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Tofersen

Peripheral and Central Nervous System Drugs Advisory Committee Meeting

March 22, 2023

Introductory Comments

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SOD1-ALS

- Serious, progressive, and fatal neurodegenerative disease
- SOD1 mutation postulated to lead to the toxic accumulation of mutated or misfolded SOD1 protein
- SOD1 genetic mutations are associated with 20% of familial cases and approximately 1-3% of sporadic ALS cases
  - prevalence estimated less than 500 patients in the US
- There are no therapies specifically for patients with SOD1-ALS

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Tofersen

- An antisense oligonucleotide (ASO) designed to bind and degrade SOD1 mRNA to reduce synthesis of SOD1 protein (both mutant and wild-type)
- It is anticipated that any effects of tofersen would apply to all SOD1-ALS patients, regardless of the mutation type

Evidence

- Study 101C - a 24-week placebo-controlled, double-blind study of 108 patients with SOD1-ALS
  - Failed to win on the prespecified primary analysis
  - Reductions observed in biomarkers relevant to the pathophysiology of the disease (i.e., SOD1 protein and neurofilament light chain (NfL))
- Study 102 - open-label extension in which patients and study staff remained blinded to original treatment in Study 101C
  - Trends for treatment effect on clinical outcomes at Week 52 in patients who received tofersen in 101C compared to those with a delayed start in 102
  - Reduction in SOD1 and NfL in patients newly started on tofersen

Regulatory Flexibility

- 2019 FDA Draft Guidance, "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products," discusses that certain situations, such as when a disease is rare or the disease is life-threatening or severely debilitating with an unmet medical need, may warrant additional flexibility
- "…in certain settings, a somewhat greater risk (compared to placebo-controlled or other randomized superiority trials) of false positive conclusions – and therefore less certainty about effectiveness – may be acceptable, when balanced against the risk of rejecting or delaying the marketing of an effective therapy, (…) for an unmet medical need."

Potential Approval Pathways

- Accelerated Approval
  - Consider reduction in NfL as a surrogate endpoint reasonably likely to predict clinical benefit for patients with SOD1-ALS
- Traditional Approval
  - Consider clinical data from studies 101C and 102 extension, combined with confirmatory evidence of reduction in SOD1 and NfL, as sufficient to establish a treatment benefit of tofersen in patients with SOD1-ALS

Voting Questions

- Is the available evidence sufficient to conclude that a reduction in plasma NfL in tofersen-treated patients is reasonably likely to predict clinical benefit of tofersen for treatment of patients with SOD1-ALS?
- Does the clinical data from the placebo-controlled study and available long-term extension study results, with additional supporting results from the effects on relevant biomarkers (i.e., changes in plasma NfL and/or reductions in SOD1), provide convincing evidence of the effectiveness of tofersen in the treatment of patients with SOD1-ALS?

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FDA Summary Presentation

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE MEETING

March 22, 2023

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BIIB067 (tofersen)

Proposed Indication: Amyotrophic Lateral Sclerosis (ALS) in adults with confirmed mutation of the Superoxide Dismutase 1 (SOD1) gene

CLINICAL OVERVIEW

SOD1-ALS

- ALS is a rapidly progressive and fatal neurodegenerative disease
  - 5-10 % of all ALS cases are familial
- SOD1-ALS is associated with about 20% of familial ALS cases
  - approximately 2% ALS cases in US
- Age of onset, rate of progression, degree of upper motor neuron involvement may vary with specific SOD1 variant
  - p.Ala4Val (A4V/A5V) pathogenic variant is consistently associated with a rapid course, average disease course of 1 year

Unmet Need in ALS

- No treatments approved for SOD1-ALS
- FDA approved treatments for ALS
  - riluzole, edaravone, sodium phenylbutyrate/taurursodiol
- Significant unmet need remains for patients living with ALS

Tofersen

- Tofersen is an antisense oligonucleotide (ASO) that binds to the SOD1 mRNA
- Administered intrathecally (every 2 weeks x 3 doses, then every 28 days)
- Proposed Mechanism of Action
  - Reduces synthesis of SOD1 protein
  - Decreases accumulation of toxic SOD1 aggregates that are implicated in the pathophysiology of SOD1-ALS

Key Regulatory Background

- IND opened November 27, 2015
- Initiated pivotal study in 2019 after discussions regarding primary endpoint and analysis population
- Discussed proposal for ongoing study in presymptomatic carriers with confirmed SOD1 mutations (Study 233AS303) in Aug 2020
- Discussed topline results of pivotal study in September 2021
- December 2021 Type C meeting - Applicant proposed accelerated approval based on neurofilament light (NfL) results from pivotal study given findings on SOD1 and NfL and positive trends in clinical outcomes
- NDA submitted on May 25, 2022 requesting accelerated approval

Background on NfL

- Neurofilament protein expressed in myelinated axons
- Elevated levels of NfL in cerebrospinal fluid (CSF) and blood are found in a variety of neurological disorders
  - Significantly more elevated in ALS compared to other neurodegenerative disorders
  - Elevated plasma NfL levels have been observed as early as 1 year before symptom onset in patients with SOD1-ALS
- Recent studies indicate NfL levels correlate with disease severity, progression rate, and survival in ALS

Accelerated Approval

- Applicant proposes use of NfL as a reasonably likely surrogate endpoint for accelerated approval of tofersen in SOD1-ALS
- Accelerated approval
  - may be granted for a serious and life-threatening disease
  - product has an effect on a surrogate endpoint that is not itself a direct measure of clinical benefit but is instead reasonably likely to predict that clinical benefit
- Additional studies may be required to confirm anticipated clinical benefit

Proposed Confirmation of Clinical Benefit

- Given small pool of patients with SOD1-ALS, a second, double-blind and placebo-controlled study does not appear feasible
- Applicant has an ongoing Phase 3 study in presymptomatic carriers of the SOD1 mutation
  - Aim to evaluate if tofersen can delay symptom onset in presymptomatic patients who have evidence of disease activity based on reaching a threshold of NfL
- Applicant also plans to leverage results of the ongoing open-label extension study (Study 102)
  - Will follow patients, assess survival, and compare delayed-start patients to early-start patients, as well as natural history comparisons

Single Pivotal Study 233AS101 Part C (Study 101C)

- Randomized, double-blind, placebo-controlled study
- 108 patients, randomized 2:1
- Primary analysis: Change from baseline in ALS Functional Rating Scale-Revised (ALSFRS-R) total score at Week 28 in a prespecified "fast progressor" population
  - Defined based on prerandomization ALSFRS-R slope and mutation type
- Secondary endpoints: Change from baseline to week 28 in
  - total CSF SOD1 protein
  - plasma NfL
  - Slow Vital Capacity (SVC)
  - Handheld dynamometry (HHD) megascore
  - Time to death or permanent ventilation (> 22 hours of mech vent/day x 21 days)

Study 102 – Open Label Extension Study

- All patients had option to enroll in OLE after completion of double-blind study
- All patients and site staff remained blinded to treatment received in Study 101C
- Primary objective was safety and tolerability
- Biomarker and clinical endpoint data were collected
- Study remains ongoing

Study 101C Results

- Primary analysis of change from baseline in ALSFRS-R total score at Week 28 in the fast progressors (mITT) was not statistically significant
- Exploratory analyses also conducted in the full population (ITT)
- Secondary endpoints of SVC, HHD, and time to death/permanent ventilation
  - Not statistically significant
  - Numerically trended in direction favoring tofersen
- Additional secondary endpoints
  - Reduction was seen in CSF SOD1 protein levels compared to placebo at Week 28
  - Plasma NfL was reduced in patients receiving tofersen compared to placebo at Week 28

Study 102 results at Week 52

- Compare patients who received “early-start” treatment vs. those who received “delayed-start” treatment
- Different approaches to analyzing the data based on prespecified analyses and post hoc, exploratory analyses
- Clinical improvement noted in the full ITT population
  - ALSFRS-R compared to baseline demonstrated numerically less worsening in early-start group compared to delayed start
  - SVC, HHD, and quality of life scales with numerically less worsening
  - Reductions in CSF SOD1 and NfL were seen in patients previously on placebo who initiated tofersen in the open-label phase

Presentations

- Statistical presentation
  - Evidence of effect on clinical outcomes and biomarker
  - Statistical limitations of NfL as a reasonably likely surrogate
- Clinical Pharmacology Presentation
  - Background on NfL and SOD1
  - Biomarker results
  - Prognostic value of NfL
  - Evaluation of relationship between NfL reduction and clinical function decline

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Statistical Presentation

Tristan Massie, PhD
Division of Biometrics I, Office of Biostatistics

Key Points

- No statistically significant effects on primary or other clinical outcomes in prespecified analyses
- Additional post hoc analyses by applicant challenging to interpret due to data-driven exploratory nature
- Limited conclusions are possible from statistical analyses to evaluate relationship between tofersen effects on neurofilament (NfL) and ALSFRS-R

Outline

- Evidence of effect on clinical outcomes
- Evidence of effect on NfL
- Evidence for NfL as a reasonably likely surrogate endpoint

Prespecified Analysis Methods for Study 101C

- Final version of statistical analysis plan (SAP) prior to database lock was SAP Version 2 (August 14, 2021)
- Primary analysis of change from baseline in ALSFRS-R at Week 28 was based on an ANCOVA of joint ranked scores (ALSFRS-R and survival) in the mITT population, adjusting for pre-specified covariates: baseline ALSFRS-R, edaravone or riluzole use, and time since symptom onset. Multiple imputation (MI) was used for missing data in survivors.
- Descriptive analyses conducted in non-mITT and ITT populations but no formal hypothesis testing

Prespecified Analysis Methods for Study 101C

- Sequential testing strategy used to control Type I error probability across the following secondary endpoints:
  - Change from baseline to Week 28 in total CSF SOD1 protein
  - Change from baseline to Week 28 in NfL in plasma
  - Change from baseline to Week 28 in SVC
  - Change from baseline to Week 28 in HHD megascore to assess muscle strength, as measured by the HHD device
  - Time to death or permanent ventilation
  - Time to death
- Secondary endpoint analysis methods
  - Continuous endpoints: similar to ALSFRS-R
  - Time-to-event endpoints: Cox proportional hazards model adjusted for disease duration, baseline ALSFRS-R, edaravone or riluzole use

Prespecified Analysis Plan for Study 102 (Open-Label Extension)

- Primary objective was long-term safety and tolerability
- Efficacy evaluation was exploratory
- Analysis methods similar to those for Study 101C Week 28 analysis (same covariates)
- mITT population rather than ITT population was the focus

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Additional Post Hoc Applicant Analyses

- Applicant SAP Version 3 dated February 2, 2022
  - Finalized after reviewing unblinded double-blind and some Open Label Extension (OLE) results, e.g., ALSFRS-R and survival analyses through Week 40 of OLE reported in November 2021 Type C meeting
- Additional analyses included multiple changes to prespecified methods
  - Replaced time since symptom onset covariate with baseline NfL
  - Focused on ITT rather than mITT population
  - Changed MI model (adding NfL as covariate)
- Note: Post hoc modeling choices can induce substantial bias
  - Pre-specification of covariates is critical for the validity of models: "Sponsors should prospectively specify the covariates and the mathematical form of the covariate adjusted estimator in the statistical analysis plan before any unblinding of comparative data. FDA will generally give more weight in review to the prespecified primary analysis than to post-hoc analyses using different models or covariates."[1]

 [1]FDA draft guidance for industry *Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products* (2021)

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Study 101C (Double-Blind) Results: Prespecified Analyses of Primary Endpoint

- Primary analysis of Week 28 ALSFRS-R did not provide evidence of a treatment effect
  - Mean change of -8.1 on placebo vs. -7.0 on tofersen
  - Mean difference: 1.2 (95% CI: -3.2, 5.5); primary joint rank p=0.97, supportive ANCOVA/MI p=0.60
- Exploratory analysis in full (ITT) population
  - Mean difference: 1.4 (95% CI: -1.3, 4.1); joint rank p=0.91, ANCOVA/MI p=0.32

Study 101C (Double-Blind) Results: Prespecified Analyses of Secondary Endpoints

- No evidence of effects on secondary endpoints SVC or HHD megascore
  - SVC Mean difference 7.9 (95% CI: -3.5, 19.3); p=0.32 joint rank, p=0.18 ANCOVA+MI
  - HHD Mean difference 0.02 (95% CI: -0.21, 0.26) p=0.84 ANCOVA+MI
- Time to death or permanent ventilation and time to death not assessed due to lack of events (1 death in double-blind period)
- Some evidence of effects on biomarkers SOD1 and NfL (see other presentations and later slide)

Study 102 (OLE) Results: Prespecified Analyses

- Week 52 ALSFRS-R
  - mITT: Mean difference: 2.5 (95% CI:-3.2, 8.3); joint rank p=0.83, ANCOVA/MI p=0.39
  - ITT: Mean difference: 2.7 (95% CI: -0.9, 6.2); joint rank p=0.48, ANCOVA/MI p=0.14
- Time to death or permanent ventilation
  - mITT: 5/21 (24%) on placebo vs. 12/39 (31%) on tofersen
    Hazard ratio: 1.69 (95% CI: 0.53, 5.40); p=0.38 (numerically favors placebo)
  - ITT: 8/36 (22%) on placebo vs. 12/72 (14%) on tofersen
    Hazard ratio: 0.70 (95% CI:0.28, 1.75); p=0.45 (numerically favors tofersen)
- Time to death alone
  - mITT: 3/21 (14%) on placebo vs. 8/39 (21%) on tofersen
    Hazard ratio: 1.67 (95% CI: 0.39, 7.10); p=0.49 (numerically favors placebo)
  - ITT: 6/36 (17%) on placebo vs. 8/72 (11%) on tofersen
    Hazard ratio: 0.52 (95% CI: 0.18, 1.55); p=0.24 (numerically favors tofersen)

Applicant's Post Hoc ITT Analyses of Study 101C

- Week 28 Change in ALSFRS-R
  - Mean difference: 2.1 (95% CI: -0.3, 4.5); p= 0.09 (ANCOVA+MI), p=0.50 (joint rank)
- Week 28 Change in SVC
  - Mean difference: 8.5 (95% CI: 1.8, 15.2); p=0.01 (ANCOVA+MI), p=0.07 (joint rank)
- Week 28 Change in HHD
  - Mean difference: 0.10 (95% CI: -0.04, 0.23), p=0.15 (ANCOVA+MI)
- Time to death or permanent ventilation and time to death: too few events
- None of these endpoints nominally significant in primary mITT population

Applicant's Post Hoc ITT Analyses of OLE

- Week 52 ALSFRS-R
  - Mean difference: 3.5 (95% CI: 0.4, 6.7); p=0.03 (ANCOVA+ MI), p=0.21 (joint rank)
- Week 52 SVC
  - Mean difference: 9.2 (95% CI: 1.7, 16.6); p=0.02 (ANCOVA+MI)
  - Inappropriate handling of 4 deaths on tofersen, 1 on placebo before Week 52
- Week 52 HHD
  - Mean difference: 0.28 (95% CI: 0.047, 0.517); p=0.02 (ANCOVA+MI)
- Time to death or permanent ventilation:
  - Hazard Ratio: 0.36 (95% CI: 0.14, 0.94), p=0.04
- Time to death alone:
  - Hazard Ratio: 0.27 (95% CI: 0.08, 0.89), p=0.03
- None of these endpoints nominally significant in primary mITT population

Comments on Applicant's Post Hoc Analyses

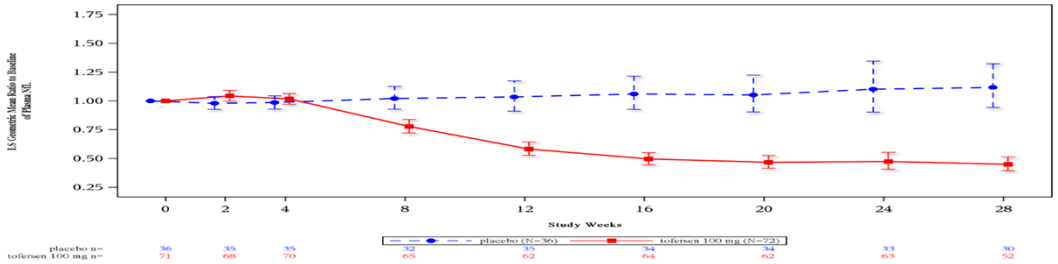
- Some of the analysis changes may have scientific rationale
  - Prognostic ability of NfL in the literature, together with the less functional decline on placebo in the "fast progressor" mITT population than anticipated
- Some of the results may be promising
- However, it is likely that part of the reason these post-hoc analyses were explored is data-driven, i.e., due to lack of evidence in prespecified analyses and search for more favorable results
  - Data-driven analyses are subject to bias and very challenging to interpret
- The pre-specified analyses are valid, not significant, and should be given substantial weight and not discounted

Outline

- Evidence of effect on clinical outcomes
- Evidence of effect on NfL
- Evidence for NfL as a reasonably likely surrogate endpoint

Effect on Neurofilament (NfL)

- Biomarker endpoint is change (i.e., ratio) from baseline in NfL
  - 2nd endpoint listed among secondary objectives after primary
  - Nominally significant treatment effects on ratio to baseline of NfL for mITT and non-mITT (both nominal p-value < 0.0001)
  - Study 101 Part B seemed to provide independent support with nominal p=0.0176
  - Totality of data provide support for a true effect on NfL



Outline

- Evidence of effect on clinical outcomes
- Evidence of effect on NfL
- Evidence for NfL as a reasonably likely surrogate endpoint

Neurofilament as a Reasonably Likely Surrogate

- Evaluation of reasonably likely surrogacy is based on a multidisciplinary approach
  - Understanding of the disease/mechanism is important
- No prespecified analyses assessing this relationship; this may introduce bias
- Challenging to assess whether a drug effect on a biomarker predicts a drug effect on a clinical outcome from a study that did not provide evidence of an effect on the clinical outcome
  - Acknowledge evidence may be limited in serious rare disease, but evaluation of the evidence supporting reasonably likely surrogacy is important

Neurofilament as Reasonably Likely Surrogate

- Magnitude of correlation between changes from baseline in NfL and ALSFRS-R in this study is small (correlation=-.21 in mITT population) and may be influenced by analysis choices
  - e.g., endpoint selection, scale for NfL, covariate selection
- Correlation necessary but not sufficient to support a candidate surrogate[1]
- Uncertainty about strong underlying assumptions of causal inference model (next slide)

[1] See, e.g., Fleming, T. R., & Powers, J. H. (2012). Biomarkers and surrogate endpoints in clinical trials. *Statistics in medicine*, *31*(25), 2973-2984.

Limitations of Applicant's Causal Inference Analysis

- Cannot conclusively establish the causal relationship between tofersen effects on NfL and ALSFRS-R.
  - Model was developed after unblinding, likely driven by the observed data
  - Supports hypothesis generating, but not confirming
- Unlike a randomized comparison, validity of results depends on
  - Form of the model, variables included in the model, specific data used to fit the model
- Uncertainty of the results depends on assumptions about the statistical error terms and missing data, which may not be appropriate in the present model
  - Completers analysis ignores missing data and 1 death of tofersen
  - Predictions on active arm assume that natural NfL progression model based on placebo arm is correct with no error added
  - Assumes equal variance despite much higher variance in mITT vs. non-mITT stratum

Summary

- No statistically significant effects on primary or other clinical outcomes in prespecified analyses
- Additional post hoc analyses of clinical outcomes by applicant challenging to interpret due to data-driven exploratory nature
- Data support an effect on NfL
- Evaluation of NfL as reasonably likely surrogate is a multidisciplinary approach
  - Understanding of disease/mechanism is important
  - Limited conclusions are possible from statistical analyses to evaluate relationship between tofersen effects on NfL and ALSFRS-R

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Clinical Pharmacology Presentation

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Office of Clinical Pharmacology
Center for Drug Evaluation and Research

Key Points

- NfL can be considered as a reasonably likely surrogate for accelerated approval of tofersen for treating SOD1-ALS based on totality of evidence
- Long term extension study provides supportive information on tofersen's treatment effect

Outline

- Background of biomarkers: SOD1 Protein and NfL
- Biomarker results from clinical studies
- NfL as a reasonably likely surrogate for accelerated approval
    1. Mechanistic evidence
    2. Prognostic value of NfL
    3. Relationship between NfL reduction and clinical function decline
- Evaluation of long-term treatment effect on ALSFRS-R total score

Study 101C: Biomarker Assessment

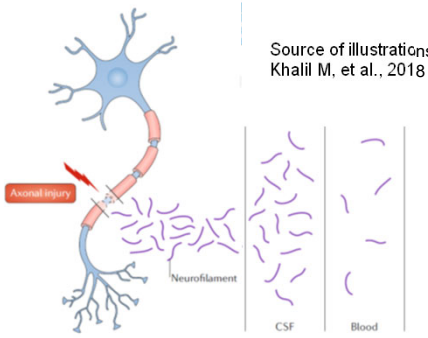
Hierarchical Testing Order	Secondary Endpoints at W28 in mITT	Tofersen-Placebo Estimated Treatment Difference (95% CI, p-value)	Sampling Plan
1	Total CSF SOD1 protein geometric mean ratio to baseline	**0.62** (0.49, 0.78) Nominal p<0.0001	Pre-dose on Day 1, 15, 29, and every 4 weeks thereafter to W28
2	Plasma NfL geometric mean ratio to baseline	**0.33** (0.25, 0.45) Nominal p<0.0001	Pre-dose on Day 1, 15, 29, and every 4 weeks thereafter to W28

SOD1 Protein

- Relevance of SOD1 Proteins in SOD1-ALS
  - Human SOD1 protein is ubiquitously expressed throughout the body and involved in removal of superoxide radicals
  - Mutations in SOD1 is thought to result in formation and accumulation of toxic SOD1 protein aggregates
  - Accumulation of the toxic SOD1 aggregates stimulates neurodegeneration, reflected by an increase in the level of neurodegenerative biomarkers, including NfL, and result in subsequent clinical decline
- Reduction of toxic SOD1 protein in SOD1-ALS patients is thought to be a promising target
  - Tofersen is an antisense oligonucleotide (ASO) inhibiting SOD1 protein translation including the toxic SOD1 protein

Neurofilament Light Chain (NfL)

- Neurofilament proteins are neurodegenerative biomarkers specific to degeneration of myelinated axons
  - NfL is the most widely studied subunit
- Release of NfL into the cerebrospinal fluid (CSF) and blood is a consequence of neuroaxonal damage
- Elevated NfL was reported in multiple neurological disorders
  - Significantly elevated NfL in ALS compared to other neurological disorders
- CSF and blood NfL levels in ALS patients are highly correlated
- NfL level correlates with ALS disease progression and survival
- NfL has not been used before as a surrogate biomarker for approval.



Source of illustrations: Khalil M, et al., 2018

Neurofilaments Subunits:
- NfL (70 kDa)
- Neurofilament medium chain (150 kDa)
- Neurofilament heavy chain (200 kDa)

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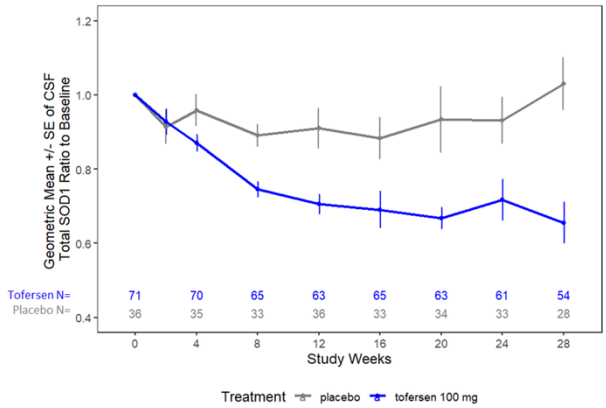
Total SOD1 Protein Reduction in CSF

- Evidence of target engagement
- The level of total SOD1 protein includes native and mutated forms



Study 101C	mITT		ITT	
	Placebo N=21	Tofersen N=39	Placebo N=36	Tofersen N=72
Adjusted GMR to baseline at W28	1.16	0.71	0.98	0.65
Treatment Difference in GMR (95% CI)	**0.62** (0.49, 0.78) (nominal p value <0.0001)		**0.66** (0.57, 0.77) (nominal p value <0.0001)	

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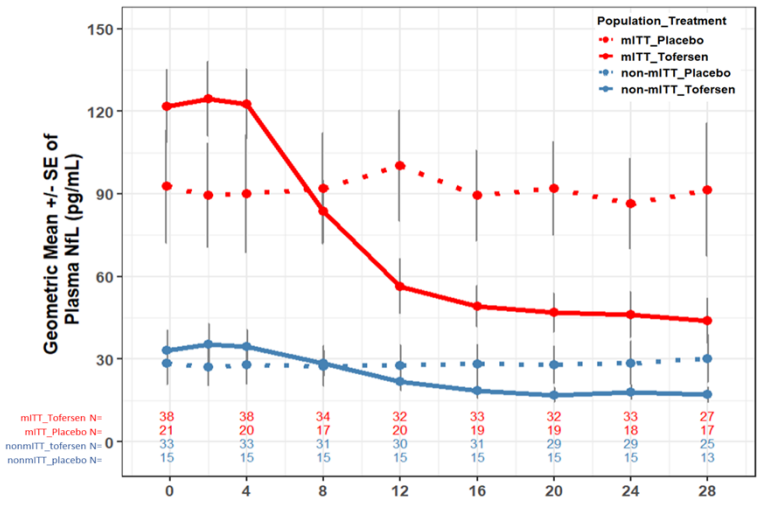
NfL Reduction in Plasma



Study 101C	mITT		ITT	
	Placebo N=21	Tofersen N=39	Placebo N=36	Tofersen N=72
Adjusted GMR to baseline at W28	1.20	0.40	1.12	0.45
Treatment Difference in GMR (95% CI)	**0.33** (0.25, 0.45) (nominal p value <0.0001)		**0.40** (0.33, 0.49) (nominal p value <0.0001)	

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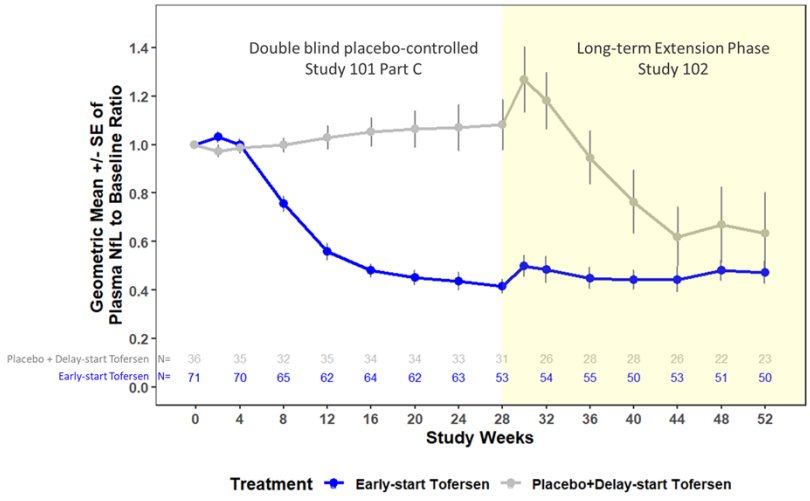
NfL Reduction in Plasma



- In patients randomized to placebo in Study 101C (N=32), treatment of tofersen in study 102 led to 44% NfL reduction comparing to the baseline of study 102

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Considerations for Reliance on a Biomarker to Support Accelerated Approval

- The biomarker is being used as a reasonably likely surrogate endpoint, defined as "an endpoint supported by strong mechanistic and/or epidemiologic rationale such that an effect on the surrogate endpoint is expected to be correlated with an endpoint intended to assess clinical benefit in clinical trials, but without sufficient clinical data to show that it is a validated surrogate endpoint"[#].
- This is a situation where there is a negative clinical study that failed to show a statistically significant treatment effect in the prespecified primary clinical endpoint. However, the biomarker, plasma NfL, is being proposed as a reasonably likely surrogate endpoint to support accelerated approval.

[#] BEST (Biomarkers, Endpoints, & Other Tools) Resources https://www.ncbi.nlm.nih.gov/books/NBK453485/

Key Points Supporting NfL Reduction as a Reasonably Likely Surrogate Endpoint for SOD1-ALS

- **Mechanistic Evidence**
  - Tofersen's mechanism of action as a targeted therapy
  - Downstream effect on a neurodegenerative biomarker, NfL
- **Prognostic Value of NfL**
  - Literature-based meta-analysis
  - Regression analysis from Study 101C
- **Relationship between NfL Reduction and ALSFRS-R Decline**
  - Longitudinal changes in NfL and ALSFRS-R
  - Correlation analyses
  - Causal inference analysis

Mechanistic Evidence - Understanding SOD1-ALS Pathophysiology

- **Pathologic mutation in SOD1 gene is the underlying cause of SOD1-ALS**
  - Mutated SOD1 gene is thought to result in toxic accumulation of mutated/misfolded SOD1 protein, leading to neuronal damage and neurodegeneration
  - Neurodegeneration causes release of NfL from axons of degenerated neurons
    - Reported NfL elevation in ALS and SOD1-ALS
  - The degeneration and loss of motor neurons lead to decline in clinical function as assessed by ALSFRS-R

Mechanistic Evidence - Tofersen's Mechanism of Action

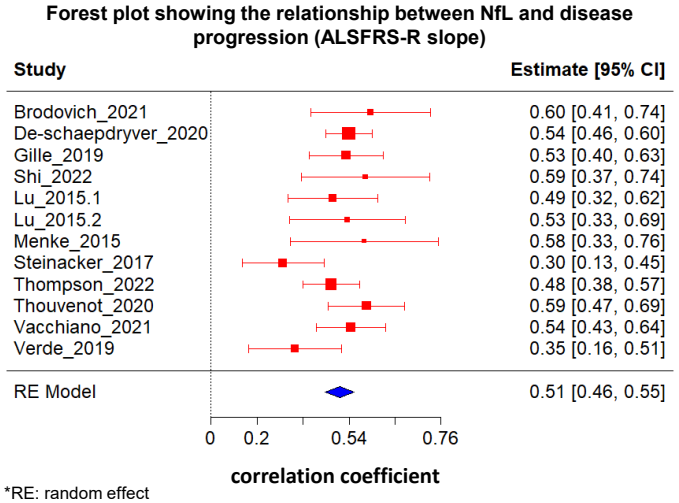
- **Tofersen is an ASO targeting the mRNA for human SOD1 and reduces SOD1 protein translation**
  - Tofersen reduces SOD1 protein translation, including the toxic SOD1 protein that contributes the SOD1-ALS pathophysiology
  - If tofersen does reduce neuronal damage by lowering SOD1, a reduction in NfL would be the expected outcome
- **Tofersen's effect in reducing plasma NfL is expected to lead to slower clinical function decline**
  - Observed reduction of total SOD1 protein in CSF suggests target engagement
  - Observed reduction in plasma NfL indicates reduced neuronal damage
  - Plasma NfL reduction is expected to lead to slower clinical function decline

Key Points Supporting NfL Reduction as a Reasonably Likely Surrogate Endpoint for SOD1-ALS

- **Mechanistic Evidences**
  - Tofersen's mechanism of action as a targeted therapy
  - Downstream effect on a neurodegenerative biomarker, NfL
- **Prognostic Value of NfL**
  - Literature-based meta-analysis
  - Regression analysis from Study 101C
- **Relationship between NfL Reduction and ALSFRS-R Decline**
  - Longitudinal changes in NfL and ALSFRS-R
  - Correlation analyses
  - Causal inference analysis

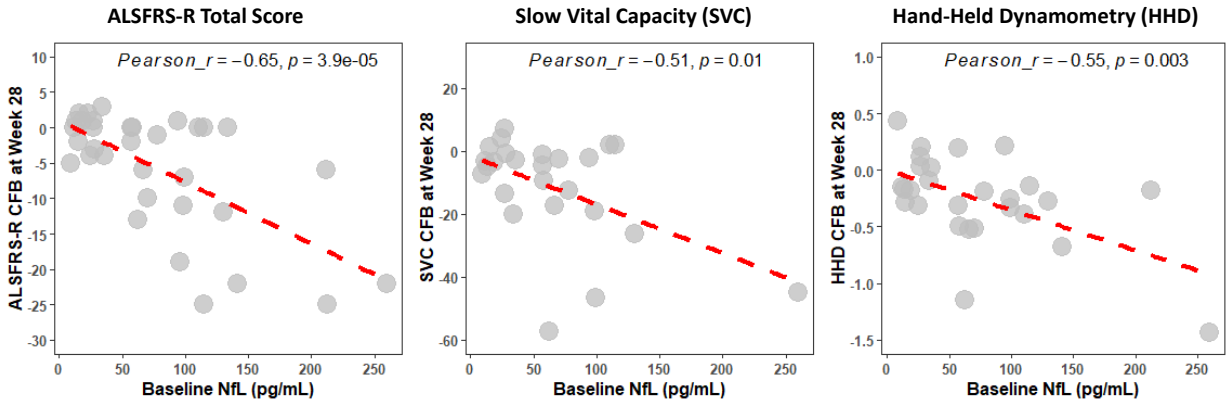
Evidence from Literature: Higher Plasma NfL is Associated with Faster Disease Progression and Unfavorable Clinical Outcomes

- Higher plasma NfL levels are associated with faster disease progression (correlation coefficient ~ 0.51)
- Patients with higher plasma NfL levels have a higher risk of unfavorable clinical outcomes (death, tracheostomy and/or permanent assisted ventilation)



*RE: random effect

Study 101C- ITT population: Subjects with Higher Baseline NfL Showed Faster Disease Progression Across Clinical Endpoints in Placebo Group



*CFB: Change from Baseline

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Study 101C- ITT population: Regression Analysis Evaluating Prognostic Value of Plasma NfL

- Regression analysis was performed to identify additional prognostic factors other than plasma NfL that can affect ALSFRS-R scores at Week 28
- The analysis suggests that plasma NfL is a significant predictor (p<0.001) for ALSFRS-R change at Week 28, even after adjusting other prognostic factors (refer to the table)
- This analysis may be limited by small sample size (n=33)

List of potential prognostic variables explored

Age	Baseline ALSFRS-R total score
Sex	ALSFRS-R slope
Weight	Plasma NfL
Height	Plasma pNfH
BMI	Slow Vital Capacity
	Time from symptom onset
	Site of Onset
	Edaravone or Riluzole use
	SOD-1 protein

These results, along with the literature based meta-analysis, support the prognostic value of plasma NfL in SOD1-ALS

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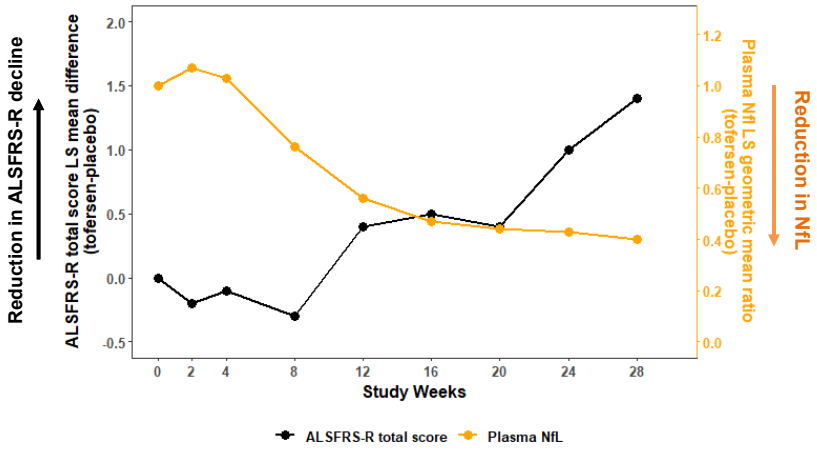
Key Points Supporting NfL Reduction as a Reasonably Likely Surrogate Endpoint for SOD1-ALS

- **Mechanistic Evidences**
  - Tofersen's mechanism of action as a targeted therapy
  - Downstream effect on a neurodegenerative biomarker, NfL
- **Prognostic Value of NfL**
  - Literature-based meta-analysis
  - Regression analysis of Study 101C
- **Relationship between NfL Reduction and ALSFRS-R Decline**
  - Longitudinal changes in NfL and ALSFRS-R
  - Correlation analysis
  - Causal inference analysis

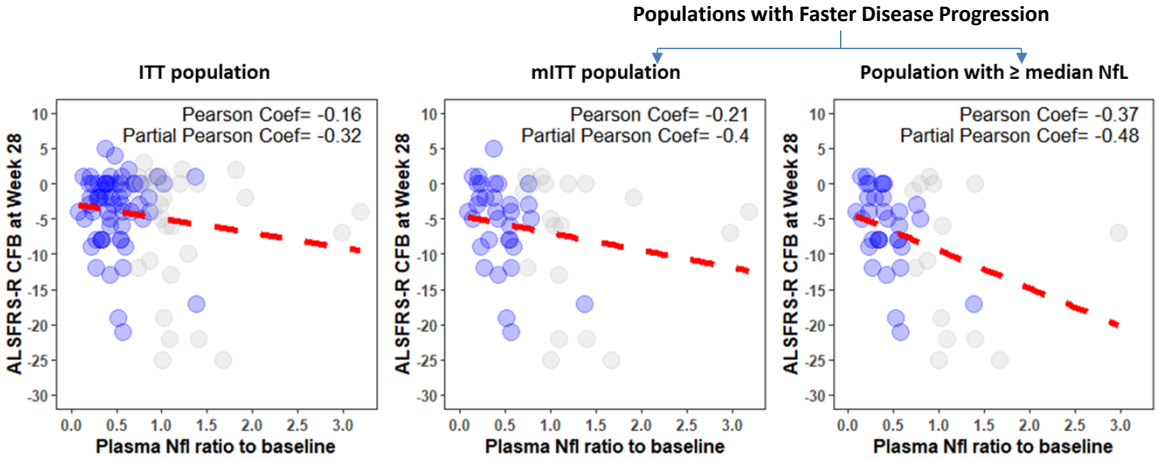
ITT population: Temporal Relationship Between Plasma NfL Reduction and Reduction in ALSFRS-R Decline

- Plasma NfL reduction appeared to start from Week 4 and reached maximum by Week 16
- Although the changes in ALSFRS-R were not statistically significant through Week 28, numerical differences were observed after Week 8 and continued through Week 28



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

Plasma NfL Reduction is Associated with Reduction in ALSFRS-R Decline at Week 28



***mITT criteria:** ALSFRS-R pre-randomization slope (>0.2 - 0.9/month) and certain SOD1 mutations; **Partial Pearson correlation** adjusted for NfL levels, SVC, sex, time since symptom onset and weight; Grey and blue circle represents placebo and tofersen group; CFB: change from baseline

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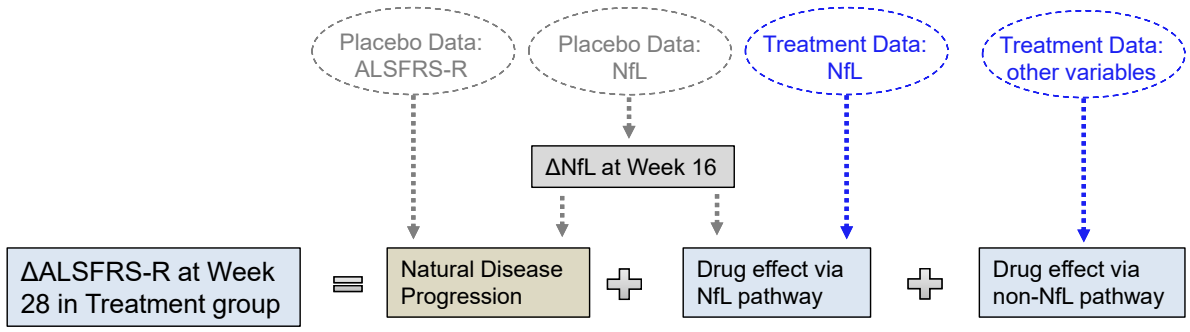
Causal Inference Analysis Quantifies Relationship Between Plasma NfL and ALSFRS-R Total Score



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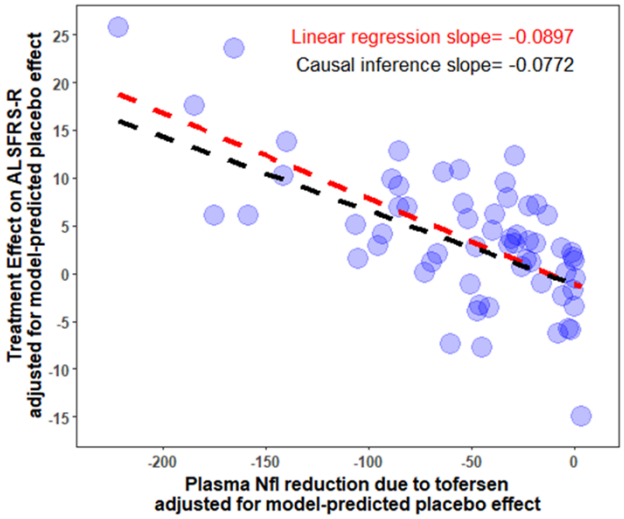
Treatment Effect Appears to be Associated with Plasma NfL Reduction



X-axis represents plasma NfL reduction at Week 16; Y-axis represents treatment effect at Week 28

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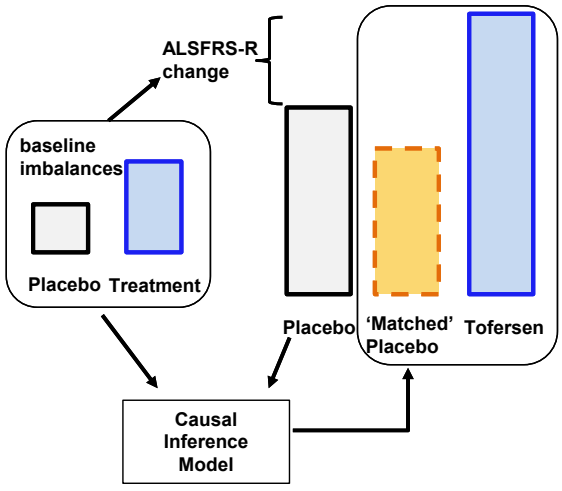
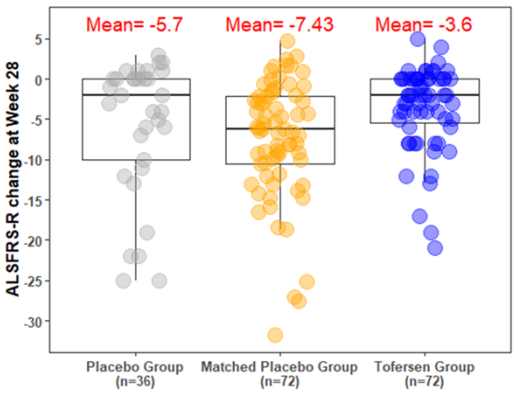
Possible Larger Treatment Effect is Projected if the Prognostic Factors were Balanced between Placebo and Tofersen Group





Mean treatment effect = 2.1
Projected treatment effect after adjusting for baseline prognostic factors= 3.8

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Additional Aspects Considered

- The analyses utilizes data from ITT population to provide the largest number of patients, and broadest range of NfL changes and ALSFRS-R changes. Of note, similar findings have been observed in the primary (mITT) population
- These analyses were based on study completers only, accounting for 90% of the enrolled patients
- The limitations must be recognized including the post-hoc nature and small size study
- Also, although a small size study, this was a randomized comparison, so "correcting" for a post-hoc imbalance (here plasma NfL) must be considered with caution

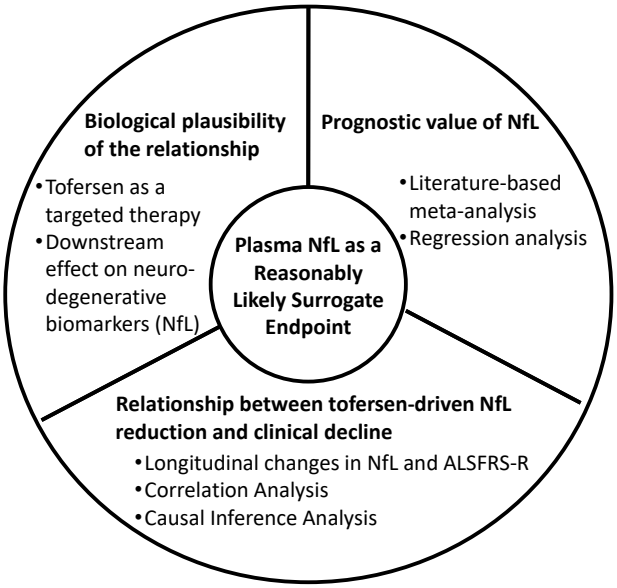
Overall, the analyses suggest that plasma NfL reduction appears to be associated with reduction in decline of clinical endpoints

Regulatory Definition for a Reasonably Likely Surrogate Endpoint

"An endpoint supported by strong mechanistic and/or epidemiologic rationale such that an effect on the surrogate endpoint is expected to be correlated with an endpoint intended to assess clinical benefit in clinical trials, but without sufficient clinical data to show that it is a validated surrogate endpoint"

https://www.fda.gov/drugs/development-resources/surrogate-endpoint-resources-drug-and-biologic-development; BEST (Biomarkers, EndpointS, and other Tools) Resource

Assessment of Plasma NfL as a Reasonably Likely Surrogate Endpoint



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EVALUATION OF LONG-TERM TREATMENT EFFECT ON ALSFRS-R TOTAL SCORE

Leveraging data from Study 101 Part C and Study 102

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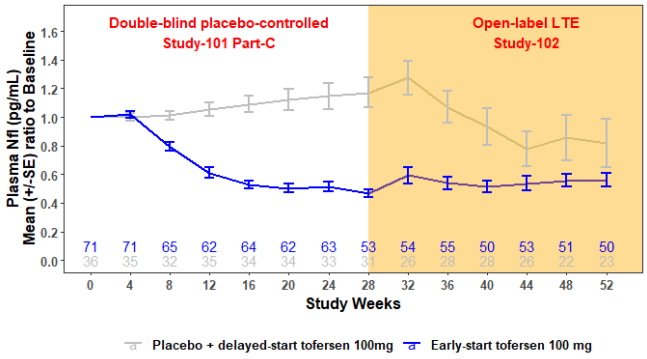
Longitudinal Changes in Plasma NfL and ALSFRS-R in Study Completers

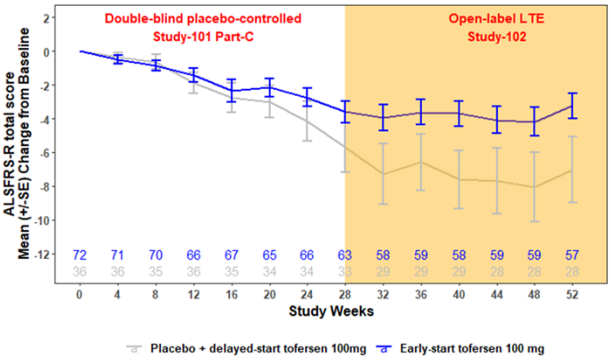
- Early-start and delayed-start group showed similar NfL reduction upon initiation of tofersen treatment

Plasma NfL



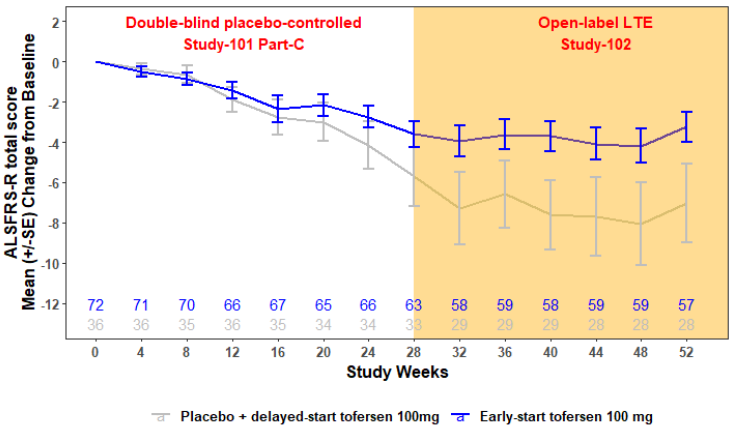
- Early-start group had consistently less numerical decline in ALSFRS-R total scores as compared to delayed-start group

ALSFRS-R total score



Consistent Separation on ALSFRS-R Between Two Groups From Week 8 Onwards Further Support the Potential Treatment Effect of Tofersen

- If one assumes that tofersen has no treatment effect, starting treatment 28 weeks earlier (or later) would not be anticipated to impact disease progression
- During open-label phase, the enrolled patients, site staff, and vendors were still blinded by the initial treatment assignment. So, it is unlikely that the initial treatment assignment would significantly affect the ALSFRS-R assessment in the open-label phase



Conclusion

- Tofersen treatment led to a reduction in total CSF SOD1 protein and plasma NfL in SOD1-ALS patients
- Plasma NfL appears to be a reasonably likely surrogate endpoint for SOD1-ALS based on the following:
  - Mechanistic support based on SOD1-ALS pathophysiology and the pharmacology of tofersen
  - Demonstration of the prognostic value of plasma NfL in ALS
  - Relationship between plasma NfL reduction and ALSFRS-R total score
- In long-term treatment study, early-start tofersen group showed a less decline in ALSFRS-R total scores from Week 8 onwards as compared to delayed-start group, which support the potential treatment effect of tofersen

Safety Overview

Safety Issues

- Approximately 116 patients treated > 1 year
- Most common adverse events(AEs) were pain, myalgia, arthralgia, fatigue, and CSF white blood cell increased.
- Permanent discontinuation due to AEs occurred in 6% of the tofersen group compared to 0% in placebo group.
  - Occurred in more than 1 subject were respiratory failure, respiratory arrest, and ALS.
- One patient died in the tofersen group (1%) from congestive heart failure.
  - This patient had prior history of cardiac disease. No deaths in placebo arm.
- Serious Adverse Events (SAEs) occurred in 18% tofersen patients vs. 14% placebo patients; largely related to underlying disease progression

Serious Neurologic Events

- Serious SAEs may be related to intrathecal route of administration
- Myelitis occurred in 4 subjects in studies 101C/102
  - None in placebo
  - 2 led to discontinuation, 2 were asymptomatic and remained on treatment
  - Additional patient in expanded access program had myelitis leading to discontinuation
- Radiculitis in 2 subjects in Studies 101C/102
  - Resolution of symptoms on treatment

Serious Neurologic Events

- Aseptic meningitis/Chemical Meningitis (1 patient each)
  - Have been reported with other intrathecal administration
  - Also reports of nonserious AEs of increased WBC in CSF
  - Chemical meningitis did lead to treatment d/c with complete resolution after discontinuation
- Papilledema and/or Increased Intracranial Pressure
  - 4 patients with SAE, none in placebo arm
  - None led to permanent discontinuation
  - One patient had concomitant aseptic meningitis (above)
  - Hydrocephalus reported with other intrathecal ASO
  - Non serious reports also noted

Safety Conclusion

- Generally well tolerated
- Other known class effects of other ASOs given intravenously (i.e., hypersensitivity, thrombocytopenia, and kidney toxicity) were not seen in the controlled study or OLE
- Risk for serious neurologic events
  - May be more related to route of administration than specific to drug
  - Majority resolved without leading to permanent discontinuation
  - Patients and providers need to be aware of potential for serious neurologic events
  - If approved, these risks should be described in labeling

Conclusions

- Rare, serious, life-threatening disease
- Targeted therapy with reduction in biomarkers suggesting target engagement
- Pivotal study failed
  - Clinical outcomes trended in the right direction
  - Separation over time between treatment groups
  - Study design limitations
- Considerations of regulatory flexibility

Questions to the Committee

1. **DISCUSSION:** Discuss whether the available evidence supports that a reduction in plasma neurofilament light (NfL) concentration observed in tofersen-treated patients with amyotrophic lateral sclerosis (ALS) secondary to a mutation in SOD1 (SOD1-ALS) is reasonably likely to predict clinical benefit for these patients.

2. **VOTE:** Is the available evidence sufficient to conclude that a reduction in plasma NfL concentration in tofersen-treated patients is reasonably likely to predict clinical benefit of tofersen for treatment of patients with SOD1-ALS?

3. **DISCUSSION:** Discuss the strengths and limitations of the available clinical data from the placebo-controlled study and long term extension regarding the effectiveness of tofersen for SOD1-ALS.

4. **VOTE:** Does the clinical data from the placebo-controlled study and available long-term extension study results, with additional supporting results from the effects on relevant biomarkers (i.e., changes in plasma NfL concentration and/or reductions in SOD1), provide convincing evidence of the effectiveness of tofersen in the treatment of patients with SOD1-ALS.

5. **DISCUSSION:** Discuss the overall benefit-risk assessment for tofersen in patients with amyotrophic lateral sclerosis (ALS) secondary to a mutation in SOD1 (SOD1-ALS). If the available evidence supports a benefit, discuss if the risks appear acceptable given the observed treatment benefit. If the benefit-risk assessment does not appear favorable, discuss what additional data would be needed for the benefit-risk assessment to be favorable.

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