Tofersen (Qalsody)

Use of a Surrogate Endpoint to Demonstrate Substantial Evidence of Effectiveness for an Accelerated Approval

Prior to reading this case study, please refer to the LEADER 3D Case Study User Guide as an informational resource. Please note this case study is not intended or designed to provide specific strategies for obtaining product approval. **Rare disease drug development is not one-size-fits-all.** The kind and quantity of data in each rare disease application will be different based on the unique considerations of each development program and must therefore be assessed on a case-by-case basis.

Introduction

This case study examines the use of a surrogate endpoint for the U.S. Food and Drug Administration's (FDA) accelerated approval of tofersen (Qalsody). For further details on this case study, please refer to the Integrated Review.

Tofersen is an antisense oligonucleotide (ASO) drug indicated for the treatment of amyotrophic lateral sclerosis (ALS) in adults who have a mutation in the superoxide dismutase 1 (*SOD1*) gene. In this case study, the Applicant engaged with the FDA to discuss the use of neurofilament light chain (NfL) as a surrogate endpoint for accelerated approval. The FDA approved tofersen under the accelerated approval pathway based on its determination that:

1. ALS is a serious condition with a lack of available therapies, and
2. Tofersen had an effect on a surrogate endpoint, NfL, that is reasonably likely to predict clinical benefit.

Introduction to the Rare Disease

ALS is a rare, serious, and life-threatening disease that causes muscle weakness and death due to respiratory failure. It is a progressive and fatal motor neuron disease characterized by the gradual degeneration and death of the motor neurons responsible for voluntary control of muscles. ALS most frequently affects people between 40 and 70 years of age. Patients with ALS become progressively weaker, losing the ability to move their bodies. Weakness of the respiratory muscles leads to respiratory failure; and death in most patients occurs within 3 to 5 years from the onset of symptoms.

Statutory and Regulatory Highlights

In 1992, FDA issued its accelerated approval regulations. In 1997, Congress codified the accelerated approval program in the Food and Drug Administration Modernization Act, adding section 506 to the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 356). In 2012, Congress amended section 506 of the FD&C Act under the Food and Drug Administration Safety and Innovation Act to provide that FDA should consider the "severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments." Section 506(c) of the FD&C Act was recently amended by the Food and Drug Omnibus Reform Act (Sec. 3210 of the Consolidated Appropriations Act, 2023) to provide the FDA with additional authorities, and obligations regarding accelerated approval.

Note on the Food and Drug Omnibus Reform Act (FDORA): FDORA (Sec. 3210 of the Consolidated Appropriations Act, 2023) amended section 506(c) of the FD&C Act (21 U.S.C. 356(c)) to provide the FDA with new authorities related to accelerated approval, such as the authority to require, as appropriate, that a confirmatory trial be underway prior to approval, or within a specified time period after the approval, of the applicable product.[1]

Key Concept: Accelerated Approval

When studying a new drug, it can sometimes take many years to learn whether a drug provides an effect on how a patient feels, functions, or survives. A positive therapeutic effect that is clinically meaningful in the context of a given disease is known as "clinical benefit". The accelerated approval pathway, in appropriate cases, provides for the approval of drugs for serious conditions that fill an unmet medical need based on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit. This often allows sponsors to obtain approval for products intended to treat an unmet medical need sooner than would be possible under traditional approval. For drugs granted accelerated approval, sponsors conduct confirmatory trials that must be completed post-approval and are intended to verify and describe the anticipated effect on irreversible morbidity or mortality (IMM) or other clinical benefit.

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[1] For more information see the FDA Accelerated Approval Program webpage.

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- The Agency accepts clinical endpoints that reflect patient benefits (i.e., how patients feel, function, or survive) or validated surrogate endpoints (i.e., those that have been shown to predict a specific clinical benefit) as the basis for traditional approval. In contrast to traditional approval, accelerated approval can be based on a demonstrated effect on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict clinical benefit.
- A surrogate endpoint is generally a biomarker, such as a laboratory measurement, radiographic image, physical sign, or other measure, that is thought to predict clinical benefit but is not itself a measure of clinical benefit.
- An intermediate clinical endpoint is an endpoint that can be measured earlier than the clinical endpoint of interest but is considered reasonably likely to predict the clinical benefit of a drug, such as an effect on IMM or other clinical benefit.
- Determining whether an endpoint is reasonably likely to predict clinical benefit is a matter of judgment that will depend on the biological plausibility of the relationship between the disease, the endpoint, and the desired effect, and the empirical evidence to support that relationship.
- To support accelerated approval, studies that demonstrate a drug's effect on a surrogate or intermediate clinical endpoint must be "adequate and well-controlled" as required by the FD&C Act.

Using surrogate or intermediate clinical endpoints can save valuable time during drug development. For example, instead of having to wait to learn if a drug actually extends survival for cancer patients, the FDA may approve a drug based on evidence that the drug shrinks tumors, because tumor shrinkage is considered reasonably likely to predict clinical benefit (e.g., survival). In this example, an approval based upon tumor shrinkage can occur far sooner than waiting to learn whether patients actually lived longer. The drug company will still need to conduct studies to confirm that tumor shrinkage actually predicts that patients will live longer. If the required confirmatory trial verifies and describes the clinical benefit, FDA considers the confirmatory trial requirement to have been met and therefore released. (The Agency sometimes refers to this determination informally as conversion of a product to traditional approval). FDA may withdraw approval of a drug approved under accelerated approval if, for example, the sponsor fails to conduct a confirmatory trial with due diligence or a confirmatory trial fails to verify and describe the effect on clinical benefit, among other reasons.

FDA Guidance Corner

Note: The FDA Guidance Corner includes excerpts of draft FDA guidance documents which, when final, will represent the Agency's current thinking on topics in the case study. For up-to-date guidance documents please search Guidance Documents for Rare Disease Drug Development | FDA.

In this case study, the Applicant was granted accelerated approval. An applicant must meet specific qualifying criteria and agree to the conditions of the accelerated approval.

This draft guidance document describes the qualifying criteria, relevant terms, and the conditions of accelerated approval:

Draft guidance for industry *Expedited Programs for Serious Conditions – Accelerated Approval of Drugs and Biologics* (December 2024)

At the time a product is granted accelerated approval, FDA has determined that an effect on the endpoint used to support approval –– a surrogate endpoint or an intermediate clinical endpoint –– is reasonably likely to predict clinical benefit. The risks of this approach include that patients may be exposed to safety risks from a drug that ultimately does not demonstrate clinical benefit. In addition, because there generally may be smaller or shorter clinical trials than is typical for a drug receiving traditional approval, there may be less information at the time of accelerated approval about the occurrence of rare or delayed adverse events. These risks inform the Agency's decision-making regarding use of accelerated approval.

The Applicant engaged with the FDA during their drug development program. Meeting with the FDA early in your drug development process is crucial so that potential issues may be addressed prior to your pivotal clinical studies.

This draft guidance document describes the types of meetings available to sponsors:

Draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Sponsors of PDUFA Products Guidance for Industry* (September 2023).

When a meeting is needed, a written request must be submitted to the FDA via the electronic gateway or, in CDER, via the CDER NextGen Portal, as appropriate. Requests should be addressed to the appropriate Center and review division or office and, if previously assigned, submitted to the application (e.g., investigational new drug application (IND), new drug application (NDA), biologics license application (BLA), pre-application tracking system (PTS) Number (CBER)).

If necessary, noncommercial IND holders may also submit the meeting request via the appropriate center's document room.

Introduction to the Rare Disease (continued)

ALS can be familial (inherited or a family history of ALS) or sporadic (spontaneous or no family history of ALS). The estimated prevalence of ALS (sporadic and familial) in the United States is 5 per 100,000 totaling around 16,000 cases overall. While most cases of ALS are sporadic, five to ten percent of ALS cases are familial. Within the familial ALS type, 20% (about 500 cases overall) are associated with a mutation in the *SOD1* gene (SOD1-ALS). SOD1-ALS generally presents with similar clinical characteristics to sporadic ALS; however, the degree of upper versus lower motor neuron involvement, age of onset, and rate of progression of the disease can vary depending on the type of SOD1 mutation. The A5V mutation of SOD1-ALS is associated with rapid disease progression, with earlier age of symptom onset and faster decline in motor functions compared to other mutations.

Current Treatment Options

Before FDA approval of tofersen, there were no approved therapies specifically for the treatment of SOD1-ALS. Most available treatments for ALS are intended to relieve symptoms such as cramps and spasticity and improve the patient's quality of life. The three FDA-approved treatments for ALS: (1) riluzole, (2) edaravone, and (3) sodium phenylbutyrate with taurursodiol, do not effectively treat SOD1-ALS, with most patients experiencing continued progression of their disease resulting in respiratory failure and death. Therefore, there was a significant unmet medical need for effective treatments for this familial form of ALS.

Tofersen Mechanism of Action

SOD1 is one of the three isoforms of SOD metalloenzymes that plays a key role in antioxidant defense in humans by destroying superoxide free radicals in the body. The SOD1 isoform is located in the cytoplasm of cells and requires copper and zinc for its activity. Acting as a homodimer, SOD1 converts toxic superoxide anion radicals (a reactive oxygen species [ROS]) into oxygen and hydrogen peroxide.[2] Subsequently, hydrogen peroxide can be broken down into water and oxygen by other enzymes, namely, glutathione peroxidase or catalase. The mechanism(s) by which SOD1 mutations cause ALS is not fully understood. However, the formation of toxic SOD1 protein aggregates in motor neurons and astrocytes, primarily due to gain-of-function mutations, is thought to be a major mechanism underlying this form of ALS (**Figure 1**). The toxic aggregates disrupt cellular processes and lead to axonal injury and motor neuron death. This degeneration is accompanied by the release of NfL into cerebrospinal fluid (CSF), and subsequently into the blood.

Tofersen is an ASO designed to target and degrade SOD1 mRNA, thereby reducing the synthesis of SOD1 protein and decreasing accumulation of mutant protein aggregates, leading to fewer neurodegenerative symptoms (**Figure 1**).

FDA Guidance Corner

In this case study, NfL was considered a surrogate endpoint reasonably likely to predict clinical benefit in patients with SOD1-ALS. The Applicant demonstrated a large, robust, and convincing reduction in plasma NfL in tofersen-treated participants.

This draft guidance document which, when final, will represent the Agency's current thinking, provides considerations for substantial evidence of effectiveness when planning and designing a clinical investigation:

Draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019)

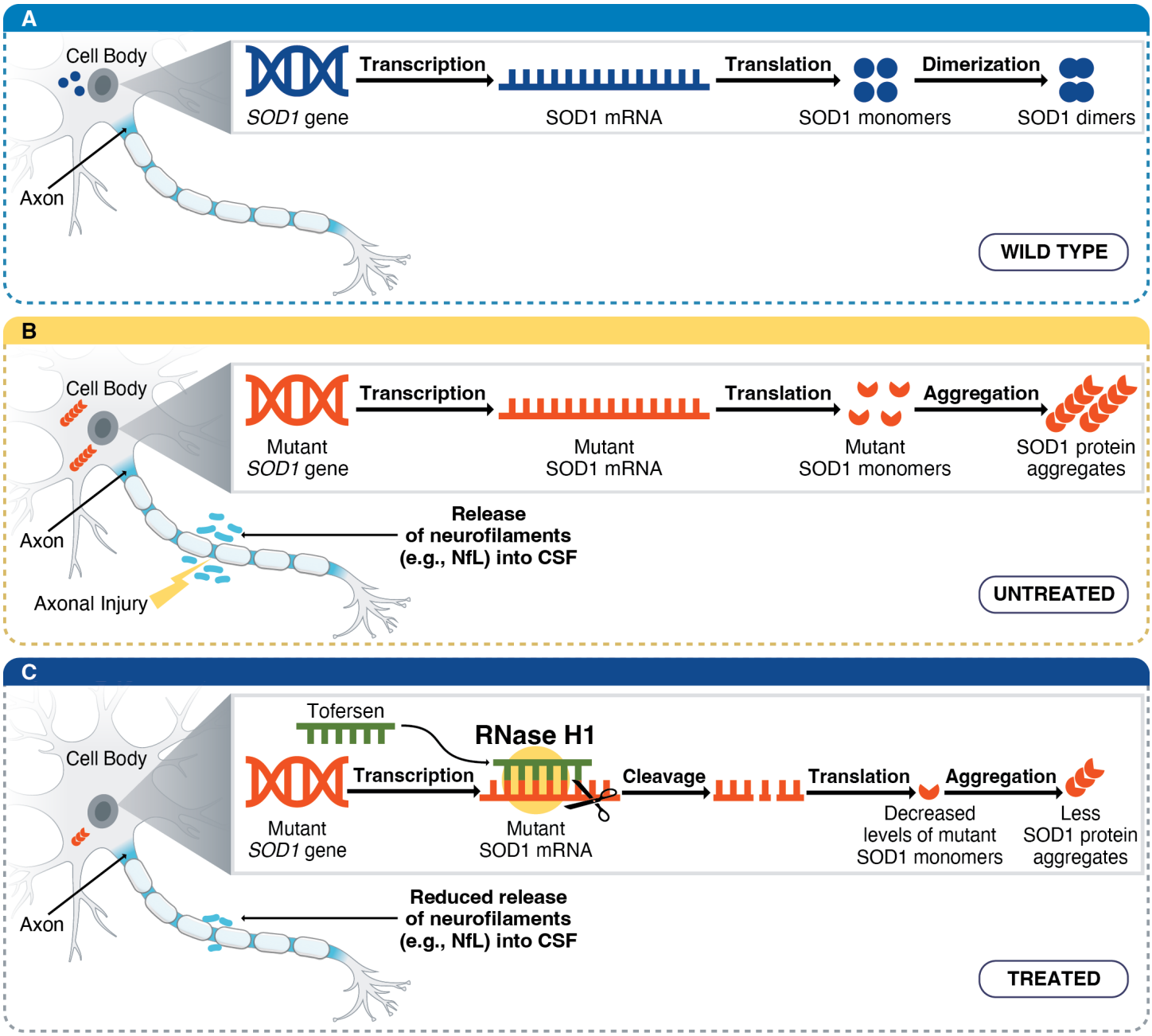
One of the characteristics of an adequate and well-controlled clinical investigation is that "the methods of assessment of subjects' response are well-defined and reliable." Such a method of assessment can be a clinical endpoint or, where appropriate, a surrogate endpoint.

The clinical endpoints studied are a critical aspect of evidence quality. The Agency accepts clinical endpoints that reflect patient benefits (i.e., how patients feel, function, or survive) or validated surrogate endpoints (i.e., those that have been shown to predict a specific clinical benefit) as the basis for traditional approval. In contrast to traditional approval, accelerated approval can be based on a demonstrated effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit but where there are not sufficient data to show that it is a validated surrogate endpoint. Effects on intermediate clinical endpoints can also be a basis for accelerated approval. For drugs granted accelerated approval, FDA requires post-approval trials to verify the predicted clinical benefit.

It will be particularly important to understand the pathophysiology and natural history of the disease to help identify potential surrogate endpoints.

[2] Bonafede, R and R Mariotti, 2017, ALS Pathogenesis and Therapeutic Approaches: The Role of Mesenchymal Stem Cells and Extracellular Vesicles, Front Cell Neurosci, 11(80).

Figure 1: (A) *The SOD1 gene is transcribed into SOD1 mRNA in neural cells, which is then translated into correctly folded (wild type) SOD1 monomers. SOD1 monomers assemble into stable homodimers, which catalyze the dismutation of toxic ROS into oxygen and hydrogen peroxide; the latter is removed by the activity of other enzymes.* ***(B)*** *Mutations in the SOD1 gene result in misfolded mutant SOD1 monomers, which form aggregates in neuronal cytoplasm that are associated with axonal damage, diminished axonal transport, and release of neural cytoskeletal protein, NfL into CSF and blood.* ***(C)*** *Tofersen, an ASO, targets both wild type and mutant SOD1 mRNAs, leading to their degradation by RNase H1. As a result, fewer misfolded SOD1 proteins are made, resulting in reduced aggregates and fewer neurodegenerative symptoms.*

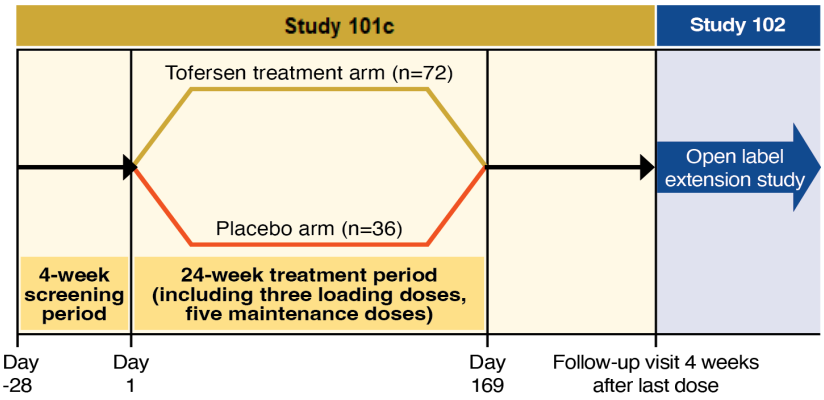


The Single Adequate and Well-Controlled Investigation

Study Design

The Applicant conducted a single 28-week, randomized, double-blind, placebo-controlled phase 3 pivotal study (Study 233AS101 Part C, also noted as 101C) in 108 adult participants with SOD1-ALS (**Figure 2**). The study included blood and CSF concentrations of NfL and CSF SOD1 protein levels. Study 101C was followed by an open-label extension (OLE) study (102) to assess the long-term safety, tolerability, pharmacokinetics, and effect on disease progression in SOD1-ALS participants previously treated with tofersen in Study 101C (early-start tofzersen group) and adults who received placebo in Study 101C (delayed-start tofersen group). Study 101C constituted a single adequate and well-controlled investigation that provided efficacy, safety, and biomarker data.

Figure 2: *Study design of 233AS101 Part C (101C) and 233AS102 (102).*



FDA Guidance Corner

In this case study, the Applicant engaged with the FDA early in the planning for their NDA to discuss considerations specific to their drug development plans.

This guidance highlights important considerations in rare disease drug and biologics development:

Guidance for industry *Rare Diseases: Considerations for the Development of Drugs and Biological Products* (December 2023)

FDA recognizes that rare diseases are highly diverse with varying prevalence, rates of progression, and degrees of heterogeneity that can affect both clinical manifestations and disease courses, even within a condition. Further complexity is added depending on what is known about a disease's natural history and pathophysiology. As such, no one program can be designed exactly like another. FDA is committed to helping sponsors create successful drug development programs that address the particular challenges posed by each disease and encourages sponsors to engage early with the Agency to discuss their drug development program.

NfL as a Surrogate Endpoint for Accelerated Approval

NfL Background[3]

NfL is a neurofilament protein highly expressed in myelinated axons. Elevated levels of NfL in the CSF and blood are found in a variety of neurological disorders including ALS and are a consequence of axonal damage. Neurofilament levels in the plasma and CSF, including neurofilament heavy chain (pNF-H) and NfL are significantly elevated in patients with ALS compared to other neurodegenerative diseases. For ALS patients who carry the SOD1 mutation, elevated serum NfL levels have been observed as early as 1 year before symptom onset.[4] Several independent studies have reported that NfL levels are correlated with disease severity, disease progression rate, and survival in patients with ALS.[5,6] A meta-analysis of published literature findings on NfL in ALS demonstrated a correlation between the rate of disease progression and plasma NfL level.[7] Additionally, higher levels of neurofilament were associated with a higher risk of unfavorable clinical outcomes, including death, tracheostomy, and/or permanent ventilation. NfL was reported to have a stronger association than other candidate biomarkers with ALS progression rate and survival.

[3] Please refer to the Integrated Review on page 59 for a complete list of references cited for the NfL background.

[4] Benatar, M, W Joanne, and RT Martin, 2022, Neurofilament light chain in drug development for amyotrophic lateral sclerosis: a critical appraisal, Brain,146(7):2711–2716.

[5] Lu, CH, C Macdonald-Wallis, E Gray, N Pearce, A Petzold, N Norgren, G Giovannoni, P Fratta, K Sidle, M Fish, R Orrell, R Howard, K Talbot, L Greensmith, J Kuhle, MR Turner, and A Malaspina, 2015, Neurofilament light chain: A prognostic biomarker in amyotrophic lateral sclerosis, Neurology, 84(22):2247–2257.

[6] Dreger, M, R Steinbach, M Otto, MR Turner, and J Grosskreutz, 2022, Cerebrospinal fluid biomarkers of disease activity and progression in amyotrophic lateral sclerosis, J Neurol Neurosurg Psychiatry, 93(4):422–435.

[7] Please refer to the Integrated Review on page 200 for the meta-analysis of the scientific literature to determine the relevance of neurofilament changes in ALS.

These findings offer support for the utility of NfL as a prognostic biomarker for ALS disease progression and survival. Also, a reduction of neurofilament levels has been reported for products approved for the treatment of other neurological diseases, including multiple sclerosis, spinal muscular atrophy, and hereditary transthyretin-mediated amyloidosis, which provides additional context regarding the use of NfL as a pharmacodynamic biomarker that may correlate with clinical benefit in patients with ALS.

NfL as a Surrogate Endpoint

The FDA reviewed biomarker data from Study 101C including CSF levels of SOD1 protein and plasma NfL data taking into consideration the:

- Mechanistic evidence that tofersen reduces the amount of SOD1 protein (the intended target of the drug and a known contributor to the pathophysiology of SOD1-ALS);
- Seriousness of SOD1-ALS;
- Lack of available options to treat SOD1-ALS;
- Scientific evidence demonstrating the prognostic value of plasma NfL in predicting disease progression and survival in ALS; and
- Observed correlation between reduction in NfL and a reduction of decline of clinical outcomes such as the ALS Functional Rating Scale-Revised (ALSFRS-R).

The FDA considered a reduction in NfL by tofersen as a surrogate endpoint that is reasonably likely to predict clinical benefit in patients with SOD1-ALS to support the accelerated approval of tofersen. Study 101C was adequate and well-controlled, and the change in NfL observed in Study 101C was large, robust, consistent, and convincing. Additionally, SOD1 protein concentrations in CSF were evaluated as indirect evidence of target engagement, i.e., the binding of tofersen to SOD1 mRNA. Reductions in CSF SOD1 protein support the mechanism of action of tofersen and provided confirmatory evidence. Therefore, FDA determined the data provided substantial evidence of a treatment effect of tofersen on NfL in patients with SOD1-ALS to support accelerated approval. This determination considers the severity, rarity and prevalence of SOD1-ALS, and the significant unmet clinical need.

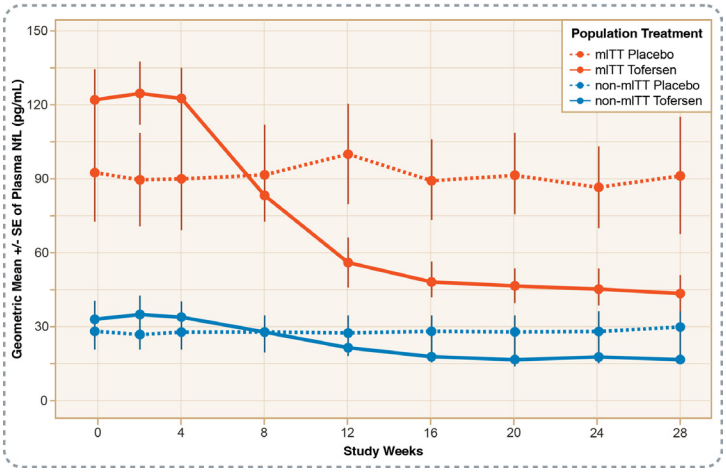
Biomarker Results

NfL biomarker results

Plasma NfL levels were analyzed from participant samples that were collected before dosing at each visit (Days 1, 15, 29, and every 4 weeks thereafter) and at the final visit (4 weeks after the last dose).

The reviewers' analysis of data in Study 101C demonstrated a reduction in plasma NfL concentration in the treatment group compared to the placebo group in the modified intent to treat (mITT) population (the mITT population consisted of the subset of participants who met the prognostic enrichment criteria for rapid disease progression, i.e., faster progressors).[8] The NfL reduction driven by tofersen in the treatment arm plateaued at Week 16 and was sustained until the end of treatment at Week 28 (**Figure 3**) (67% difference in geometric mean ratios for tofersen to placebo at Week 28, nominal p<0.0001).

Figure 3: *Plasma NfL concentration (Geometric Mean Values ±SE) in treatment groups compared to the placebo group.* ***Tofersen reduced plasma NfL levels in both mITT and non-mITT treatment populations compared to placebo (Study 101C, ITT population)***.[9]



[8] For more information on study design criteria, please refer to page 36 of the Integrated Review.

[9] Figure 3 was generated using information provided on page 62 of the Integrated Review for tofersen (Qalsody), NDA 215887.

A reduction in plasma NfL was also observed in the non-mITT population (48% difference in geometric mean ratios for tofersen to placebo, nominal p<0.0001, also see Figure 3. Correlation and causal inference analysis suggested that reduction in plasma NfL was associated with reduction in the decline of ALSFRS-R total score at Week 28.

In the intent to treat (ITT) population of Study 102 (the open label extension), participants who had received tofersen in Study 101C (early start tofersen group) maintained the previously lowered plasma NfL levels following the 24 weeks of continued tofersen treatment (Figure 4). Participants in the delayed-start tofersen group (who received placebo in Study 101C, ITT population), showed a similar reduction in plasma NfL levels by 44% (geometric mean ratio to baseline of Study 102) after receiving 24 weeks of treatment with open-label tofersen (Figure 4).

Total SOD1 in CSF

The change from baseline in total SOD1 concentration in CSF at Week 28 for the mITT population served as an additional key secondary endpoint in Study 101C. A reduction in total CSF SOD1 protein was observed at Week 28 in the tofersen group compared to the placebo group in the mITT population (38% difference in geometric means ratio for tofersen to placebo, nominal p<0.0001) and in the ITT population (approximately 34% difference in geometric means ratio for tofersen to placebo, nominal p<0.0001) (Figure 5).

Confirmatory Study

A postmarketing requirement (PMR) was issued to the Applicant to verify the clinical benefit of tofersen by completing the ongoing Study 233AS303 (ATLAS), a Phase 3 randomized, placebo-controlled study in presymptomatic adults with a confirmed SOD1 mutation, who will be enrolled into a natural history run-in period, followed by a randomized, double-blind, placebo-controlled period. Participants will remain in the double-blind, placebo-controlled study until they clinically manifest ALS or the end of the study. The primary endpoint is the proportion of participants with emergence of clinically manifested ALS. At the time of tofersen's accelerated approval, the Applicant had already submitted their final clinical protocol and indicated the PMR would be completed by a date agreed upon by the applicant and review division.[12]

Figure 4: *Plasma NfL concentration (Geometric Mean Values ±SE) during the double-blind, placebo-controlled phase (Study 101C) and the open-label extension phase (Study 102).* ***Participants who received tofersen in Study 101C maintained lower plasma NfL levels in Study 102 following the continued tofersen treatment, while participants initially given a placebo (i.e., orange placebo + delayed-start tofersen) in Study 101C showed a reduction in plasma NfL levels during the open-label period when receiving tofersen.***[10]

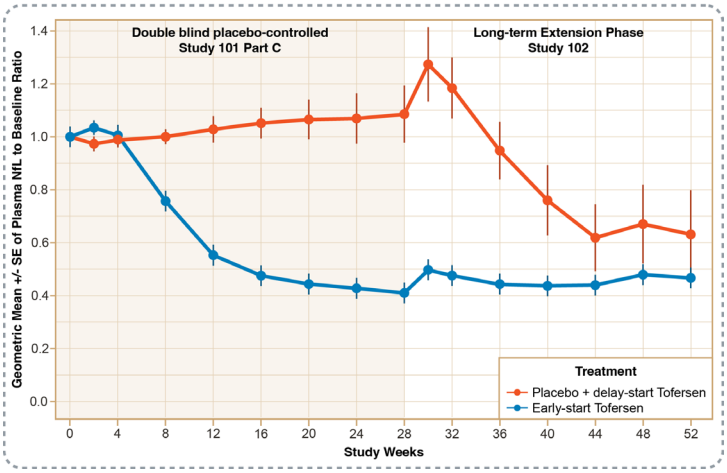
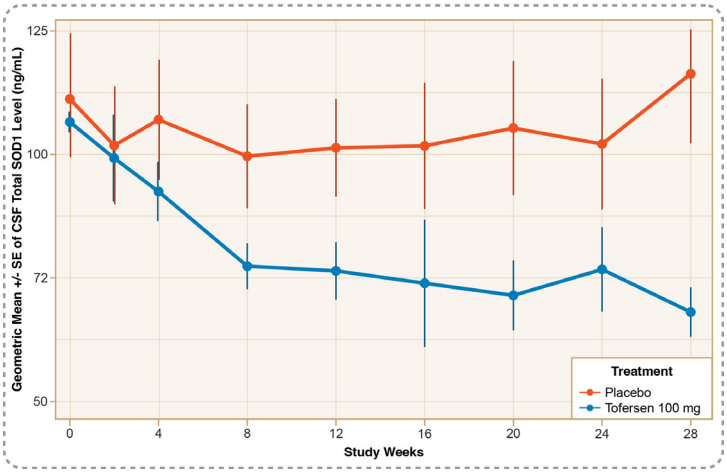


Figure 5: *Levels of total CSF SOD1 protein (Geometric Mean ±SE) in tofersen treatment group compared to placebo group over a 28-week treatment period.* ***Tofersen reduced total CSF SOD1 protein at Week 28 in the tofersen group compared to the placebo group.***[11]



[10] Figure 4 was generated using information provided on page 63 of the Integrated Review for tofersen (Qalsody), NDA 215887.

[11] Figure 5 was generated using information provided on page 64 of the Integrated Review for tofersen (Qalsody), NDA 215887.

[12] Action letter tofersen (Qalsody), NDA 215887.

Conclusion

The FDA determined that the observed reduction in plasma NfL concentration is acceptable as a surrogate endpoint that is reasonably likely to predict clinical benefit in patients with SOD1-ALS in the context of the tofersen program.

The following factors were considered in the determination that plasma NfL was an acceptable surrogate endpoint that is reasonably likely to predict clinical benefit in adult patients with SOD1-ALS:

- Mechanistic evidence that tofersen reduces SOD1 protein, the intended target of the drug and a known contributor to the pathophysiology of SOD1-ALS;
- The scientific evidence demonstrating the prognostic value of plasma NfL in predicting disease progression and survival in ALS; and
- The observed correlation between reduction in NfL and a reduction of decline of clinical outcomes such as the ALSFRS-R.

Based on the reduction in plasma NfL concentration, FDA determined that the substantial evidence of effectiveness requirement was met because:

1. Study 101C was adequate and well-controlled.
2. The reduction in plasma NfL levels in tofersen-treated participants was statistically significant as the change observed in this single study was large, robust, and convincing.

Additionally, a reduction in CSF SOD1 protein levels in tofersen-treated participants supports the mechanism of action of tofersen and provided confirmatory evidence. Together, these data provided substantial evidence of a treatment effect of tofersen on NfL in patients with SOD1-ALS to support accelerated approval. This determination also considers the severity, rarity, and prevalence of SOD1-ALS, and the significant unmet clinical need for effective treatments for this life-threatening disease.

FDA Guidance Corner

In this case study, tofersen was approved through the accelerated approval pathway based on a surrogate endpoint for SOD1-ALS, a life-threatening and severely debilitating disease. This draft guidance document which, when final, will represent the Agency's current thinking on demonstrating substantial evidence of effectiveness:

Draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (2019)

Subpart E regulations promulgated in 1988 call for FDA to exercise its broad scientific judgment in applying the evidentiary approval standards to drugs for life-threatening and severely debilitating diseases, especially where there is no satisfactory alternative therapy. In addition, the accelerated approval regulations built upon this recognition by acknowledging that reliance on a surrogate endpoint "almost always introduces some uncertainty into the risk/benefit assessment, because clinical benefit is not measured directly and the quantitative relation of the effect on the surrogate to the clinical effect is rarely known." Together these regulations recognize the importance of facilitating the development of, and access to, safe and effective treatment options for life-threatening and severely debilitating diseases with unmet medical needs.

Surrogate endpoints that are reasonably likely to predict clinical benefit can be relied on to establish effectiveness under the accelerated approval pathway.

Note that for accelerated approval the evidentiary standard still applies – that is, there must be substantial evidence that the drug has an effect on the surrogate or intermediate clinical endpoint.

Key Takeaways

1. For many rare diseases, well-characterized clinical efficacy endpoints appropriate for the disease may need to be developed. In cases where utilizing clinical endpoints is not feasible because changes in symptoms and disease status occur too slowly to be measured in a clinical investigation of reasonable duration, surrogate endpoints may be considered. It is particularly important to understand the pathophysiology and natural history of the disease to help identify potential surrogate endpoints.
2. The acceptability of surrogate endpoints for use in a particular drug or biologic development program will be determined on a case-by-case basis. It is context dependent, relying in part on the disease, studied patient population, and therapeutic mechanism of action. A surrogate endpoint that may be appropriate for use in a particular drug or biologic clinical development program, should not be assumed to be appropriate for use in a different program that is in a different clinical setting.[13]
3. FDA may grant accelerated approval to a product for a serious or life-threatening disease or condition that fills an unmet need upon a determination that the product has an effect on a surrogate endpoint or intermediate clinical endpoint that is reasonably likely to predict clinical benefit. In the context of the tofersen program, accelerated approval was based on a significant reduction of plasma NfL concentration, a surrogate endpoint reasonably likely to predict clinical benefit in SOD1-ALS patients.
4. Under accelerated approval, drug companies are required to conduct studies to confirm the anticipated clinical benefit of their product. If the confirmatory trial verifies the anticipated clinical benefit, then the FDA converts the approval to traditional approval for the product. If the confirmatory trial does not show that the product provides clinical benefit, FDA has regulatory procedures in place that could lead to withdrawal of approval. A confirmatory study was required to verify the clinical benefits of tofersen. Enrollment for the confirmatory study was underway at the time of approval.

Critical Thinking Questions for a Rare Disease Drug Development Program

1. Is use of biomarker data as a surrogate endpoint or use of an intermediate clinical endpoint appropriate in the development program?

2. Is there a good understanding of the pathophysiology and the natural history of the disease for which the product is intended to treat?

3. Is the mechanism of action of the product well understood?

4. What is the anticipated treatment effect of the medical product?

5. When considering accelerated approval:

- Is the product being developed to treat a serious condition?
- Are there meaningful advantages over available therapy? (if any)
- Is there evidence that the surrogate endpoint is reasonably likely to predict the product's intended clinical benefit?
- What is the feasibility of conducting a confirmatory trial to support the clinical benefit of the product should accelerated approval be granted?

6. When assessing whether a surrogate endpoint may be reasonably likely to predict clinical benefit in the context of a development program, consider the following:

- Does the surrogate endpoint reflect the underlying disease pathophysiology?
- Is the surrogate endpoint associated with clinical severity?

We recommend meeting with the Agency to reach alignment regarding the design of the one adequate and well-controlled clinical investigation, related confirmatory evidence, and the possibility of an accelerated approval.

[13] For more information see the FDA Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure webpage.

Case Study References by Order of Appearance

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- See the LEADER 3D Case Study User Guide available at https://www.fda.gov/media/185425/download.
- See FDA Integrated Review document for tofersen (Qalsody) available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/215887Orig1s000IntegratedR.pdf.
- See the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 356(c) (21 U.S.C. 356) for accelerated approval program statues available at https://www.govinfo.gov/content/pkg/USCODE-2023-title21/pdf/USCODE-2023-title21-chap9-subchapV-partA-sec356.pdf.
- See the Federal Food, Drug, and Cosmetic Act (FD&C Act) 356(c) (21 U.S.C. 356) available at https://www.govinfo.gov/content/pkg/USCODE-2023-title21/pdf/USCODE-2023-title21-chap9-subchapV-partA-sec356.pdf
- See the FDA Accelerated Approval webpage available at https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/accelerated-approval.
- See the FDA Accelerated Approval Program webpage available at https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approval-program.

Page 2

- See the FDA Guidance Documents for Rare Disease Drug Development webpage available at https://www.fda.gov/drugs/guidances-drugs/guidance-documents-rare-disease-drug-development.
- See draft guidance for industry *Expedited Programs for Serious Conditions – Accelerated Approval of Drugs and Biologics* (December 2024) available at https://www.fda.gov/media/184120/download. When final, this guidance will represent the Agency's current thinking on this topic.
- See draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (September 2023) available at https://www.fda.gov/media/172311/download. When final, this guidance will represent the Agency's current thinking on this topic.

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- See draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019) available at https://www.fda.gov/media/133660/download. When final, this guidance will represent the Agency's current thinking on this topic.
- See Bonafede, R and R Mariotti, 2017, ALS Pathogenesis and Therapeutic Approaches: The Role of Mesenchymal Stem Cells and Extracellular Vesicles, Front Cell Neurosci, 11(80) available at https://www.frontiersin.org/journals/cellular-neuroscience/articles/10.3389/fncel.2017.00080/full.

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- See guidance for industry *Rare Diseases: Considerations for the Development of Drugs and Biological Products* (December 2023) for important considerations in rare disease drug and biologics development, available at https://www.fda.gov/media/119757/download.
- See page 59 of the tofersen (Qalsody) FDA Integrated Review for a complete list of references cited for the NfL background available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/215887Orig1s000IntegratedR.pdf.
- See Benatar, M, W Joanne, and RT Martin, 2022, Neurofilament light chain in drug development for amyotrophic lateral sclerosis: a critical appraisal, Brain,146(7):2711–2716 available at https://pmc.ncbi.nlm.nih.gov/articles/PMC10316774/.

- See Lu, CH, C Macdonald-Wallis, E Gray, N Pearce, A Petzold, N Norgren, G Giovannoni, P Fratta, K Sidle, M Fish, R Orrell, R Howard, K Talbot, L Greensmith, J Kuhle, MR Turner, and A Malaspina, 2015, Neurofilament light chain: A prognostic biomarker in amyotrophic lateral sclerosis, Neurology, 84(22):2247–2257 available at https://pmc.ncbi.nlm.nih.gov/articles/PMC4456658/.
- See Dreger, M, R Steinbach, M Otto, MR Turner, and J Grosskreutz, 2022, Cerebrospinal fluid biomarkers of disease activity and progression in amyotrophic lateral sclerosis, J Neurol Neurosurg Psychiatry, 93(4):422–435 available at https://pubmed.ncbi.nlm.nih.gov/35105727/.
- See page 200 of the tofersen (Qalsody) FDA Integrated Review for more information on the meta-analysis of the scientific literature to determine the relevance of neurofilament changes in ALS available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/215887Orig1s000IntegratedR.pdf.

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- See page 36 of the tofersen (Qalsody) FDA Integrated Review for more information on study design criteria available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/215887Orig1s000IntegratedR.pdf.

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- See the Action Letter for tofersen (Qalsody) available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2023/215887Orig1s000Correctedltr.pdf.

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- See draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019) available at https://www.fda.gov/media/133660/download. When final, this guidance will represent the Agency's current thinking on this topic.

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- See the FDA Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure webpage for more information on the acceptability of surrogate endpoints for use in a particular drug available at https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure.