U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

Leverage Quantitative Tools to Select Novel Endpoint for Tofersen Development in Treating SOD1-ALS

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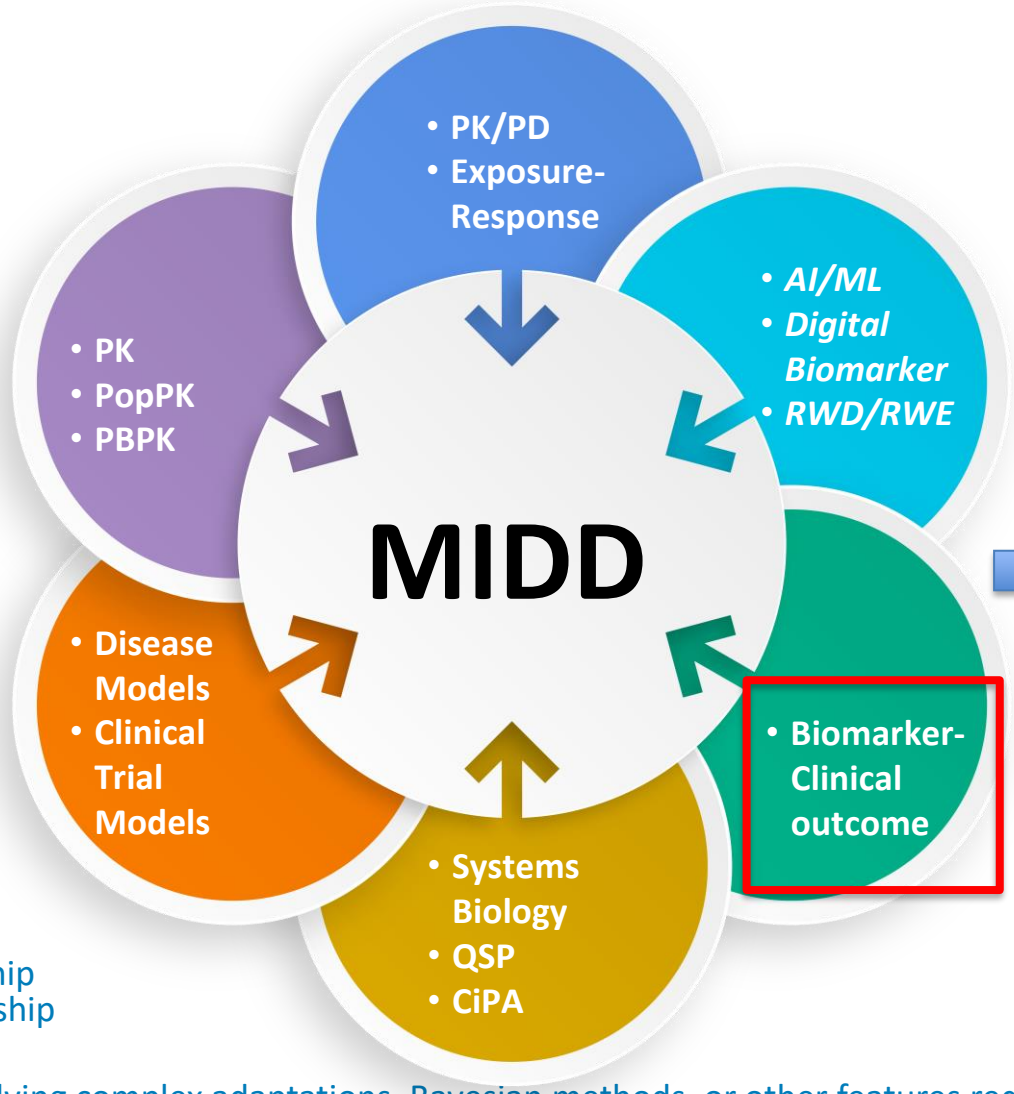
Disclaimer: This presentation reflects the views of the presenter and should not be construed to represent those of the FDA or the United States Government.

Introduction

- Introduction
  - MIDD
- MIDD for Endpoint Selection – Tofersen Case Example
- Take Home Message

MIDD as Technical Tool

Development and application of exposure-based, biological, and pharmacological models derived from preclinical and clinical data sources to address drug development or regulatory issues*



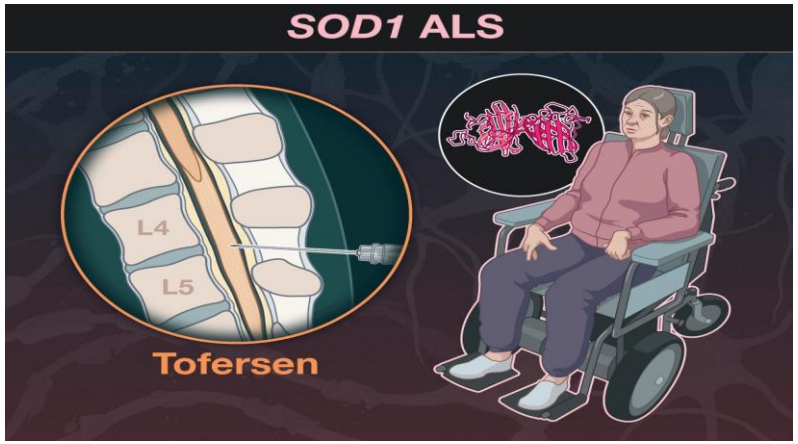
- **Modernize New Drug Development.**
- **Improve Patient Care**

QSAR: Quantitative structure–activity relationship
QSPR: Quantitative structure–property relationship

* From PDUFA 6; Excludes statistical designs involving complex adaptations, Bayesian methods, or other features requiring computer simulations to determine the operating characteristics of a confirmatory clinical trial.

Huang SM 2019 AAPS

Endpoint Identification - Tofersen



- Accelerated approval in April, 2023.
- Antisense oligonucleotide
- Indicated for treatment of ALS in adults with a mutation in the superoxide dismutase 1 (SOD1) gene.

- ALS is a rare disease.
- SOD1-ALS accounts for 2% of the ALS patient population. The estimated patients are < **500 in the US**.
- No approved treatment for SOD1-ALS

*: US package insert: <https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/215887Orig1s000Correctedlbl.pdf>

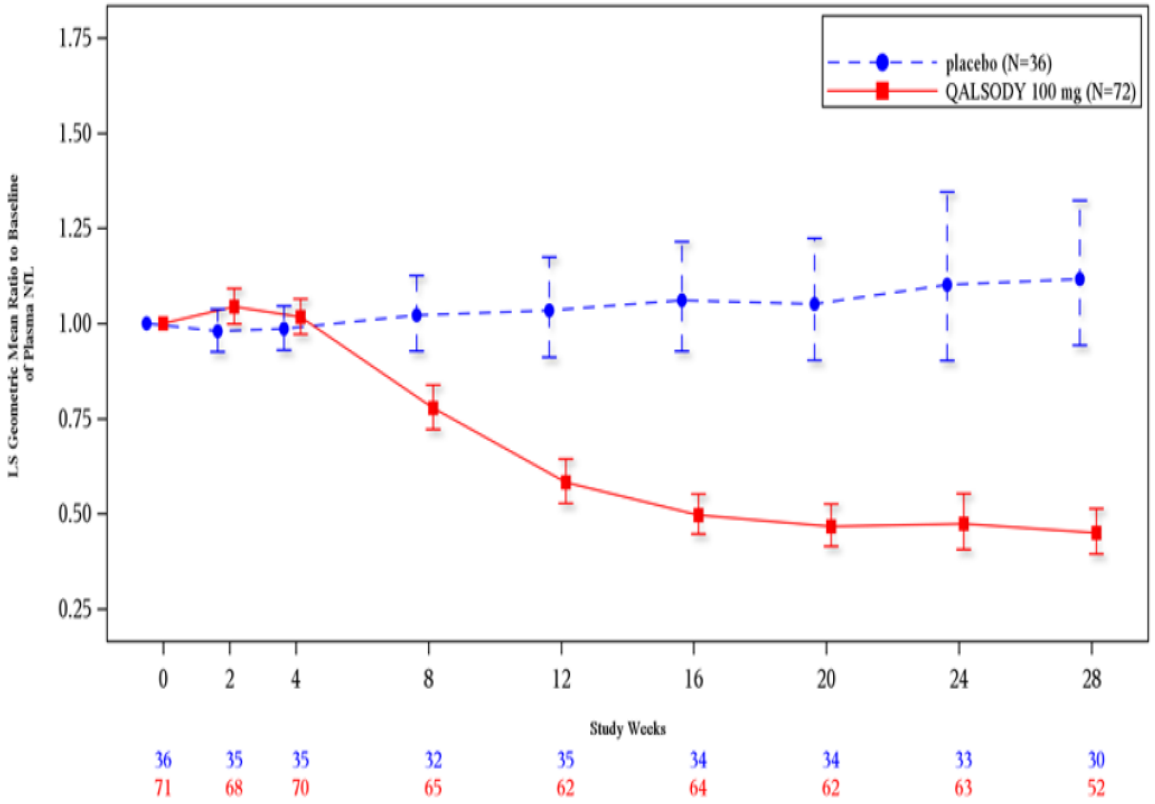
Tofersen Clinical Program

- A 28-week, randomized, double-blinded, placebo-controlled clinical trial in patients with SOD1-ALS.
- A total of 108 patients were randomized at 2:1 ratio to receive either tofersen 1000 mg or placebo for 24 weeks (3 loading doses + 5 maintenance doses).

- Primary efficacy analysis was change from baseline to Week 28 in ALSFRS-R total score in mITT population.
- Patients with treatment shows less decline in ALSFRS-R total score as compared to placebo, but not statistically significant. (1.2 [-3.2, 5.5])

*: US package insert: <https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/215887Orig1s000Correctedlbl.pdf>

Biomarker Results

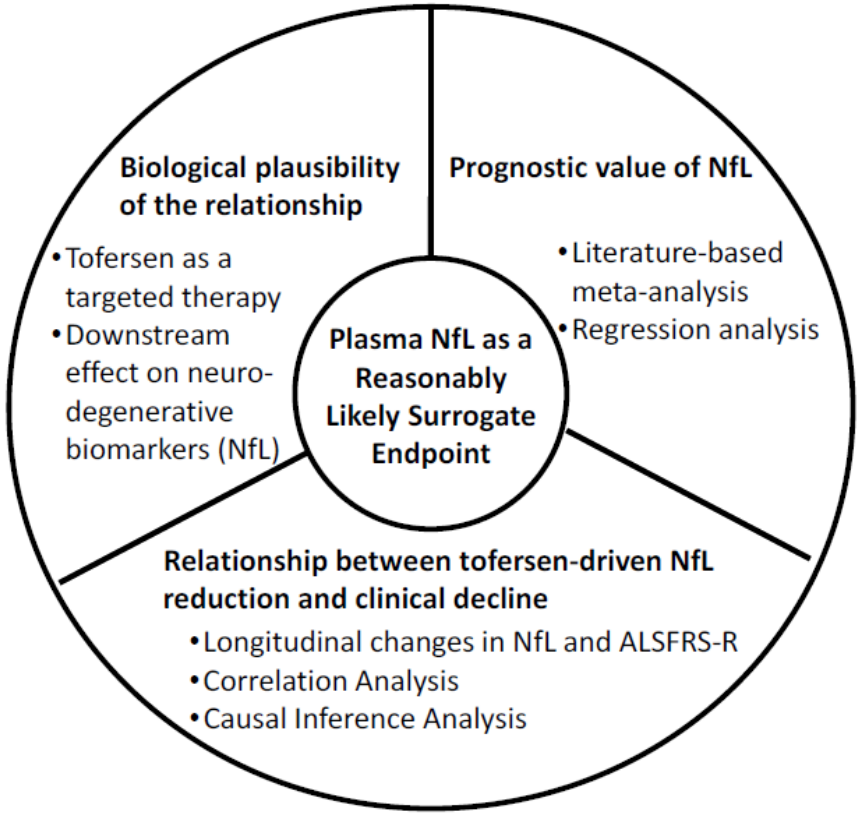


- Plasma neurofilament light chain (NfL) is a blood-based biomarker of axonal injury and neurodegeneration.
- The reduction of NfL is nominally statistically significant at Week 28.
- NfL change was consistently observed for all subgroups based on sex, disease duration since symptom onset, and riluzole/edaravone use.

*: US package insert: <https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/215887Orig1s000Correctedlbl.pdf>

Key Question

Can NfL be considered as a reasonably likely surrogate endpoint for accelerated approval of tofersen for treating SOD1-ALS?



*: FDA Presentation at the AC meeting <https://www.fda.gov/media/166392/download>

Biological Mechanism

Pathophysiology

Pharmacology

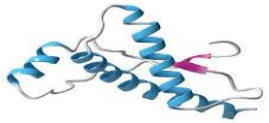
Mutation in SOD1 Gene

SOD1 Mutation

mRNA

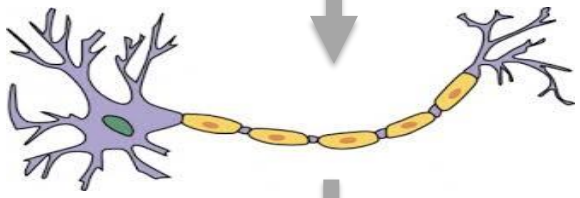
Tofersen

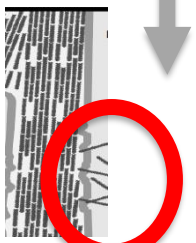
(X)



SOD1 protein

Neuron axonal damage





NFL is released to CSF or plasma

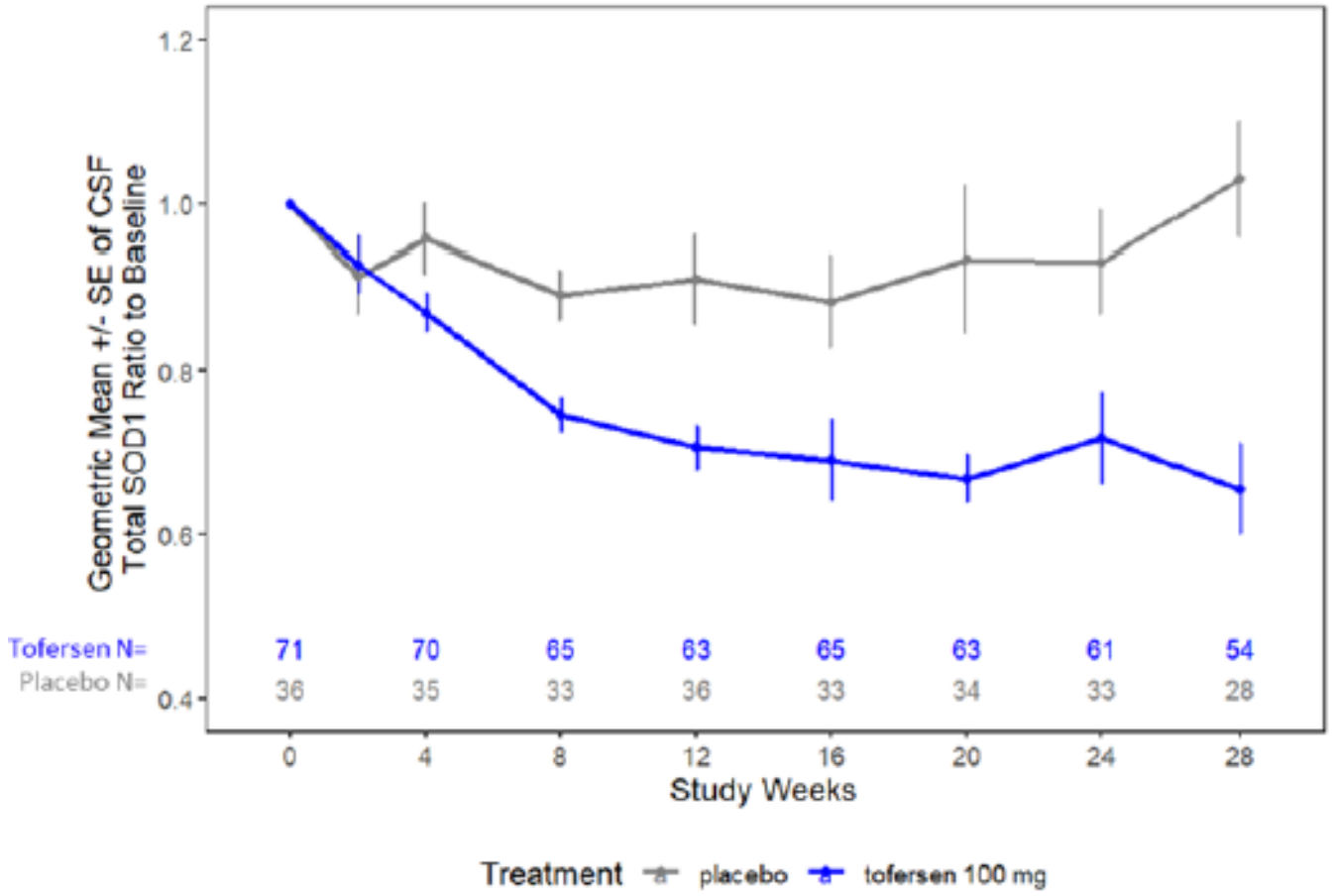
Functional Loss

Functional Loss

Review Focus

To establish the relationship

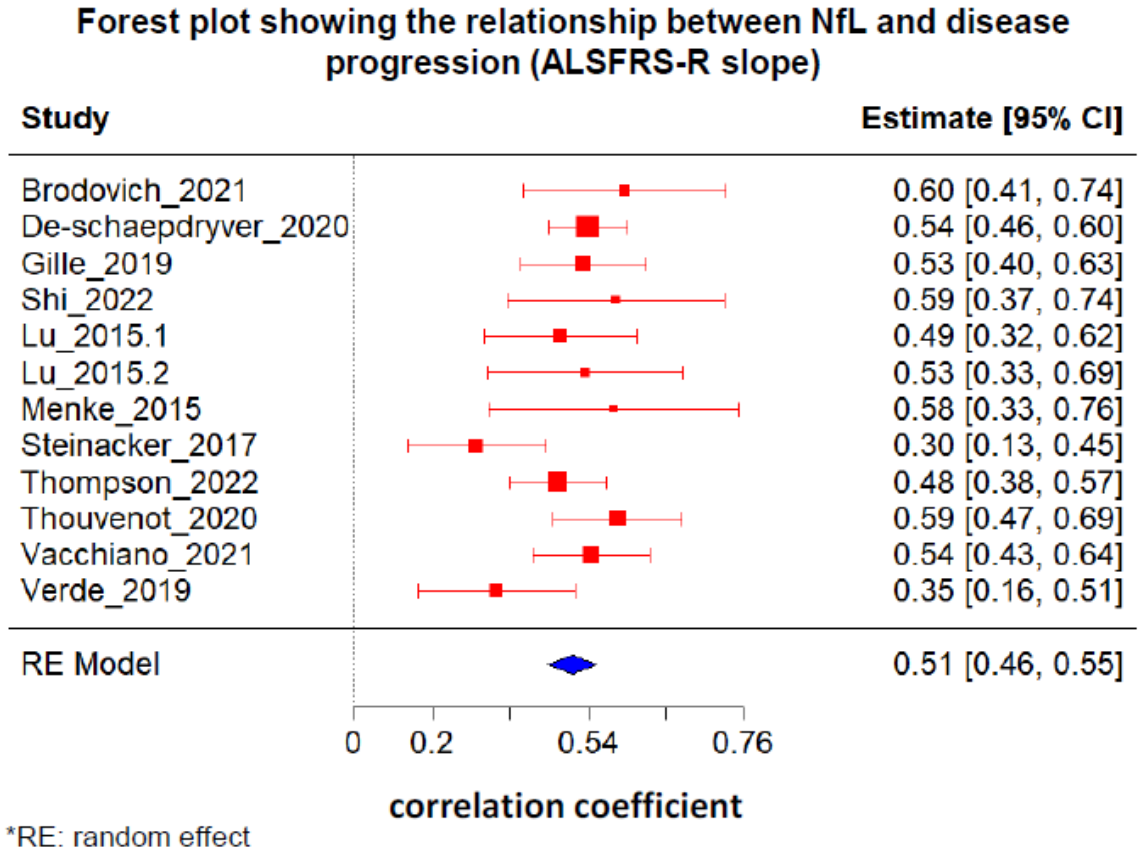
SOD1 Protein Reduction



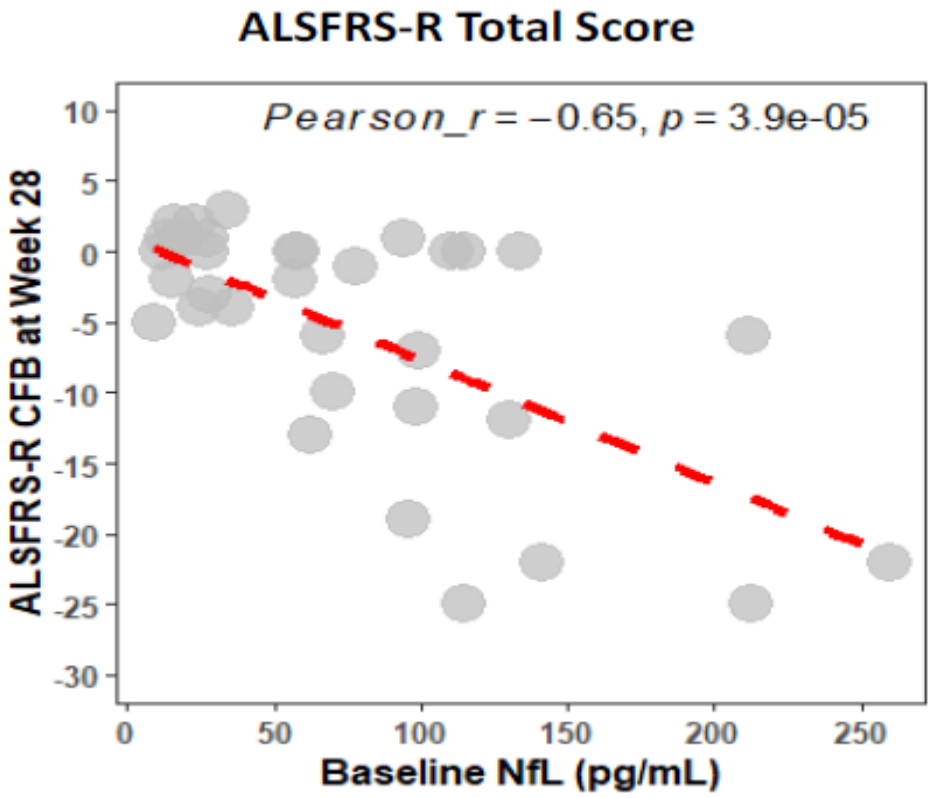
- Evidence of target engagement
- SOD1 protein includes both naïve and mutated forms.

Source: FDA presentation at the AC meeting for Tofersen P-48

Prognostic Value of NfL



*RE: random effect

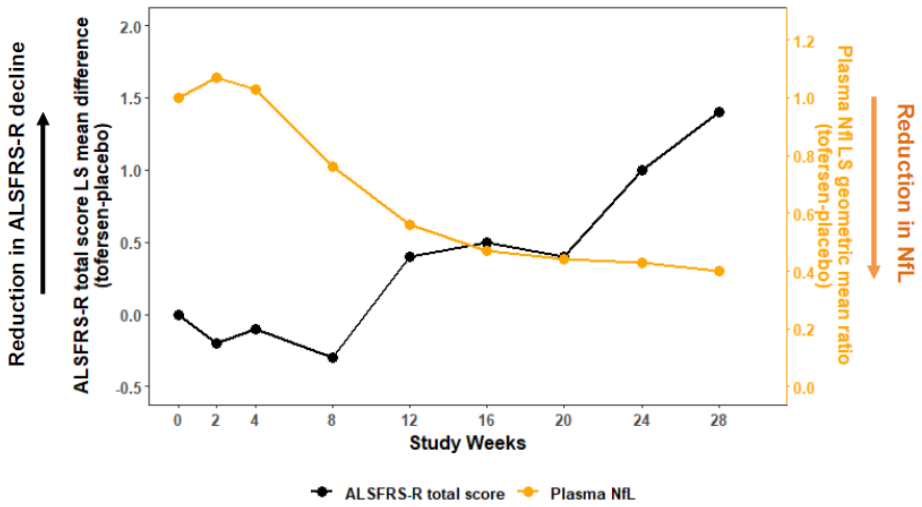


Summary of Literature Reported Cases

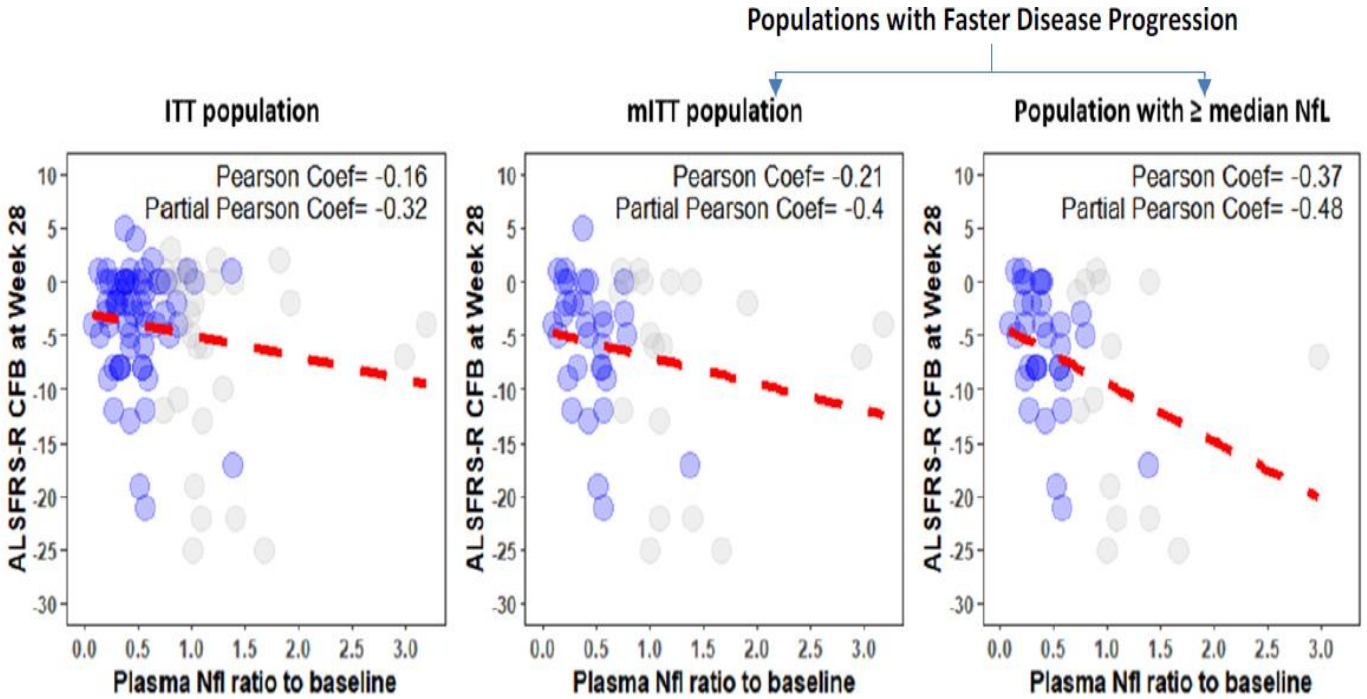
Clinical Program of Tofersen

*: FDA Presentation at the AC meeting <https://www.fda.gov/media/166392/download>

Reduction of NFL and ALSFRS-R Decline



The values for **ALSFRS-R** and NfL changes are shown on left- and right-side Y-axis respectively

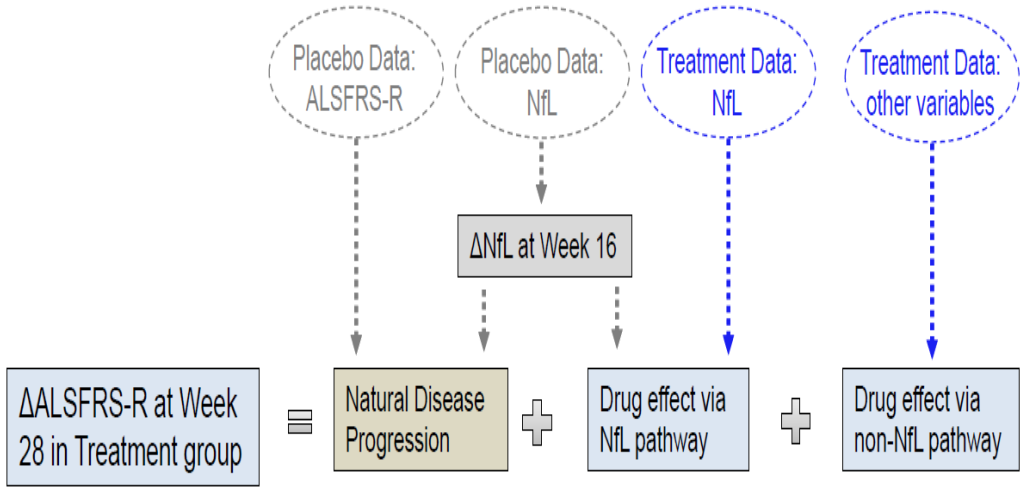


Temporal Relationship between Reduction of Plasma NfL and Reduction of ALSFRS-R Decline

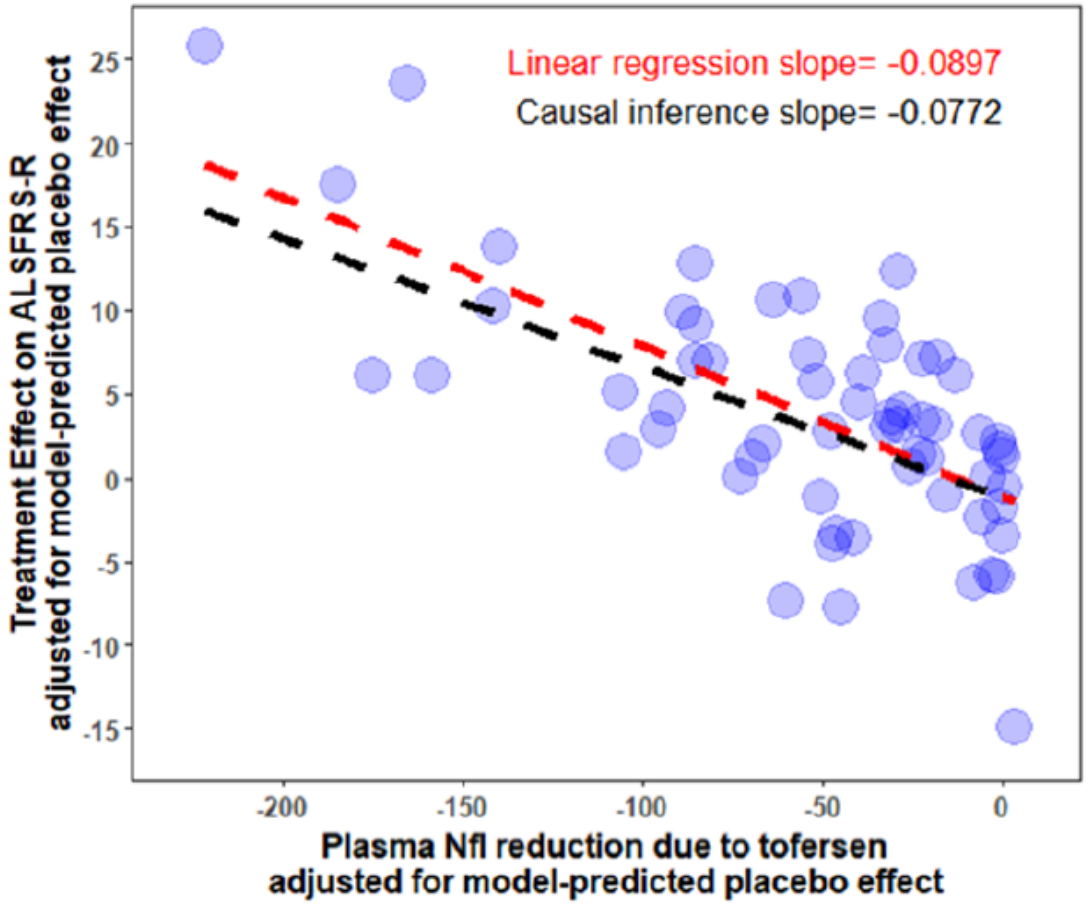
Plasma NfL Change vs. Reduction in ALSFRS-R Decline at Week 28

*: FDA Presentation at the AC meeting <https://www.fda.gov/media/166392/download>

Causal Inference Analysis



Model Structure



Take Home Message

- MIDD is a powerful tool to support new drug development and regulatory decision making. The scope of the MIDD application has been expanding.

- With the joint effort from academia, industry, and regulatory agencies, we expect that MIDD approaches can be further used to facilitate new drug development and to improve patient care.

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