Tofersen (QALSODY)
National Drug Monograph
June 2023

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Approval is under the accelerated approval pathway. Continued approval for the following indication may be contingent upon verification of clinical benefit in confirmatory trial(s).

Description/Mechanism of Action

- Tofersen is an antisense oligoneucleotide. Via binding to superoxide dismutase 1 (SOD1) mRNA, tofersen causes degradation of SOD1 mRNA and reduction of SOD1 protein synthesis.

Indication(s) Under Review in This Document

- Adults with amyotrophic lateral sclerosis (ALS) who have a mutation in the SOD1 gene.

Dosage Form(s) Under Review

- For intrathecal injection: 100mg/15mL solution in a single dose vial
- Tofersen administration is 100mg intrathecally every 14 days for 3 doses, then starting 28 days after the third dose, 100mg intrathecally every 28 days

Clinical Evidence Summary

Efficacy Considerations

Phase III VALOR and open label extension (OLE)

VALOR was a phase III, double blind, randomized, placebo-controlled trial. Patients were included in the trial if they had a documented SOD1 mutation and a forced vital capacity (FVC) of 50% or higher (45 – 50% was also included if the FVC had not declined more than 5% in the last 6 months).[1] Patients in the trial could not be on other investigational ALS disease modifying therapies (DMTs). Co-treatment with riluzole and/or edaravone was allowed so long the patient had been on each medication for 30 and 60 days respectively prior to day 1 of VALOR. About 60% of participants across the treatment groups were on riluzole. Less than 10% of participants were on edaravone. Participants were randomized 2:1 tofersen 100mg or placebo for a treatment period of 24 weeks[2]. There then was a 4-8

week follow up phase at which time participants could opt for continuing in the OLE. The OLE is currently ongoing and analysis of OLE data is planned when there is at least 3.5 years of follow-up data.

VALOR sub-categorized patients as "faster-progression" or "slower-progression". The primary and key secondary endpoints were formally tested for statistical significance in the faster-progression group only. The slower-progression group results were included as a combined exploratory analysis. Per VALOR's supplementary appendix, patients needed to meet the following to be considered faster-progression:

- SVC of 65% or greater at screening

AND, one of the following:

- One of the following SOD1 mutations: p.Ala5Val, p.Ala5Thr, p.Leu39Val, p.Gly42Ser, p.His44Arg, p.Leu85Val, p.Gly94Ala, p.Leu107Val, and p.Val149Gly AND a pre-study ALSFRS-R slope decline of 0.2 or more per month
- A SOD1 mutation not listed above with an ALSFRS-R slope decline of 0.9 or more per month

ALSFRS-R slope decline was calculated by: ([48 minus baseline ALSFRS-R total score]/time since symptom onset). Patients meeting the eligibility criteria for the study but not the criteria for faster-progression were sub-categorized in to the slower-progression group. One benefit to the slower progression group is that it allowed for observation of tofersen in patients with longer disease duration. The slow progression group's time from symptom onset ranged from 3.9 to 145.7 months. There also was no baseline ALSFRS-R inclusion criteria, apart from baseline respiratory function as represented by FVC. The ALSFRS-R scores averaged 36 and 38 in the fast- and slow-progression groups respectively. This design contrasts with other recent studies for edaravone and sodium phenylbutyrate/taurursodiol that preselected patients to be earlier in disease[3,4].

The primary endpoint for VALOR was the change in ALSFRS-R in the faster-progression subgroup from baseline to week 28. The treatment difference at week 28 was 1.2 points on the ALSFRS-R. This change was not statistically significant. This outcome also contrasts with the initial exploratory findings of the phase I/II trial for tofersen where the 100mg dose of tofersen resulted in a 4.44 point treatment difference on the ALSFRS-R at day 85[5]. It is difficult to predict the rationale for this drastic difference in efficacy, though the phase I/II had much fewer participants (n=10 in tofersen 100mg group and n=12 in placebo group). In retrospect, this could indicate that there is a potential for wider than initially thought variability in clinical response to tofersen; which led to VALOR being underpowered. As the primary endpoint of VALOR did not meet statistical significance, none of the secondary endpoints could be evaluated for statistical significance (see Table 1).

Eighty-eight percent of participants originally randomized to tofersen in VALOR continued to the OLE. Though the OLE is still ongoing, early data was reported at week 52, and ALSFRS-R treatment differences were still not statistically significant[6]. Survival data at week 52 is conflicting between the intention to treat (ITT, fast- and slow-progression aggregate) and modified intention to treat (mITT, fast-progression) groups and could be a function of low overall number of events.

FDA accelerated approval based on neurofilament light chain (NfL) data

Though VALOR failed its primary outcome, accelerated approval was pursued on the basis of the tofersen group having a reduction of serum NfL levels as a surrogate marker for slowed

neurodegeneration[6]. Neurofilament proteins are highly expressed in myelinated axons and elevated levels in the blood and cerebrospinal fluid (CSF) have been associated with multiple neurologic diseases including ALS. Thus, this is not an ALS-specific biomarker, but it is heavily evidenced to be correlated with axonal damage. There are some studies that have correlated higher NfL levels with a higher risk of unfavorable outcomes with ALS. Lastly, in other diseases associated with higher NfL levels like multiple sclerosis and hereditary transthyretin-mediated amyloidosis, DMTs for these diseases have been associated with decreased NfL levels. Thus, indicating that NfL could be an indicator for efficacy of a therapy for a disease associated with axonal damage.

Reduced NfL levels were nominally statistically significant for the ITT, mITT, and non-mITT populations; signifying a consistent positive effect at reducing NfL despite disease progression rate. See Table 1. As of week 52 in the OLE, patients originally randomized to placebo maintained lowered NfL levels and patients originally randomized to placebo now on tofersen for 24 weeks have experienced a 44% reduction in NfL levels.

The fact that ALSFRS-R treatment difference was not statistically significant but the NfL reduction was nominally statistically significant in the same study population highlights the lack of correlation knowledge between the timing and magnitude of NfL changes to clinical change in ALS. For example, NfL levels were relatively plateaued at their lower level in the tofersen group by week 16. On the other hand, there continued to be, albeit non-significant, steady numerical treatment improvement on the ALSFRS-R up to week 28. There is also the potential that varied baseline disease characteristics could impact what NfL change is needed to see a clinically meaningful difference. Until these correlations are better described, it is very difficult to predict the expected efficacy of tofersen. Thus, the need for continued data to establish this correlation better is needed if full FDA approval is sought.

Table 1: Efficacy results from clinical trial and additional FDA data from accelerated approval

<table>
<tr><th>Study</th><th>Design</th><th>Results</th></tr>
<tr><td>VALOR phase III

Primary and secondary endpoints assessed for significance in the mITT population only (N = 60)</td><td>2:1 tofersen 100mg vs placebo. Double-blind trial.

<u>Key Inclusion Criteria:</u>
- Weakness attributable to ALS and documented SOD1 mutation
- FVC ≥50% or <50% but ≥45% if FVC has not declined by more than 5% in the past 6 months
- If taking riluzole, stable dose for ≥30 days
- If taking edaravone, stable dose for ≥60 days

<u>Key Exclusion Criteria:</u></td><td>All results are described as change from baseline to week 28 in the mITT population. Treatment difference described with a 95% confidence interval:
<u>Primary:</u>
<table>
<tr><th></th><th>Tofersen N = 39</th><th>PBO N = 21</th><th>PBOTD (95% CI)</th><th>p value</th></tr>
<tr><td>ALSFRS-R total</td><td>-6.98</td><td>-8.14</td><td>1.2 (-3.2, 5.5)</td><td>p = 0.97</td></tr>
</table>
<u>Secondary:</u>
<table>
<tr><th></th><th>Tofersen N = 39</th><th>PBO N = 21</th><th>PBOTD (95% CI)</th><th>p value</th></tr>
<tr><td>SOD1 CSF concentration</td><td>0.71</td><td>1.16</td><td>0.62 (0.49, 0.78)</td><td>n/a</td></tr>
<tr><td>Plasma NfL</td><td>0.4</td><td>1.2</td><td>0.33 (0.25, 0.45)</td><td>n/a</td></tr>
<tr><td>SVC</td><td>-14.31</td><td>-22.2</td><td>7.9 (-3.5, 19.3)</td><td>n/a</td></tr>
<tr><td>Handheld dynamometry megascore</td><td>-0.34</td><td>-0.37</td><td>0.02 (-0.21, 0.26)</td><td>n/a</td></tr>
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<tr>
<td></td>
<td>- History of or positive HIV test
- Current Hep C infection with detectable HCV RNA
- Current Hep B infection
- Enrollment in any other investigational study</td>
<td>
<table>
<tr><td>Death or permanent ventilation events</td><td>4/39 (10%)</td><td>2/21 (10%)</td><td>Hazard Ratio: 1.39 (0.22, 8.88)</td><td>n/a</td></tr>
<tr><td>Death events</td><td>1/39 (3%)</td><td>0/21</td><td>Hazard Ratio: na</td><td></td></tr>
</table>
</td>
</tr>
<tr>
<td>Selected NfL data from FDA Briefing Document for consideration of accelerated approval of tofersen[6]</td>
<td>mITT = faster-progression group
non-mITT = slower-progression group
ITT = aggregate of fast- and slow- progression group</td>
<td>Adjusted geometric mean ratio to baseline in plasma NfL at week 28. Treatment difference described with a 95% confidence interval:
<table>
<tr><td></td><td>Tofersen</td><td>PBO</td><td>PBOTD (95% CI)</td><td>Nominal p value</td></tr>
<tr><td>ITT</td><td>0.45</td><td>1.12</td><td>0.4 (0.33, 0.49)</td><td><0.0001</td></tr>
<tr><td>mITT</td><td>0.4</td><td>1.2</td><td>0.33 (0.25, 0.45)</td><td><0.0001</td></tr>
<tr><td>Non-mITT</td><td>0.5</td><td>0.95</td><td>0.52 (0.43, 0.63)</td><td><0.0001</td></tr>
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Safety Considerations[2,7]

- **Boxed warnings:** none
- **Contraindications:** none
- **Other warnings / precautions**:
    - Myelitis and/or radiculitis – There were six total cases of myelitis or radiculitis in participants on tofersen across all clinical trials. Two of the six patients discontinued tofersen and symptoms resolved with discontinuation and symptomatic management. The other four patients continued tofersen and only pursued symptomatic management. These cases also experienced resolution of symptoms without tofersen discontinuation. If patients experience symptoms of myelitis or radiculitis, symptomatic management with or without tofersen discontinuation may be required.
    - Papilledema and elevated intracranial pressure (ICP) – Four patients receiving tofersen in clinical trials developed papilledema and/or elevated ICP. All patients received treatment which led to resolution of symptoms and did not require discontinuation of tofersen.
    - Aseptic meningitis – There were two serious cases of aseptic meningitis in the clinical trials of tofersen. One required discontinuation of tofersen and the other did not. Nonserious elevations of white blood cells in the cerebrospinal fluid (CSF) have also been reported (10% in VALOR and 18% incidence in early OLE data).

- **Adverse reactions**
    - **Common** (occurred in 10% or more of participants on tofersen in VALOR and Jan 2022 OLE data cutoff data): headache, procedural pain, fall, back pain, pain in arm or leg, arthralgia, CSF protein concentration increase, CSF white blood cell

concentration increase, fatigue, post-lumbar puncture syndrome, myalgia, nausea, constipation, pyrexia.

- **Serious Adverse events / Deaths / Discontinuation (VALOR, Jan 2022 OLE data cutoff incidence):** respiratory failure (1%, 10%), pneumonia aspiration (3%, 9%), pulmonary embolism (4%, 4%), acute respiratory failure (1%, 4%), dysphagia (0, 3%)
  - Most of these serious adverse events are also associated with the natural course of ALS.
  - There was one death in VALOR, attributed to the natural course of ALS

Other Considerations[7]

- Tofersen is an intrathecal injection that must administered by a healthcare professional experienced in lumbar punctures.
- There is currently not adequate data to assess the birth defect, miscarriage, developmental, or other fetal and/or maternal risks associated with tofersen use in people who are pregnant.
- There is currently no data to assess the presence of tofersen in breast milk. In animal studies, tofersen has been detected in breast milk after subcutaneous administration. The unknown developmental and health risks of breastfeeding for the infant should be weighed with the mother's clinical need for tofersen.

Other Therapeutic Options

Alternative treatments for ALS are listed in table 2 below

Table 2 Treatment Alternatives

Drug	Formulary status	Clinical Guidance	Other Considerations
Tofersen, intrathecal inj	TBD	Indicated in SOD1 ALS only. Antisense oligonucleotide that decreases SOD1 protein synthesis. Accelerated approval based on NfL level reduction. Impact on specific functional domains and/or survival unclear.	Intrathecal injection that must be administered by a healthcare provider experienced in lumbar punctures.
Riluzole, tab	Formulary, PA-F	Glutamate inhibitor (other mechanisms have also been proposed) No evidence for slowing functional decline. A modest increase in survival	Twice daily oral medication. Requires frequent liver function lab tests in the first year of treatment.
Edaravone, IV and oral solution	Formulary, PA-N	Free radical scavenger No evidence for increasing survival. Modest reduction in rate of decline of motor function.	Oral and IV formulations considered bioequivalent. Both administered in monthly cycles.
Sodium Phenylbutyrate/Taurursodiol (PB-TURSO), powder for oral suspension	Formulary, PA-N	Reduces endoplasmic reticulum stress and mitochondrial dysfunction Evidence only from one relatively small Phase II study and its OLE. Modest reduction in rate of decline of motor function and modest increase in survival. Data for both outcomes come with many confounders. Phase III trial data, expected in 2024, may bring more clarity to true efficacy.	Oral medication taken twice daily. Powder must be dissolved in water for administration. Most common intolerance is GI related (bitter taste, diarrhea)

Projected Place in Therapy

- Amyotrophic lateral sclerosis (ALS) is a fatal degenerative disease that affects both upper and lower motor neurons, leading to progressive muscle weakness with related deficits in activities of daily living. Average life expectancy is three to five years after symptom onset[8]. The pathophysiology and heterogeneity of disease is poorly understood in ALS; and may in part be why strong predictable efficacy is difficult to ascertain in pharmaceuticals.
- Only 5-10% of ALS cases are estimated to be familial, and these cases are distributed across about 30 different known causative genes. Mutations of the SOD1 gene are associated with about 20% of all familial cases of ALS, about 2% of all ALS cases. It is unknown how many Veterans are affected by SOD1 ALS. The FDA estimated that the prevalence is less than 500 cases in the United States total[6].
- Edaravone, sodium phenylbutyrate/taurursodiol, and riluzole are the only other FDA-approved treatments for ALS. They all work by different mechanisms of action compared to tofersen and provide limited benefit to patients.
- Tofersen did not meet its primary endpoint of ALSFRS-R slowed progression in its phase III trial. The FDA granted accelerated approval of tofersen based on lowered serum NfL levels. The fact that ALSFRS-R treatment difference was not statistically significant but the NfL reduction was nominally statistically significant in the same study population highlights the lack of correlation knowledge between the timing and magnitude of NfL changes to clinical change in ALS. Until these correlations are better described, it is very difficult to predict the expected efficacy of tofersen in any specific functional domain and/or survival.
- Confirmation data required with tofersen's accelerated approval could come from two possible ongoing trials at the current time: the VALOR OLE and/or the ATLAS trial (NCT04856982) which is evaluating tofersen efficacy in presymptomatic carriers of the SOD1 mutation.
- There is no evidence that tofersen would be effective in any other familial type of ALS or sporadic ALS.
- Discussion of implications for treatment administration (e.g. travel to clinic, tolerance of routine lumbar punctures) and realistic expectations for treatment with the patient/family/caregiver are imperative to the place in therapy for tofersen.
- Patients should also be made aware that initial FDA approval is under the accelerated approval pathway and what potential impact that can have to continued therapy. Continued FDA approval may be contingent upon verification of clinical benefit in confirmatory trial(s), see above.

References

1. Biogen. (2022). An efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics study of BIIB067 in adults with inherited amotrophic lateral sclerosis (ALS) (VALOR (Part C)). Retrieved from: https://beta.clinicaltrials.gov/study/NCT02623699
2. Miller TM, Cudkowicz ME, Genge A, et al. Trial of Antisense Oligonucleotide tofersen for SOD1 ALS. N Engl J Med (2022) 387;12: 1099-110
3. Abe K, Itoyama Y, Sobue G, et al on behalf of the Edaravone ALS Study Group. Confirmatory double-blind, parallel-group, placebo-controlled study of efficacy and safety of edaravone (MCI-186) in amyotrophic lateral sclerosis patients. Amyotroph Lateral Scler Frontotemporal Degener. (2014) 15:610-617.
4. Paganoni S, Macklin EA, Hendrix S. Trial of sodium phenylbutyrate taurursodiol for amyotrophic lateral sclerosis, N Engl J Med. (2020) 383;10:919-30
5. Miller T, Cudkowicz M, Shaw PJ, et al. Phase 1-2 trial of antisense oligoneucleotide tofersen for SOD1 ALS. N Engl J Med (2020) 383;2:109-19
6. Food and Drug Administration (FDA). FDA Briefing Document for the March 22, 2023 Peripheral and Central Nervous System Drugs Advisory Committee Meeting on tofersen. (2023) Retrieved from: https://www.fda.gov/media/166326/download
7. Tofersen (Tofersen) [prescribing information online]. Biogen. Cambridge, MA. April 2023
8. Makam AN, Suh K, Nikitin D, Carlson JJ, Richardson M, Mohammed R, McKenna A, Pearson SD, Rind DM. AMX0035 and Oral Edaravone for ALS; Final Evidence Report. Institute for Clinical and Economic Review, September 13, 2022. https://icer.org/assessment/amyotrophic-lateral-sclerosis-2022/#timeline

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