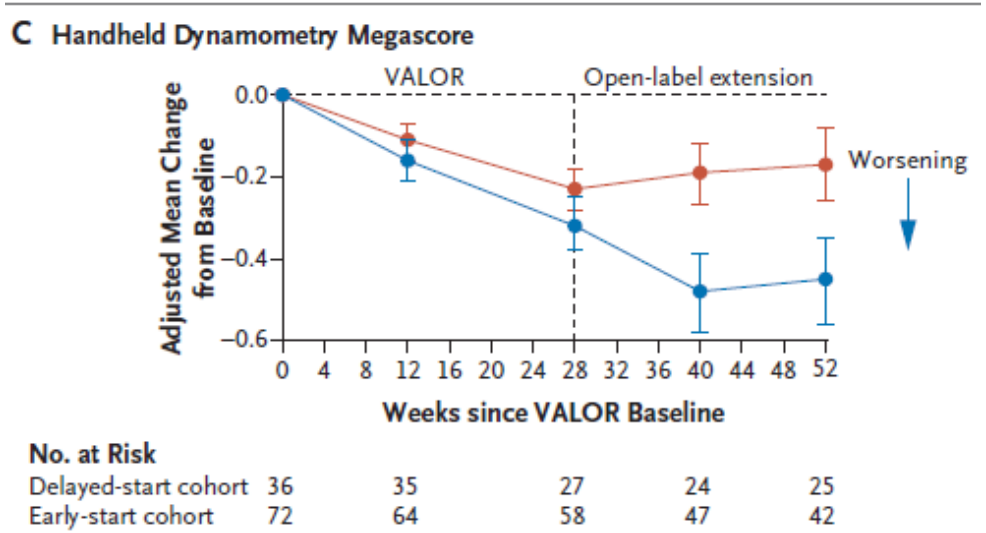
Integrated VALOR+OLE analyses

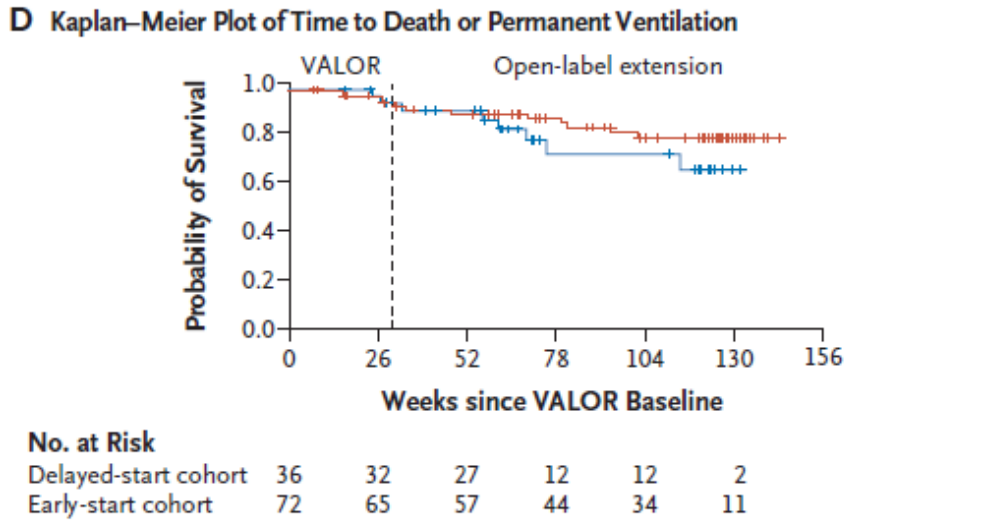


To preserve the integrity of ongoing data collection, participants, site staff, and the Biogen study team remain blinded to VALOR treatment assignments through completion of the OLE

Delayed start analysis consistent with Tofersen benefit







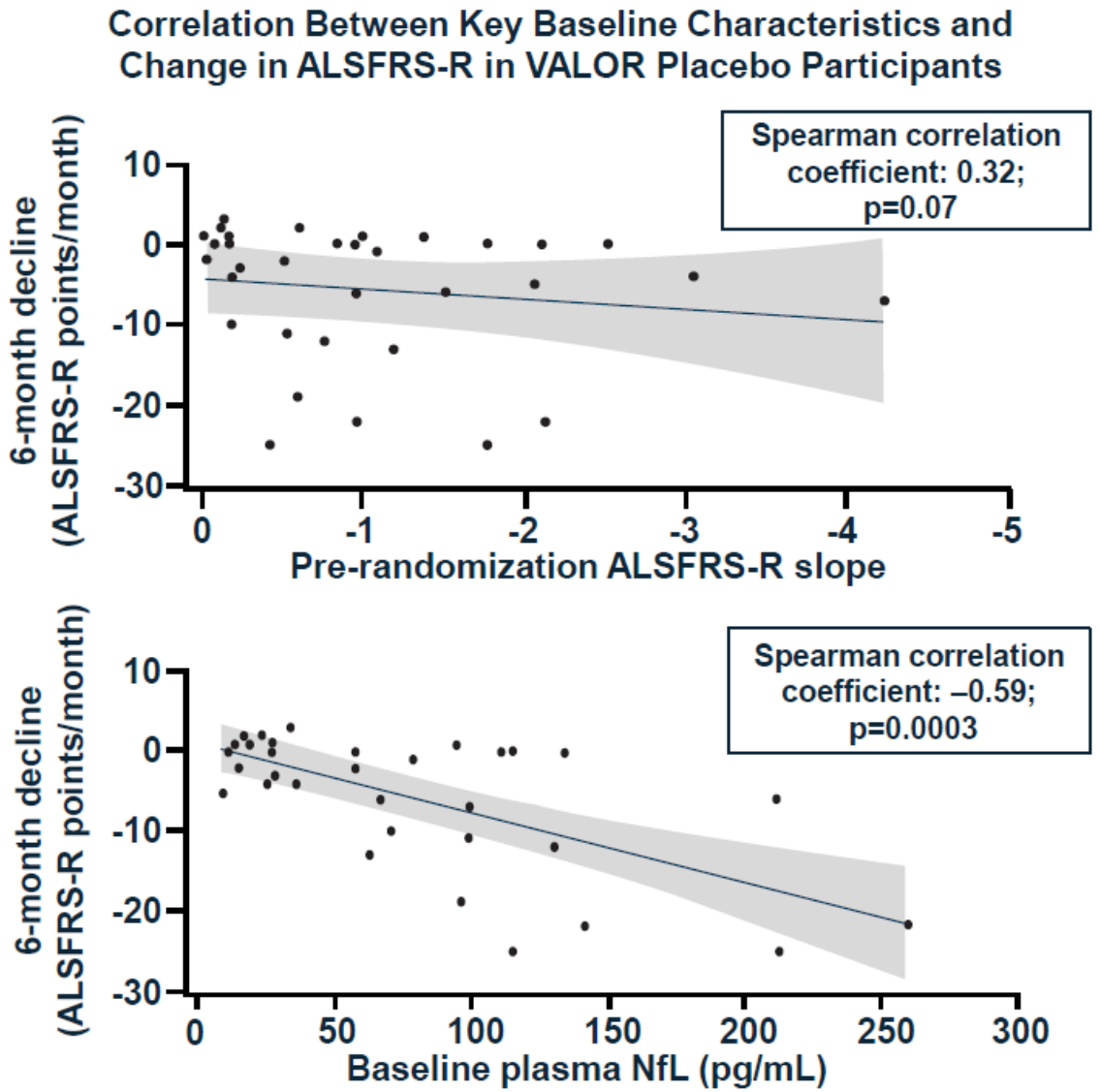
Miller TM et al. NEJM 2022

Tofersen Approved

Tofersen Approved by FDA 25 April 2023 under accelerated approval mechanism

Tofersen received European Commission Approval 30 May 2024

Using baseline neurofilament to control for disease heterogeneity



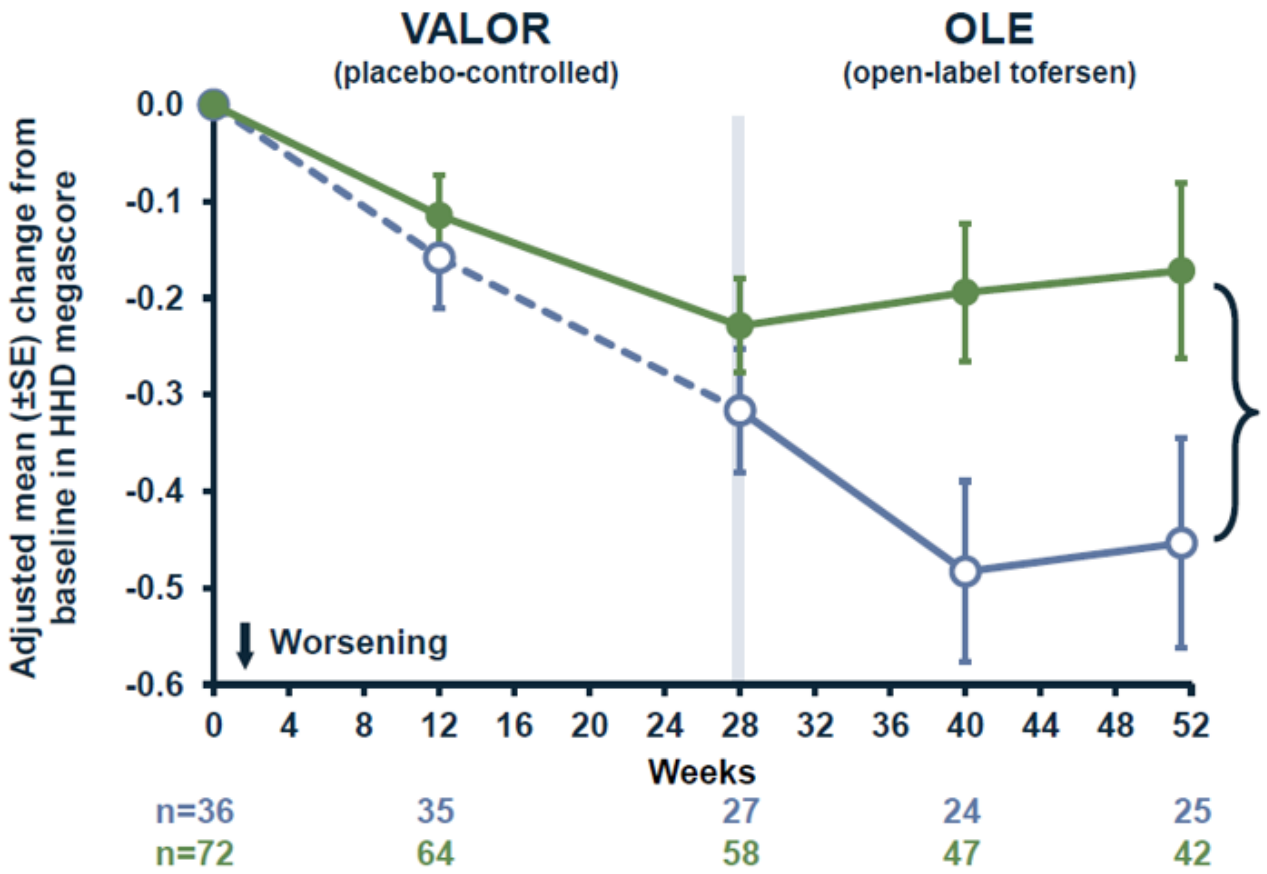
Mechanisms to control for disease heterogeneity

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

Effect on muscle strength (HHD)

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%

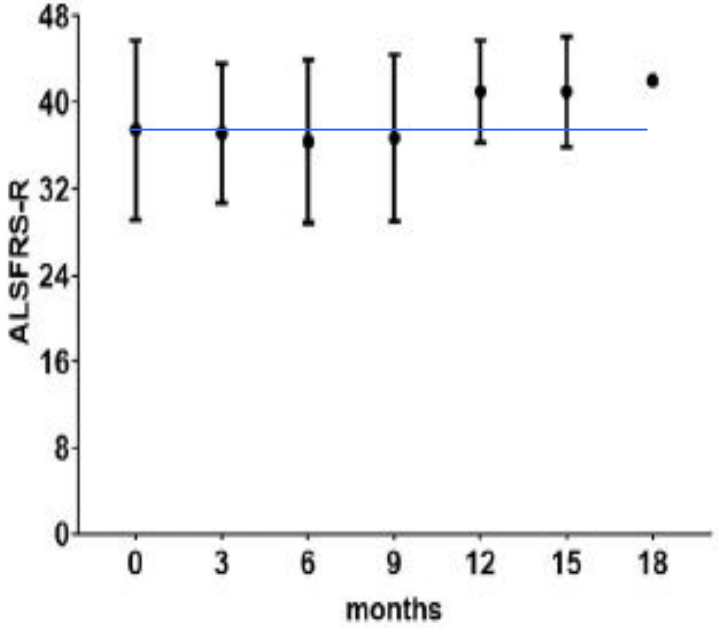
Early-start tofersen: 26.9%

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

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

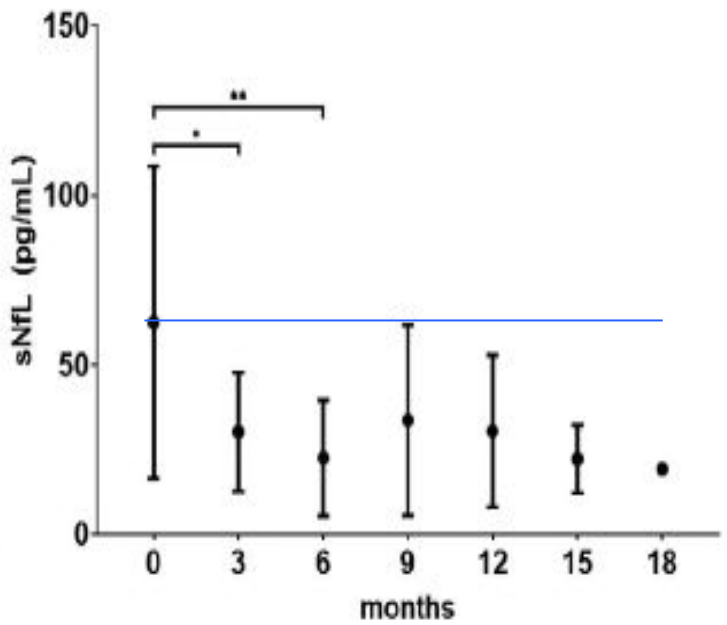
Tofersen post-approval efficacy consistent with VALOR including biomarkers and clinical improvement

ALSFRS-R

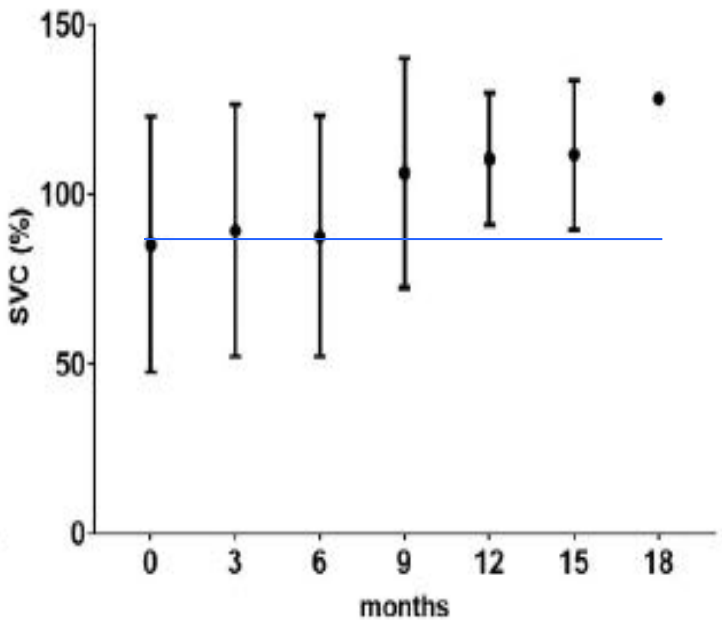


8/16 stable or improved

NFL



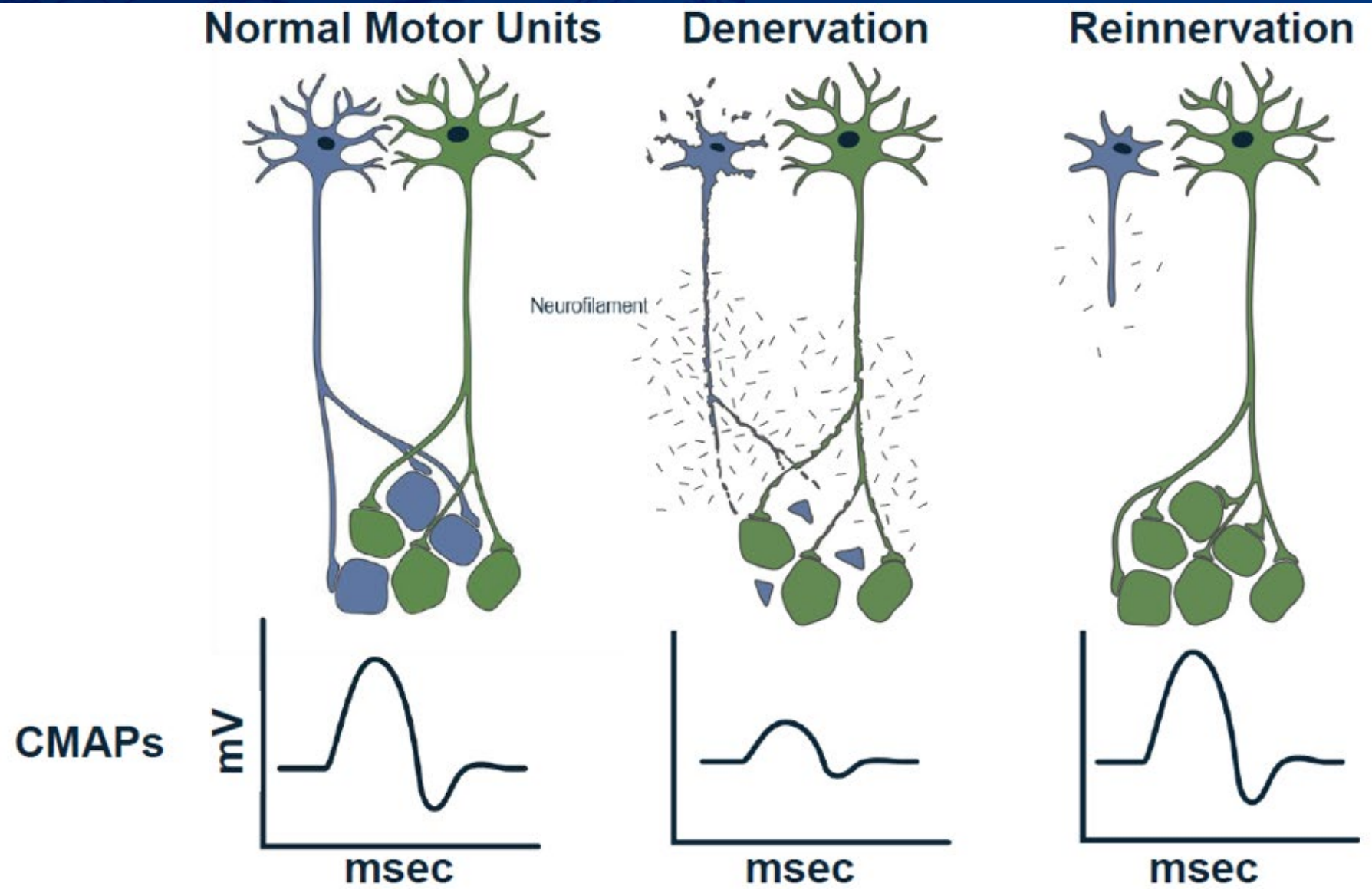
SVC



8/16 stable or improved

Meyer T et al. Muscle & Nerve 2024

Reinnervation may account for increases in strength

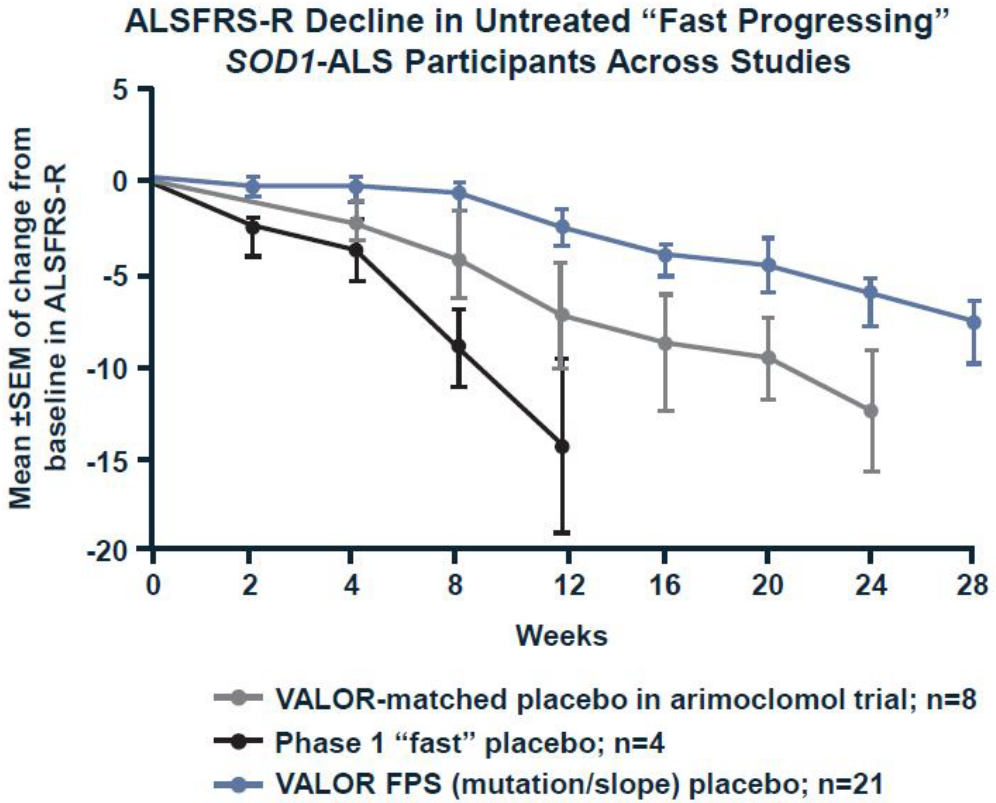


Conclusions

- Tofersen is the first genetically targeted ALS therapy and is approved in the USA (accelerated approval) and EU (exceptional circumstances) as well as in Japan and China more recently.
- Tofersen efficacy (USA) is subject to confirmation based on ongoing ATLAS study in presymptomatic SOD1 ALS
- Tofersen, as evidenced by neurofilament reduction, is a disease modifying therapy and clinical improvement has been observed in multiple people with SOD1 ALS
- Neurofilament is an important biomarker of therapeutic response and prognosis in ALS

Study duration was short and contributed to failed primary outcome

Duration

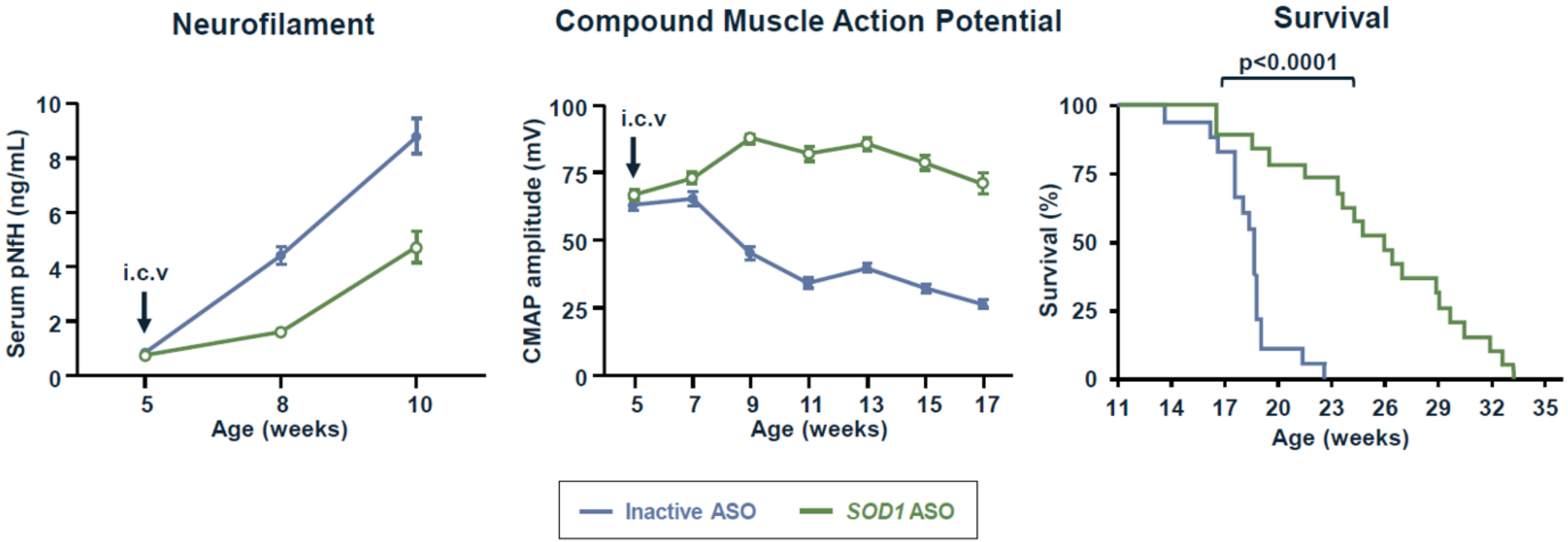


Longer study duration (> 6 months) needed to:

- 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

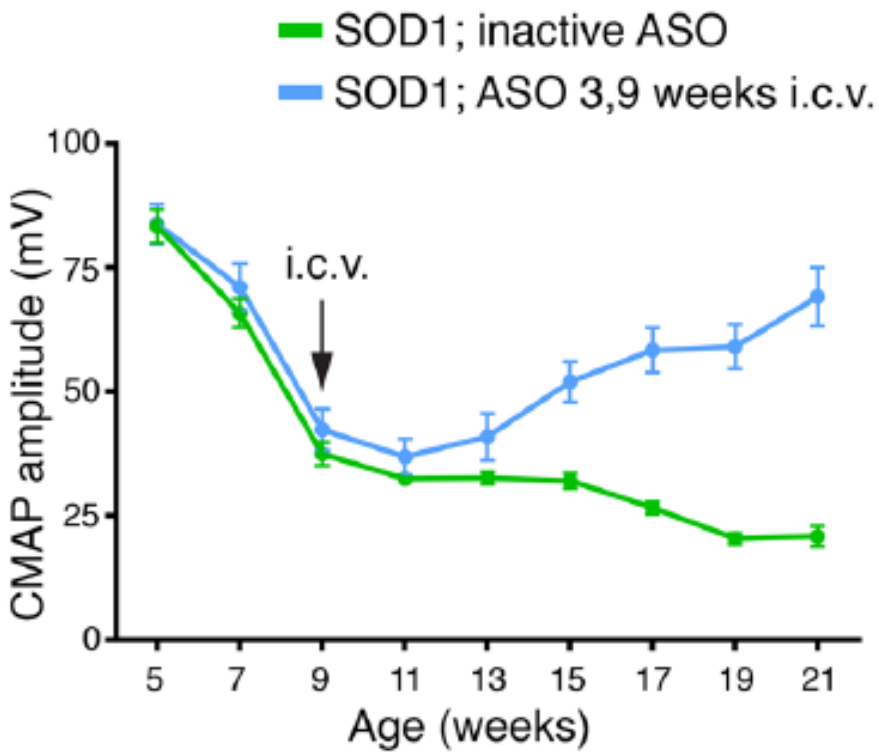
ALSFRS-R, ALS Functional Rating Scale-Revised; FPS, faster progression subgroup; SOD1, superoxide dismutase-1.

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



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

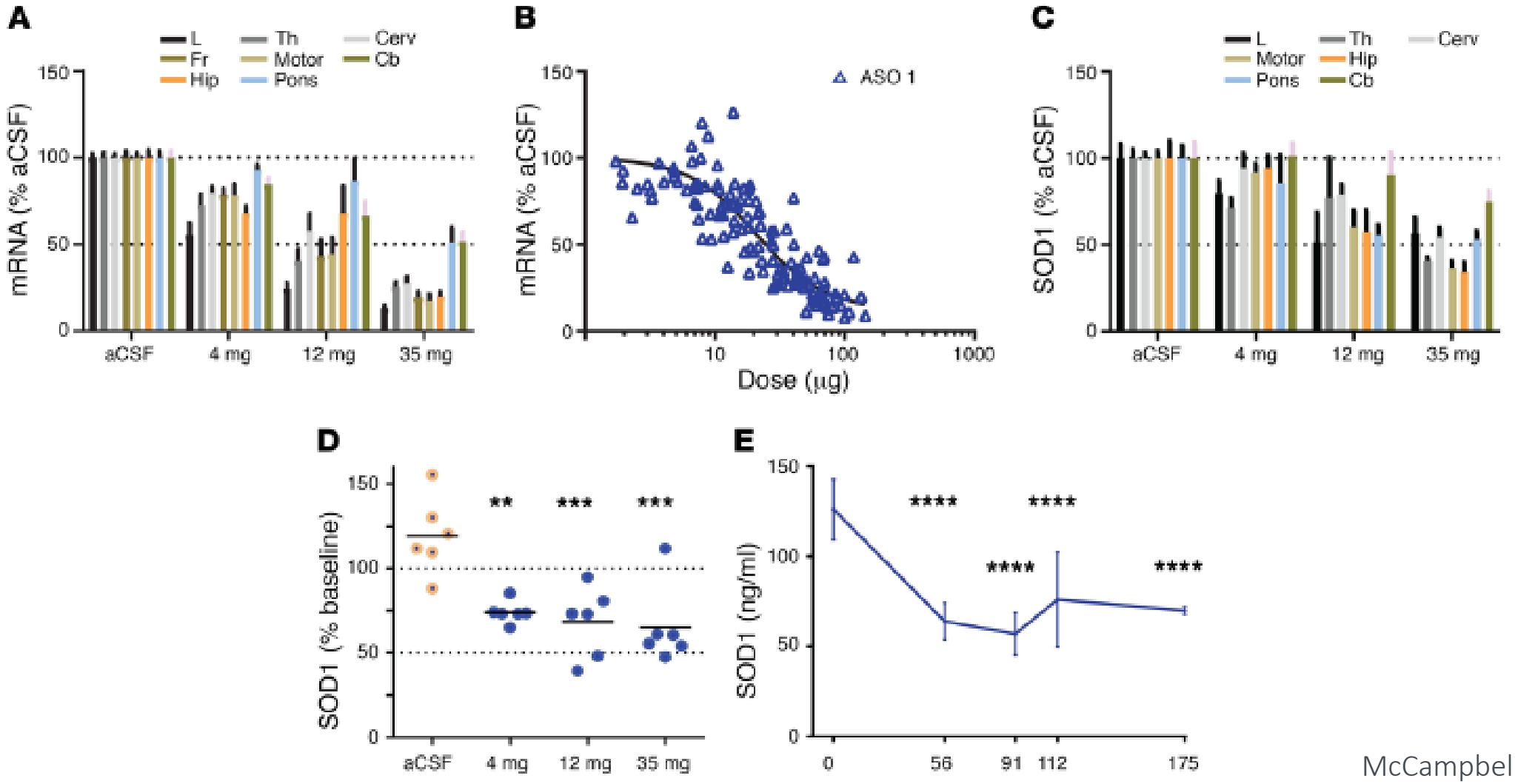
In SOD1-G93A transgenic mice, tofersen dosed after CMAP decline lead to improved CMAP



McCampbell et al., 2018

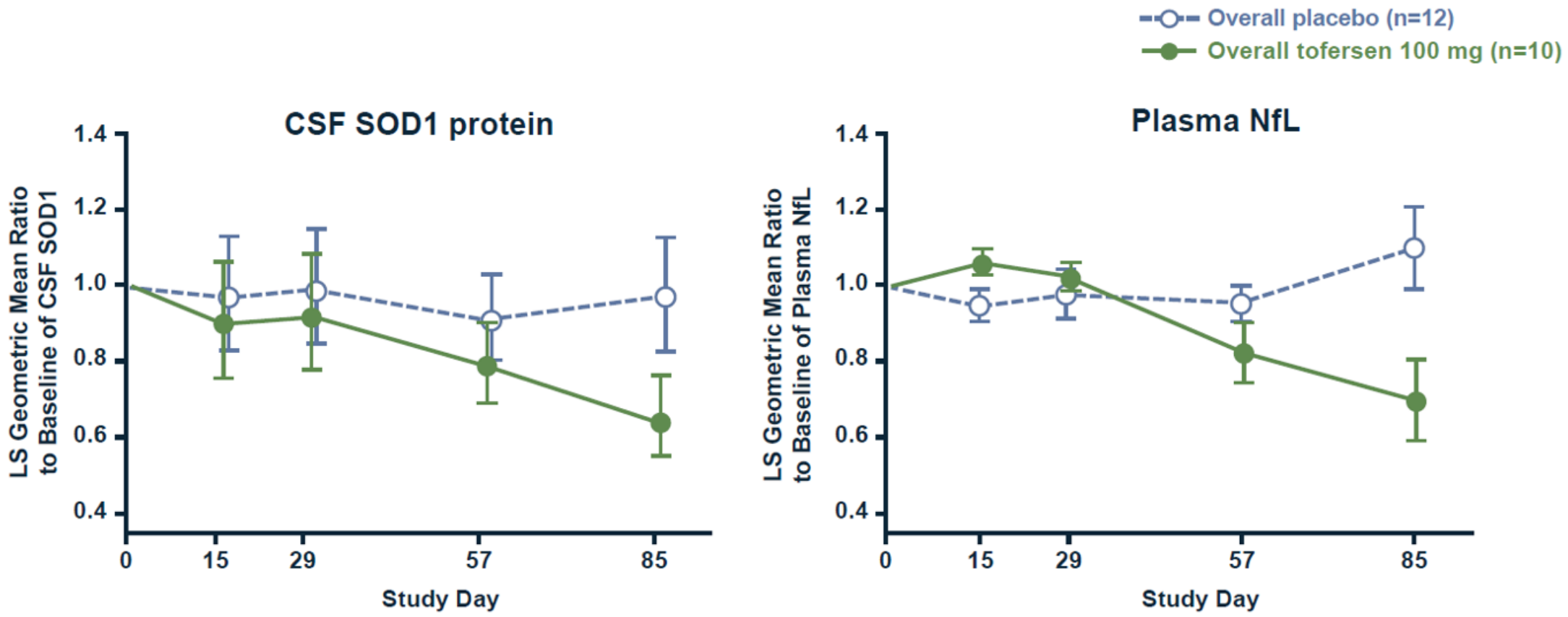
Preclinical testing is critical to demonstrate intended therapeutic behaves as predicted

SOD1 Reduction in Primate



McCampbell et al., 2018

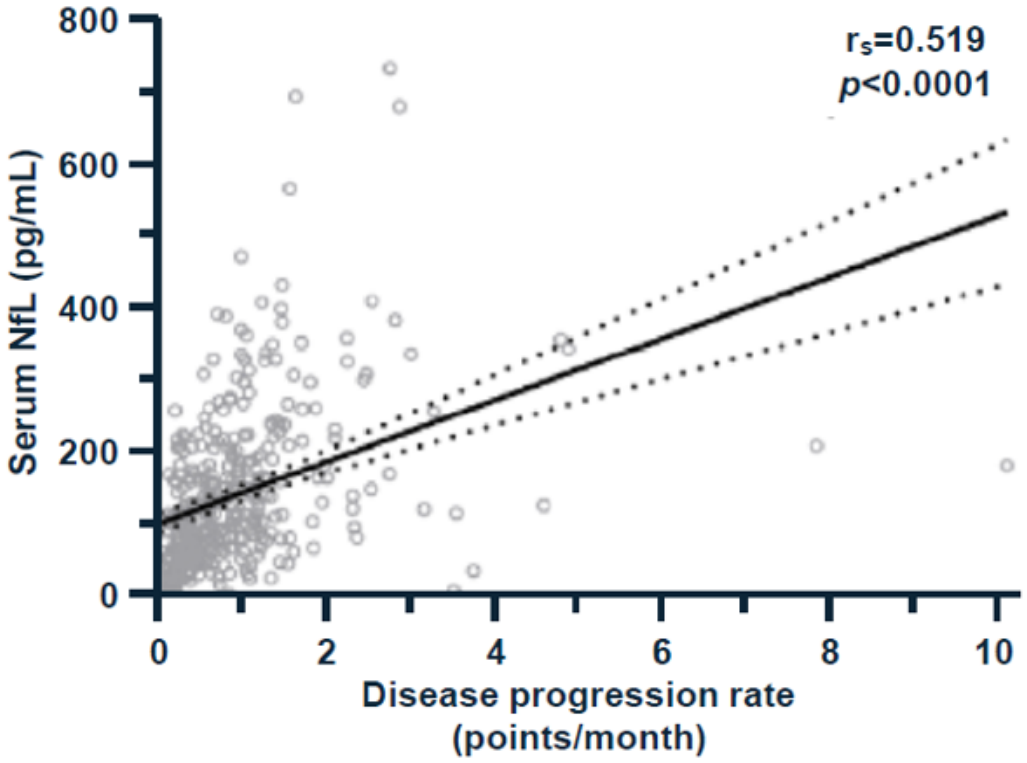
In the phase 1/2 clinical study, tofersen reduced levels of CSF SOD1 and plasma NfL



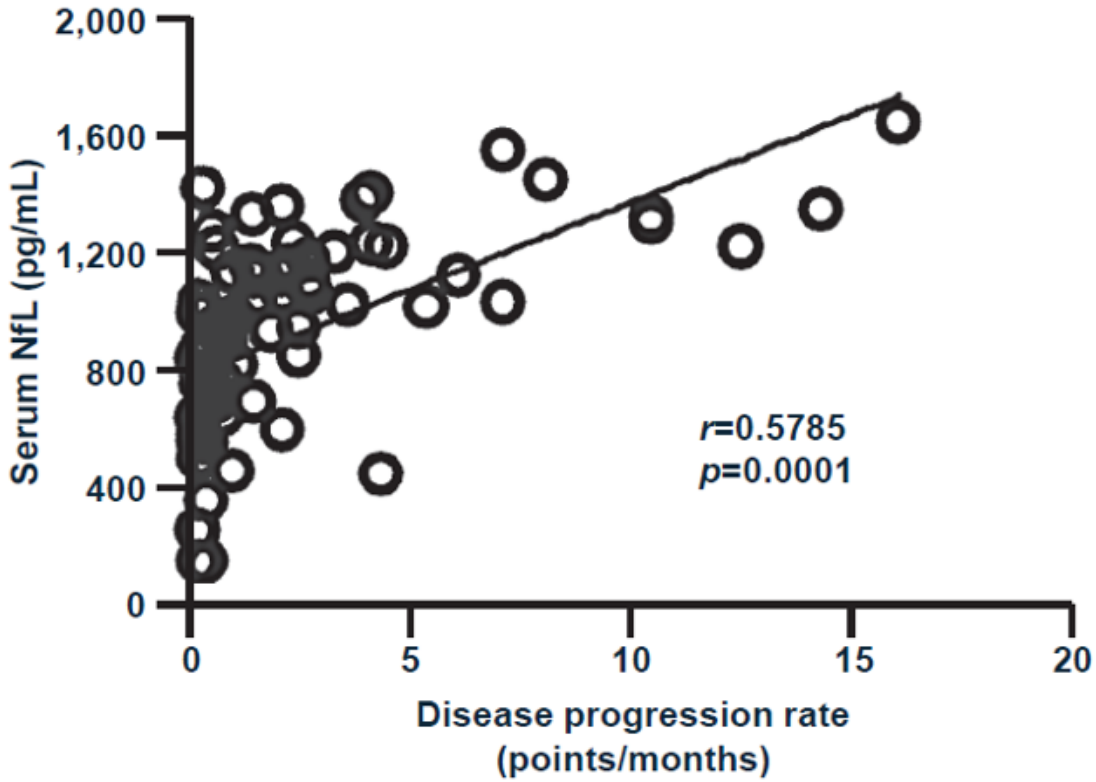
Miller T, et al. *N Engl J Med*. 2020;383(2):109-119.

Neurofilament levels correlate with disease progression rate in ALS

De Schaepdryver 2020[1]



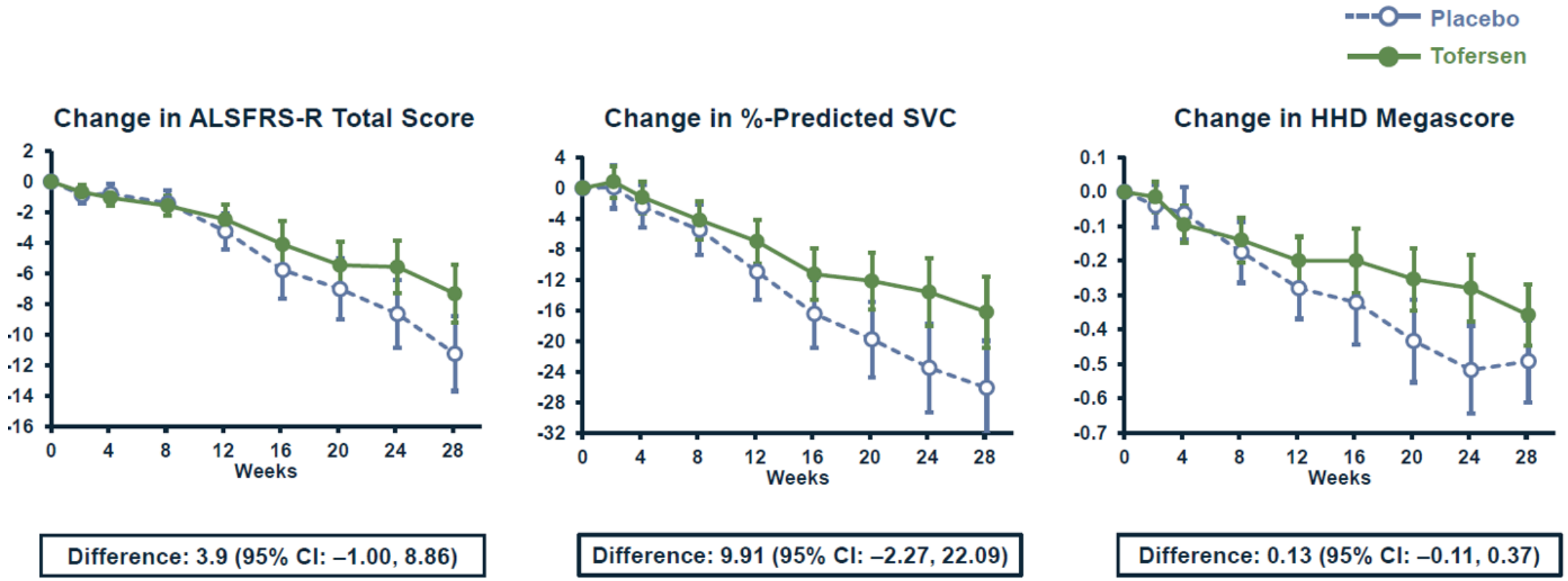
Gong 2018[2]



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.

Greater differentiation observed in faster progression subgroup with baseline plasma NfL incorporated as covariate

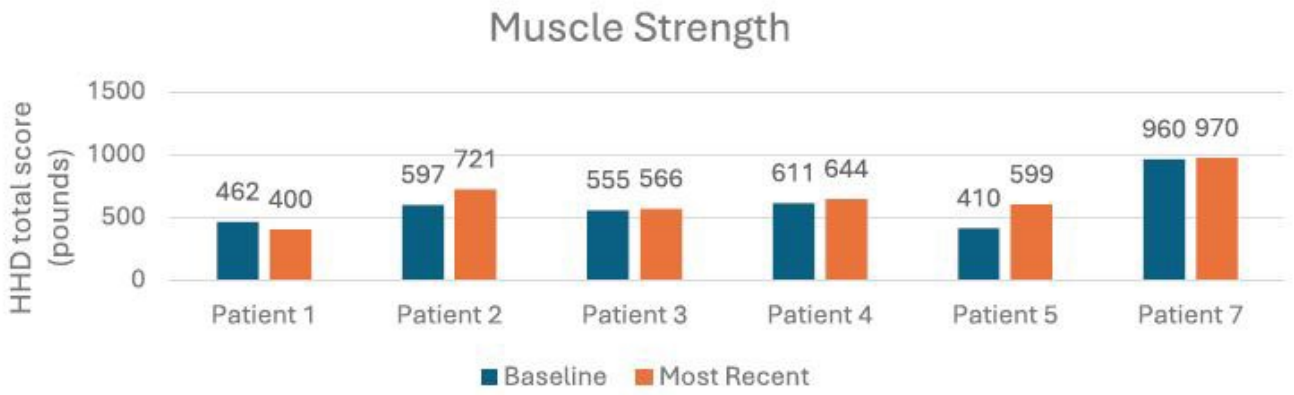
VALOR, FPS (mutation/slope)

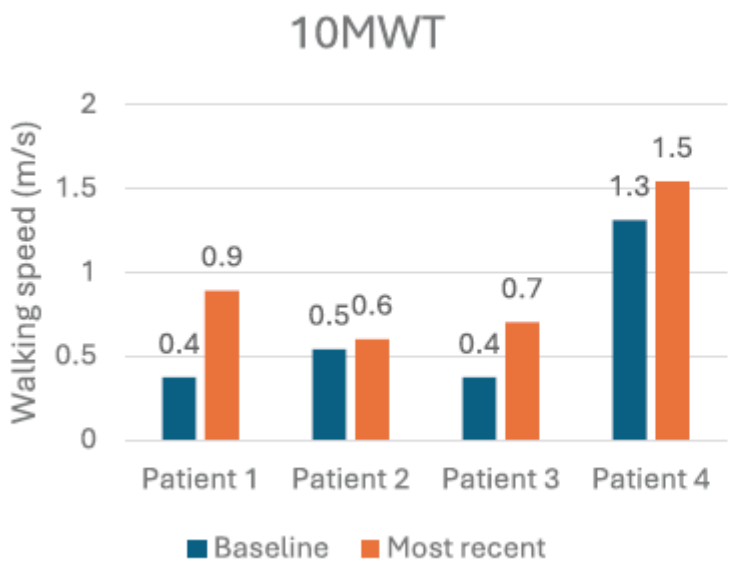


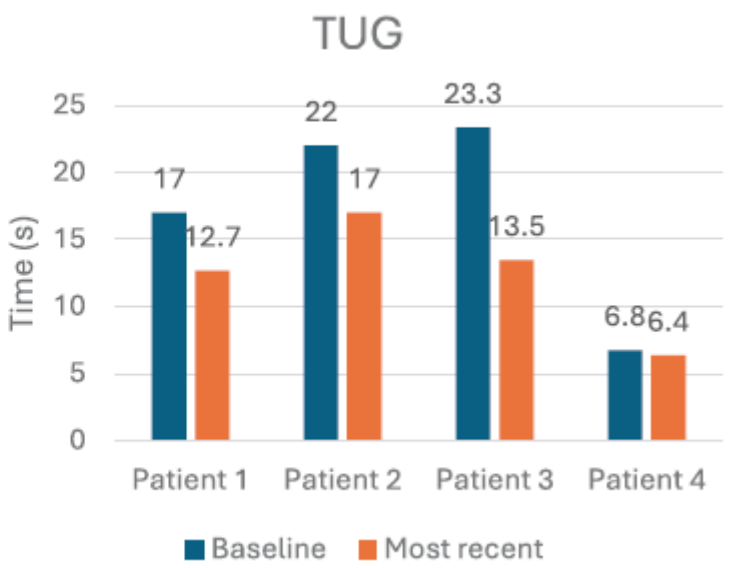
* Median plasma NfL = 75.6 pg/mL.

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

Tofersen Post-Approval efficacy consistent with VALOR including biomarkers and clinical improvement



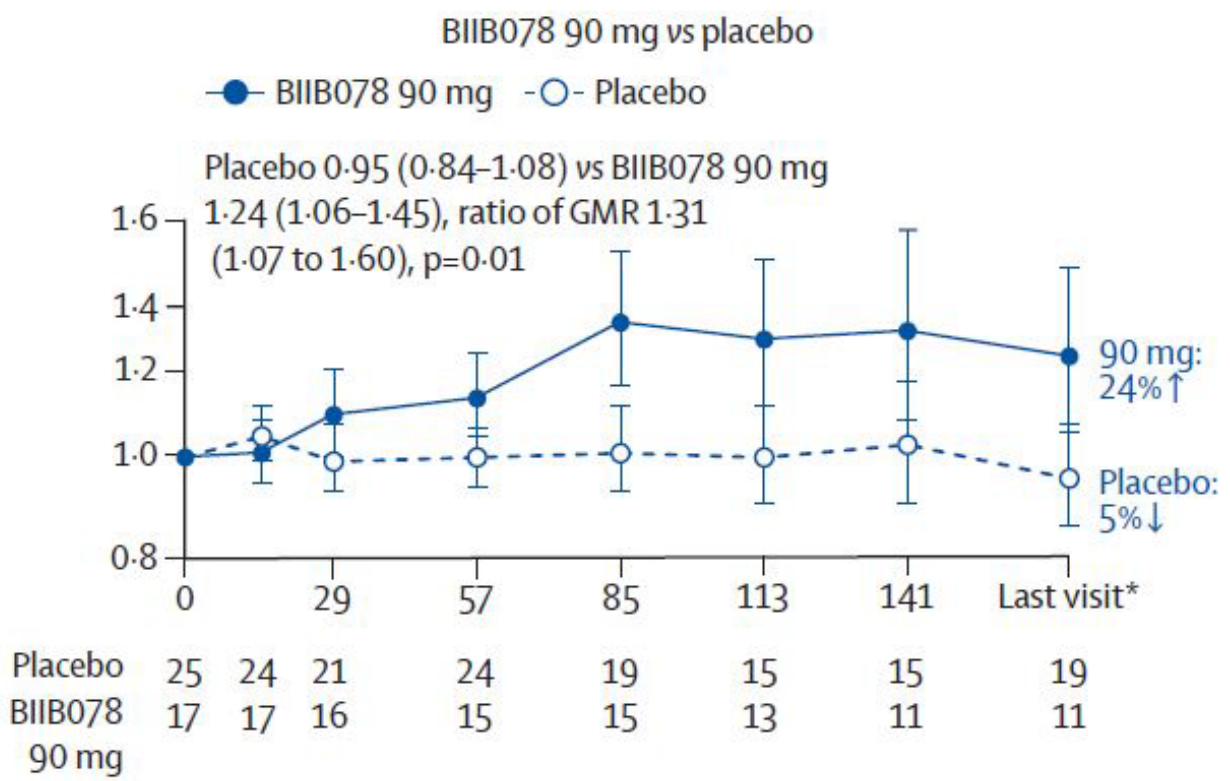




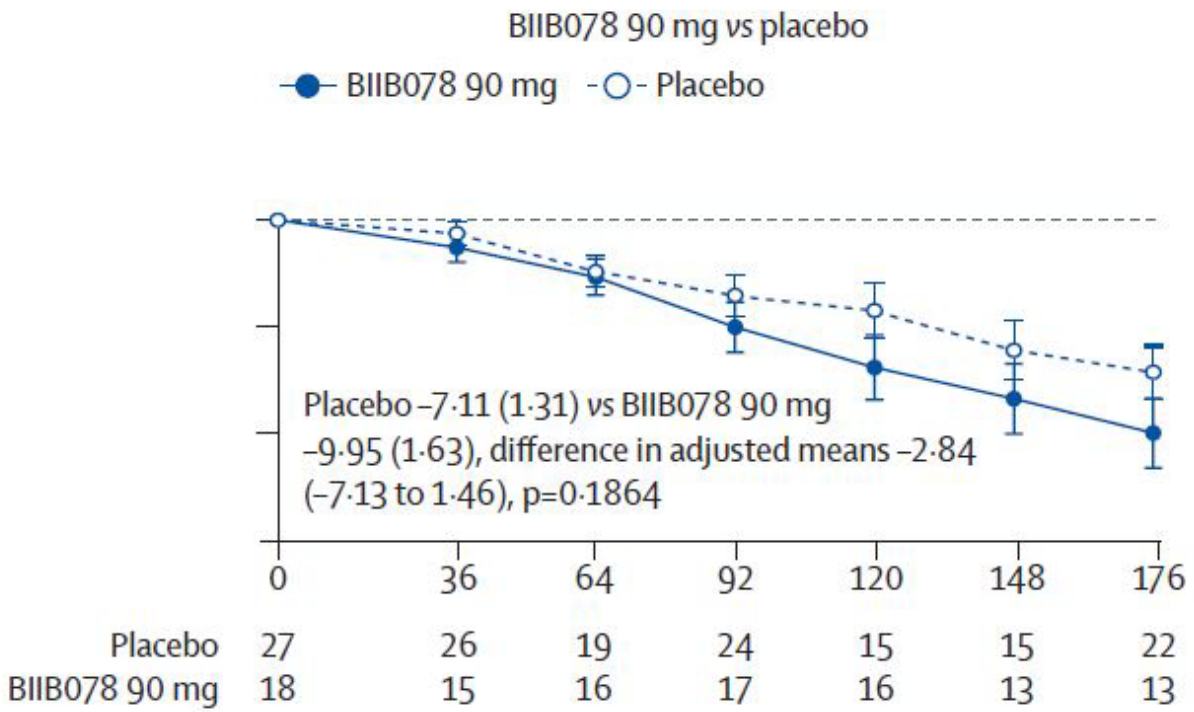
Smith et al., 2025

Treatment of c9orf72 ALS with an ASO increased NfL and was consistent with clinical observations

Neurofilament



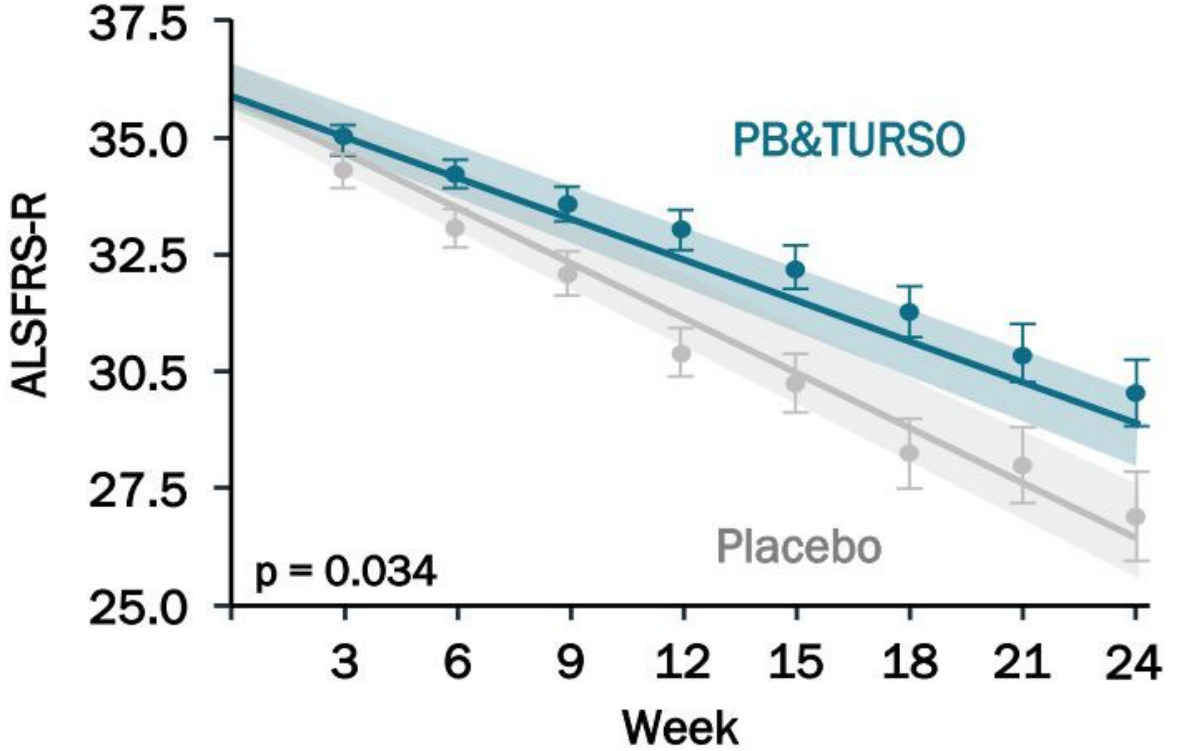
ALSFRS-R



van den Berg et al., 2024

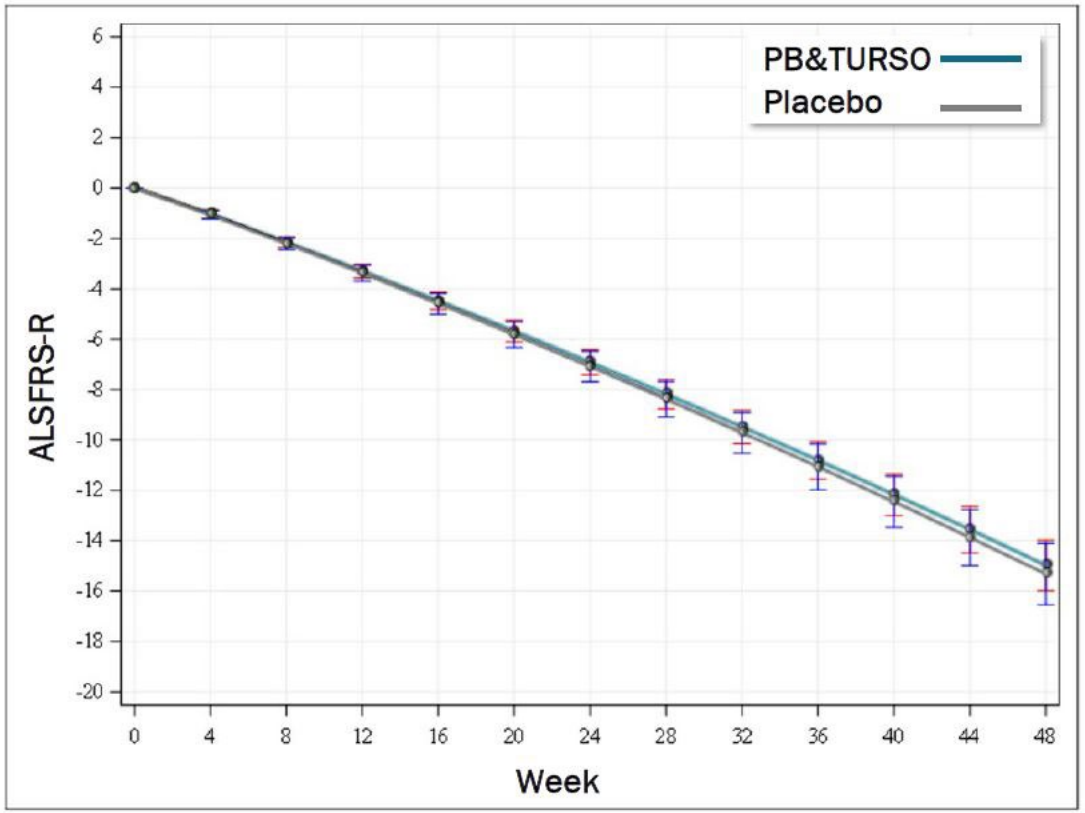
AMX0035 positive phase 2 data was not reproduced in phase 3 study

Phase 2 Centaur Study: primary endpoint[1]



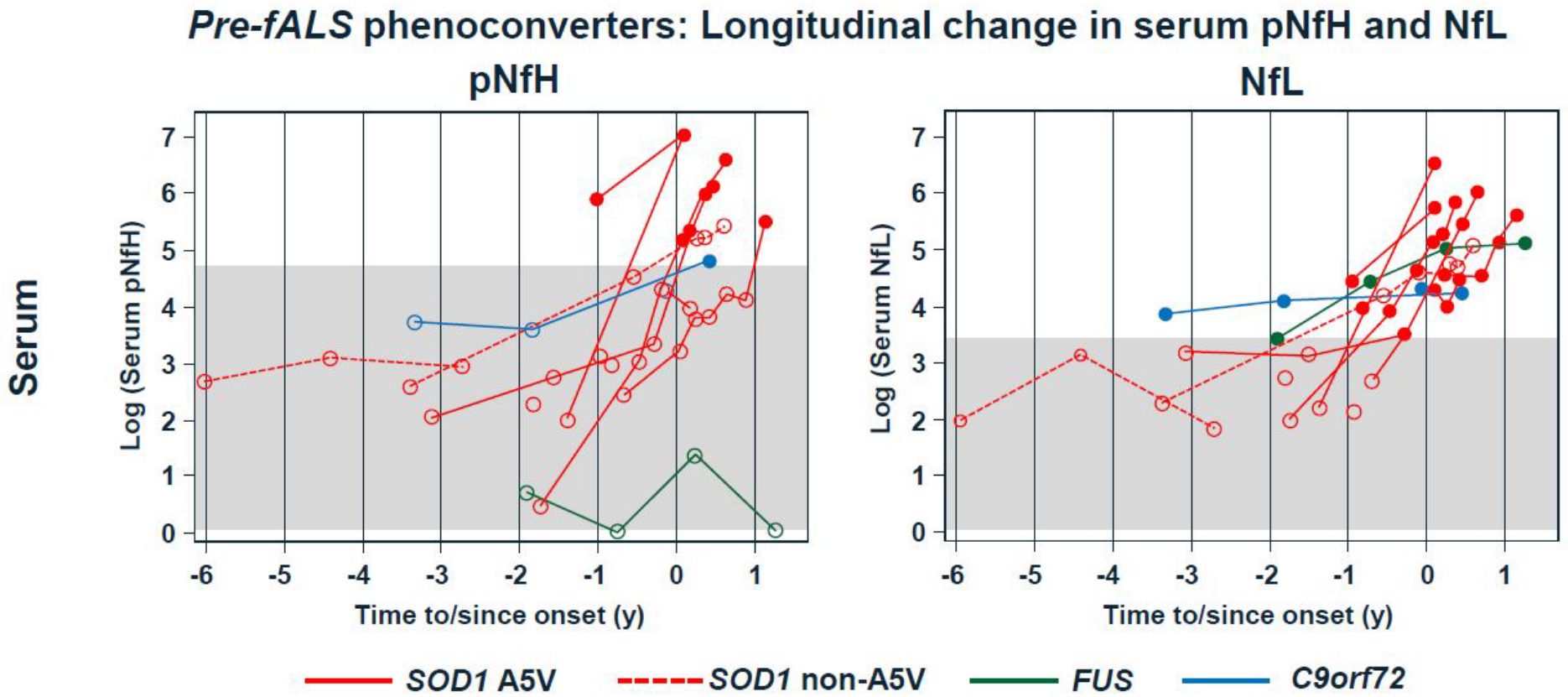
No difference in NfL observed in Centaur

Phase 3 Phoenix Study: primary endpoint[1]



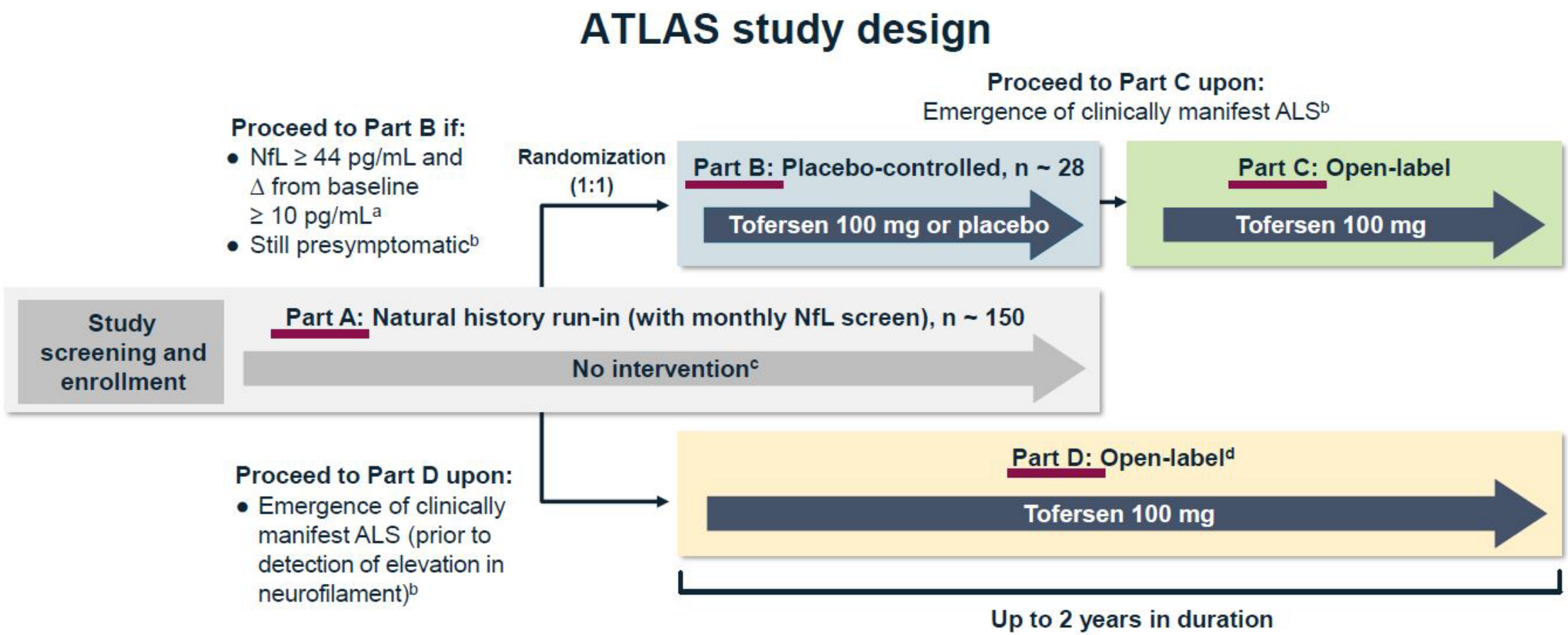
[1]Results From the Global Phase 3 Trial Evaluating Sodium Phenylbutyrate and Ursodoxicoltaurine in ALS ENCALS 2024

Neurofilament levels are elevated prior to onset of clinical ALS



Reprinted from Benatar M, et al. *Amyotroph Lateral Scler Frontotemporal Degener*. 2019;20(7-8):538-548. Reprinted by permission of the publisher, Informa UK Limited, trading as Taylor & Francis Group, http://www.tandfonline.com.

ATLAS Study is confirmatory study designed to confirm tofersen efficacy



[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.