FirstChoice VIP CARE
by Select Health of South Carolina

Medical Policy Bulletin

Title:
Tofersen (Qalsody™)
Policy #:
MA08.162a

The Company makes decisions on coverage based on the Centers for Medicare and Medicaid Services (CMS) regulations and guidance, benefit plan documents and contracts, and the member's medical history and condition. If CMS does not have a position addressing a service, the Company makes decisions based on Company Policy Bulletins. Benefits may vary based on contract, and individual member benefits must be verified. The Company determines medical necessity only if the benefit exists and no contract exclusions are applicable. Although the Medicare Advantage Policy Bulletin is consistent with Medicare's regulations and guidance, the Company's payment methodology may differ from Medicare.

When services can be administered in various settings, the Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition. This decision is based on the member's current medical condition and any required monitoring or additional services that may coincide with the delivery of this service.

This Policy Bulletin document describes the status of CMS coverage, medical terminology, and/or benefit plan documents and contracts at the time the document was developed. This Policy Bulletin will be reviewed regularly and be updated as Medicare changes their regulations and guidance, scientific and medical literature becomes available, and/or the benefit plan documents and/or contracts are changed.

Policy

Coverage is subject to the terms, conditions, and limitations of the member's Evidence of Coverage.

The Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition.

EXPERIMENTAL/INVESTIGATIONAL

Tofersen (Qalsody™) is considered experimental/investigational and, therefore, not covered for all indications, including treatment of amyotrophic lateral sclerosis (ALS), because the safety and effectiveness of the service cannot be established by review of the available published peer-reviewed literature.

Guidelines

BENEFIT APPLICATION

Subject to the terms and conditions of the applicable benefit contract, tofersen (Qalsody) is not eligible for payment under the medical benefits of the Company's commercial products because the drug is considered experimental/investigational and, therefore, not covered.

Services that are experimental/investigational are a benefit contract exclusion for all products of the Company. Therefore, they are not eligible for reimbursement consideration.

US FOOD AND DRUG ADMINISTRATION (FDA) STATUS

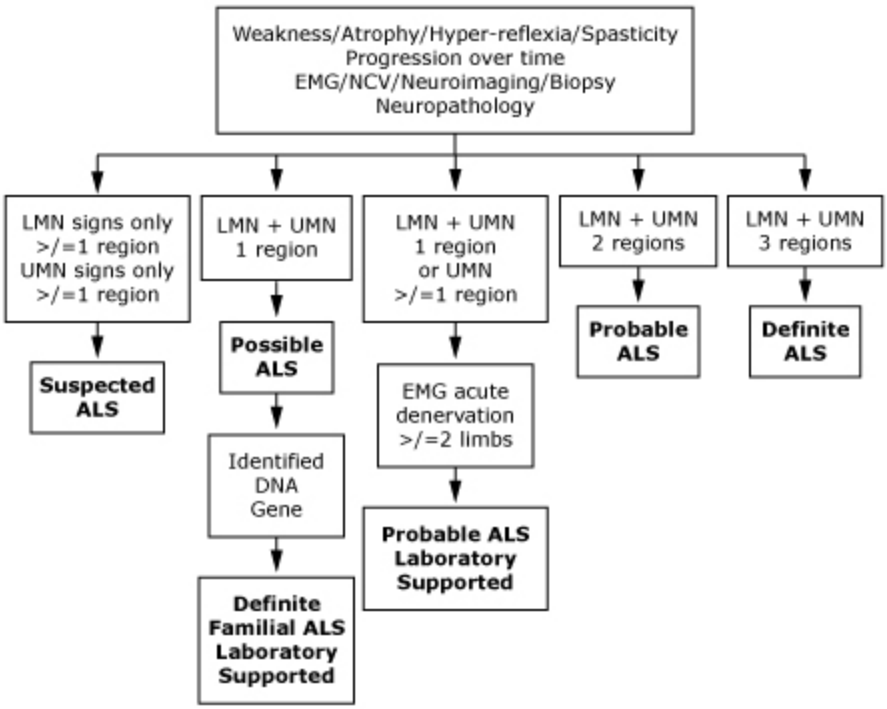
Tofersen (Qalsody) was approved by the FDA on April 25, 2023, for the treatment of adult individuals with amyotrophic lateral sclerosis (ALS) who have a mutation in the superoxide dismutase 1 (SOD1) gene. This indication is approved under accelerated approval based on reduction in plasma neurofilament light chain observed in

individuals treated with tofersen (Qalsody). Tofersen (Qalsody) is administered as an intrathecal bolus injection over 1 to 3 minutes.

PEDIATRIC USE
The safety and effectiveness of tofersen (Qalsody) in pediatric individuals have not been established.

EI ESCORIAL CRITERIA

Revised EI Escorial schema for the clinical diagnosis of amyotrophic lateral sclerosis (ALS)



LMN: lower motor neuron signs (i.e., weakness, atrophy, fasciculations, dysarthria, dysphagia)

UMN: upper motor neuron signs (i.e., slowness of movement, incoordination, stiffness, poor dexterity, spastic gait with poor balance, dysarthria and dysphagia)

Brooks BR, Miller RG, Swash M, Munsat TL. World Federation of Neurology Research Group on Motor Neuron Diseases. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Other Motor Neuron Disord.* 2000;1(5):293-299.

ALS FUNCTIONAL RATING SCALE- REVISED (ALSFRS-R)

Physical Function	Score
1. Speech	4 – Normal speech processes
	3 – Detectable speech disturbance
	2 – Intelligible with repeating
	1 – Speech combined with nonvocal communication

	0 – Loss of useful speech
2. Salivation	4 – Normal
	3 – Slight but definite excess of saliva in mouth; may have nighttime drooling
	2 – Moderately excessive saliva; may have minimal drooling
	1 – Marked excess of saliva with some drooling
	0 – Marked drooling; requires constant tissue or handkerchief
3. Swallowing	4 – Normal eating habits
	3 – Early eating problems-occasional choking
	2 – Dietary consistency changes
	1 – Needs supplemental tube feeding
	0 – Nothing by mouth (exclusively enteral or parenteral nutrition)
4. Handwriting	4 – Normal
	3 – Slow or sloppy: all words are legible
	2 – Not all words are legible
	1 – Able to grip pen but unable to write
	0 – Unable to grip pen
5a. Cutting food and handling utensils (individuals without a gastrostomy tube)	4 – Normal
	3 – Somewhat slow and clumsy, but no help needed
	2 – Can cut most foods, although clumsy and slow; some help needed
	1 – Food must be cut by someone, but can still feed slowly
	0 – Needs to be fed
5b. Cutting food and handling utensils (individuals with a gastrostomy tube)	4 – Normal
	3 – Clumsy but able to perform all manipulations independently
	2 – Some help needed with closures and fasteners
	1 – Provides minimal assistance to caregiver
	0 – Unable to perform any aspect of task
6. Dressing and hygiene	4 – Normal function
	3 – Independent and complete self-care with effort or decreased efficiency
	2 – Intermittent assistance or substitute methods
	1 – Needs attendant for self-care
	0 – Total dependence
7. Turning in bed and adjusting bed clothes	4 – Normal
	3 – Somewhat slow and clumsy, but no help needed
	2 – Can turn alone or adjust sheets, but with great difficulty
	1 – Can initiate, but not turn or adjust sheets alone
	0 – Helpless
8. Walking	4 – Normal
	3 – Early ambulation difficulties
	2 – Walks with assistance
	1 – Nonambulatory functional movement
	0 – No purposeful leg movement
9. Climbing stairs	4 - Normal
	3 – Slow
	2 – Mild unsteadiness or fatigue
	1 – Needs assistance
	0 – Cannot do
10. Dyspnea	4 – None
	3 – Occurs when walking

	2 – Occurs with one or more of the following: eating, bathing, dressing (activities of daily living [ADL])
	1 – Occurs at rest, difficulty breathing when either sitting or lying
	0 – Significant difficulty, considering using mechanical respiratory support
11. Orthopnea	4 - None
	3 – Some difficulty sleeping at night due to shortness of breath, does not routinely use more than two pillows
	2 – Needs extra pillows in order to sleep (more than two)
	1 – Can only sleep sitting up
	0 – Unable to sleep
12. Respiratory insufficiency	4 – None
	3 – Intermittent use of bilevel positive airway pressure (BiPAP)
	2 – Continuous use of BiPAP during the night
	1 – Continuous use of BiPAP during the night and day
	0 – Invasive mechanical ventilation by intubation or tracheostomy

Cedarbaum JM, Stambler N, Malta E, et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. *J Neurol Sci.* 1999;169(1-2):13-21.

Description

AMYOTROPHIC LATERAL SCLEROSIS (ALS)

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a progressive neurodegenerative disorder that causes muscle weakness, disability, and ultimately, death. It is caused by gradual degeneration, and eventual death, of the upper and lower motor neurons. Motor neurons are nerve cells that extend from the brain to the spinal cord and then to the muscles throughout the body. Death of the motor neurons inhibits signals from the brain to the muscles, resulting in muscle atrophy. Eventually, the brain loses the ability to initiate and control voluntary movements. The rate of neuronal degeneration can be affected by the specific gene mutation that the individual has. Some mutations are associated with a faster rate of disease progression than others. There is currently no cure for ALS. There are some US Food and Drug Administration (FDA)-approved treatments, which are intended to slow the progression of the disorder, but they cannot reverse its progression. Riluzole (available US brands: Rilutek, Exservan, Tiglutik) is the only drug specifically mentioned in the American Academy of Neurology (AAN) guidelines at this time.

There are approximately 7000 new cases of ALS in the United States diagnosed each year. ALS has been found to have a higher rate of occurrence in Caucasians, and has an average age of onset of 62 years. The median survival of those diagnosed with ALS is 3 to 5 years, with most individuals succumbing to respiratory failure; however, a very small percentage of individuals with ALS can survive for 10 years or more.

Diagnosing ALS can take an extended period of time because there is no one test that can be used to definitively determine the presence of the disorder. Other possible causes for the individual's symptoms will need to be ruled out. One way the diagnosis of ALS can be made is by using the El Escorial World Federation of Neurology criteria, also known as the Airlie House criteria. Per this criteria, a diagnosis of ALS requires the presence of evidence of lower motor neuron (LMN) degeneration by clinical, electrophysiologic, or neuropathological exam; evidence of upper motor neuron (UMN) degeneration by clinical exam; and progressive spread of symptoms or signs within a region, or to other regions, as determined by history or exam. The four body regions are cranial/bulbar, cervical, thoracic, and lumbosacral. Another set of criteria used to aid in the diagnosis of ALS is the Gold Coast criteria. This set of criteria would allow the diagnosis of ALS to be made for individuals with only UMN signs. The Gold Coast criteria has a similar diagnostic sensitivity and specificity to the El Escorial criteria.

SUPEROXIDE DISMUTASE 1 (SOD1)
Most cases of ALS are considered to be sporadic, but approximately five to ten percent of cases are familial. Some of these cases of familial ALS have been found to be due to pathogenic variations in the SOD1 gene. The SOD1 protein normally acts to destroy free superoxide radicals, which are produced in cells but can be toxic to the individual. Pathogenic variations in the SOD1 gene can lead to misfolding and aggregation. This leads to the protein gaining

toxic function and is considered to be the cause of the neuronal degeneration experienced by individuals with some familial form of ALS. Interventions aimed at the SOD1 protein could result in the slowing of disease progression.

AMYOTROPHIC LATERAL SCLEROSIS FUNCTIONAL RATING SCALE-REVISED (ALSFRS-R)

The ALSFRS-R scale is a series of 12 questions used by professional healthcare providers to assess changes in physical functioning in individuals with ALS. The 12 questions are in the following categories: speech, salivation, swallowing, handwriting, cutting food, dressing and hygiene, turning in bed, walking, climbing stairs, dyspnea, orthopnea, and respiratory insufficiency. Each question is graded from 0 (cannot do) to 4 (normal ability). The higher the score on the scale, the higher the level of physical functionality of the individual. Besides being a validated tool, it has high inter-rater and intra-rater reliability. It is the most widely used scale in clinical trials as either a primary or secondary endpoint. In FDA guidance, using a scale, such as the ALSFRS-R, to demonstrate treatment effect in clinical trials is recommended. The ALSFRS-R scale has been translated into multiple other languages, and can be administered to the individual, or their caregiver, in person, via the internet, over the telephone, or self-administered.

NEUROFILAMENT LIGHT CHAIN (NfL)

Neurofilaments (NFs) are proteins that form the basic structure of axons. There are four types that have been identified: NF light (NfL) chain, NF medium (NfM) chain, NF heavy (NfH) chain, and alpha-internexin. When axonal injury occurs, NFs are released into the cerebrospinal fluid (CSF) and eventually enter the bloodstream. This allows NFs to be detected in plasma, serum, and CSF when an axonal injury has occurred. Elevated levels of NFs may be detected in individuals with a variety of neurodegenerative conditions, including ALS, multiple sclerosis (MS), multiple system atrophy (MSA), headache and neurologic deficits with CSF lymphocytosis (HaNDL) syndrome, COVID-19 and other infections, myelitis, meningoencephalitis, Parkinson's disease (PD), Alzheimer's disease (AD), Guillain-Barré syndrome (GBS), and Charcot-Marie-Tooth disease. Individuals with subarachnoid hemorrhage have been found to have NF levels higher than individuals with ALS. NFs can be found in peripheral axons as well as CNS axons, so NF levels may be elevated due to peripheral axonal injury as well as CNS axonal injury. There are some data to suggest that individuals who are carriers of certain SOD1 mutations may experience elevated NfL levels up to 3.5 years prior to the onset of symptoms of AL.

NF levels in the CSF can be highly elevated in individuals with ALS. NF levels in plasma and serum are much lower, by about five- to tenfold. The CSF levels of NFs can be easily detected using enzyme-linked immunosorbent assay (ELISA). Some ELISAs do not have the analytical sensitivity to detect the low levels present in peripherally obtained blood. Two other assays have superior analytical sensitivity compared to ELISA, for detecting CSF as well as plasma and serum levels of NFs, and have demonstrated higher correlations between CSF levels with plasma and serum levels of NFs than ELISA. These two assays are electrochemiluminescence (ECL) assay and single-molecule array (Simoa), a digital form of ELISA. ELISA is the most widely used method of detecting plasma and serum NF levels, however. This may be due to lack of availability of the two other assays, or the expense of the technology. If ELISA is used, the detection threshold may need to be lowered in order to detect the low NF levels.

Using NFs as pharmacodynamic biomarkers has been, and is still being, investigated. In some individuals, levels of NFs may begin to elevate years prior to the onset of any symptoms of ALS. This is postulated to be due to axonal degeneration occurring in the early stages of the disease. The levels of NFs can rise in both the presymptomatic period of ALS, as well as the early symptomatic period. The rise in the levels of NFs is temporary, however. The levels of NFs then reach an expected plateau, often around the time that the individual becomes enrolled in a clinical trial. The NF levels remain stable over the course of ALS and tend to decline during the late stages of the disease. Given that raised NF levels are not specific for ALS, the most useful role of NF levels for clinical investigation is likely to be in monitoring duration, progression, or prognosis of disease. NfL's direct clinical role and impacts in these fields still need to be verified and replicated with larger cohorts by using same or standardized measurement scale in these three fields. There were some attempts to correlate NF levels with disease phenotype, but these were few.

Studies using NFs as a biomarker for ALS have varied results and often find contradictory results. Elevated NF levels are not specific to ALS, and can be elevated due to multiple other conditions and disease states. Longitudinal studies assessing the correlation between CSF, plasma, and serum levels of NfL and NfH in individuals with various ALS gene mutations have not been done. Studies assessing the correlation between the NF levels and the slope of the ALSFRS-R decline have not been done. Clinical trials assessing differences in NF levels in individuals with primary UMN, primary LMN, both UMN and LMN involvement, and individuals with extra-motor involvement have not been

done. Standardization of analytical methods (ELISA versus ECL versus Simoa), the source of the samples (CSF versus plasma versus serum), which NF marker to use (NfH versus NfL), and clinical cut-off levels still need to be addressed. There are no definitive high-quality studies that have demonstrated that lowering the NF levels results in clinical benefit for the individuals with ALS. A systematic review with meta-analysis (Xu, 2016), and a separate meta-analysis (Zhou et al., 2021), both concluded that the use of NF levels in regards to their establishment for clinical relationships with, and impacts on, ALS need further research. The current state of evidence only leads to conclusions about the role of blood neurofilaments in the prognosis and other areas and measures of ALS, which are inconsistent. Therefore, it is necessary to further investigate the role of NF levels in the prognosis, among other areas, of ALS. Currently, few relevant and qualified studies could be included in the aforementioned analyses; even fewer articles could be included after serum and plasma were distinguished. Finding that NFH levels are higher in ALS than in healthy controls/non-CNS parenchymal disease is consistent with the view that damage to axons releases NF; however, there are relatively few, and only questionable, studies on the relationship between blood NF levels and the prognosis of ALS. Blood NF levels (NfL/pNfH) still need to be established as predictive biomarkers of ALS. That is, higher blood NF levels need to be clinically and physiologically linked to faster disease progression rate (DPR) and higher risk of death in individuals with ALS. Since neurofilaments are not specific markers of ALS (e.g., neurofilaments are also promising biomarkers for multiple sclerosis, Alzheimer's disease, and Charcot-Marie-Tooth disease), the theoretical and perceived predictive effect of NFs on the prognosis of individuals with ALS needs to be definitively differentiated. For instance, the suggestion that the pathophysiological mechanism of ALS may be related to changes in the function and concentration of FNs requires high-quality and direct evidence for further assessments of this potential clinical relationship. Neurodegenerative diseases are complex, and biomarkers are just one of the tools that may assist with diagnosis and treatment. Combination of many aspects, including clinical features, laboratory results, and other useful information, are needed to facilitate disease diagnosis and treatment, especially to establish clinical benefit, if any, for the latter.

TOFERSEN (QALSODY)

Tofersen (Qalsody) was approved by the FDA on April 25, 2023, for the treatment of adult individuals with ALS who have a mutation in the SOD1 gene. This indication is approved under accelerated approval based on reduction in plasma NfL light chain observed in individuals treated with tofersen (Qalsody). Tofersen (Qalsody) is an antisense oligonucleotide that causes degradation of SOD1 messenger ribonucleic acid (mRNA) through binding to SOD1 mRNA, which results in a reduction of SOD1 protein synthesis. The FDA label dosing schedule for tofersen (Qalsody) is as follows:

- Loading doses: 100 mg intrathecally every 14 days for 3 doses
- Maintenance doses: 100 mg intrathecally every 28 days after the 3 loading doses

CLINICAL STUDIES

The efficacy and safety of tofersen (Qalsody) was evaluated in a randomized, multicenter, quadruple masked, parallel assignment clinical trial (NCT02623699; VALOR). The trial was made up of parts A, B, and C, which correlated to phases 1, 2, and 3, respectively. Part C, the phase 3 portion of the clinical trial, will be discussed here. The study enrolled 108 individuals (the intent-to-treat [ITT] population), who were randomly assigned 2:1 to receive treatment with tofersen (Qalsody; n=72) or placebo (n=36) for 24 weeks. The individuals were permitted to receive concomitant riluzole (available US brands: Rilutek, Exservan, Tiglutik) and edaravone (Radicava). The primary endpoint for the clinical trial was change from baseline in the ALSFRS-R total score at week 28. Secondary endpoints for the study were CSF levels of total SOD1 protein concentration ratio compared to baseline at week 28, plasma NfL concentration ratio compared to baseline at week 28, change from baseline in percent predicted slow vital capacity (SVC) at week 28, change from baseline in handheld dynamometry (HHD) megascore at week 28, time to death or permanent ventilation up to week 28, time to death up to week 28, and number of participants experiencing adverse events (AEs) and serious adverse events (SAEs) up to day 236. The prespecified modified intent-to-treat (mITT) population (n=60 [39 individuals received tofersen {Qalsody}, 21 individuals received placebo]) had a predicted SVC of 65 percent or greater and met criteria for rapid disease progression based on the pre-randomization ALSFRS-R decline slope and SOD1 mutation type. The non-mITT population (n=48 [33 individuals received tofersen {Qalsody}, 15 received placebo]) had a predicted SVC of 50 percent or greater and did not meet criteria for rapid disease progression. When compared, individuals in the ITT population who received tofersen (Qalsody) had slightly shorter time from symptom onset and higher plasma NfL levels at baseline when compared to individuals in the ITT population who received placebo.

In the mITT population, the primary endpoint of mean change in ALSFRS-R scores from baseline to 28 weeks was -6.98 points in the group who received tofersen (Qalsody) and -8.14 points in the group who received placebo (adjusted mean difference, 1.2 points; 95 percent confidence interval [CI], −3.2 to 5.5; *P*=0.97). Because statistical significance was not achieved for the primary endpoint, the differences between the group who received tofersen (Qalsody) and the group who received placebo for the secondary endpoints were considered to be nonsignificant and, therefore, had no *P* values calculated. In the mITT population, the CSF levels of SOD1 protein decreased from baseline to 28 weeks by 29 percent in individuals treated with tofersen (Qalsody) versus an increase of 16 percent in the individuals treated with placebo (between-group difference in geometric mean ratio of 0.62 [95 percent CI, 0.49 to 0.78]). The mean plasma NfL levels from baseline to 28 weeks were reduced by 60 percent in the mITT group who received tofersen (Qalsody) versus increased by 20 percent in the group treated with placebo (between-group difference in geometric mean ratio of 0.33 [95 percent CI, 0.25 to 0.45]). The percentage of decline in the predicted SVC from baseline to 28 weeks in the mITT group who received tofersen (Qalsody) was 14.3 points versus a decline of 22.2 points in the group who received placebo (difference, 7.9 points [95 percent CI, −3.5 to 19.3]). The change from baseline to 28 weeks in HHD megascore in the mITT population in individuals treated with tofersen (Qalsody) was −0.34 versus −0.37 in the placebo group (difference, 0.02 [95 percent CI, −0.21 to 0.26]). The median time to death or permanent ventilation (10 percent in both groups), and the median time to death (one event in the group treated with tofersen [Qalsody] versus none for the group treated with placebo), for individuals treated with tofersen (Qalsody) versus individuals treated with placebo up to 28 weeks could not be estimated because of the small number of events. Adverse events occurred more often in the group treated with tofersen (Qalsody) versus the group treated with placebo. Some common AEs included pain, fatigue, arthralgia, myalgia, neuralgia, musculoskeletal stiffness, and both increased white blood cells and protein in CSF. Four individuals (6 percent) who received tofersen (Qalsody) experienced SAEs including respiratory failure (n=1 [1 percent]), aspiration pneumonia (n=2 [3 percent]), pulmonary embolism (n=3 [4 percent]), and acute respiratory failure (n=1 [1 percent]). Only one individual in the group who received placebo experienced a SAE (3 percent; pulmonary embolism).

In their discussion of the results of the clinical trial, the authors discuss that although there were reductions in the CSF levels of the SOD1 protein and plasma NfL levels, at 28 weeks, there was no significant change from baseline in the individuals who received tofersen (Qalsody), compared to the individuals who received placebo, in the mITT population in the ALSFRS-R scores. This was the subgroup with faster progression of the disease, so was expected to experience the most benefit from the drug. There were also no definitive clinically significant differences in other clinical endpoints between the group that received tofersen (Qalsody) and the group that received placebo.

There are currently two ongoing clinical trials involving the use of tofersen (Qalsody). NCT03070119 is a phase 3 open-label extension study to assess the long-term safety and efficacy of tofersen (Qalsody). NCT04856982 (ATLAS) is a phase 3 confirmatory trial evaluating the efficacy and safety of the use of tofersen (Qalsody) versus placebo in individuals who have confirmed SOD1 gene mutation and are presymptomatic for ALS versus individuals who receive treatment at the time that clinical symptoms of ALS manifest.

SUMMARY

The FDA approved the use of tofersen (Qalsody) for the treatment of adult individuals with ALS with SOD1 pathogenic variation(s) through the accelerated pathway using the surrogate endpoint of reduction in plasma NfL. The efficacy of Qalsody was assessed in a 28-week randomized, double-blind, placebo-controlled clinical study in individuals 23 to 78 years of age with weakness attributable to ALS and a SOD1 mutation confirmed by a central laboratory (Study 1 Part C, NCT02623699). One hundred eight (108) individuals were randomly assigned 2:1 to receive treatment with either Qalsody 100 mg (n=72) or placebo (n=36) for 24 weeks (three loading doses followed by five maintenance doses). Concomitant riluzole and/or edaravone use was permitted for individuals.

According to Hartmaier et al. (2022), the ALSFRS-R "has become the most widely applied rating scale in ALS in clinical trials as a primary or secondary outcome and is considered the gold standard measure of functional disability and disease progression in ALS patients. It is an accepted primary endpoint measure for Phase 3 ALS clinical trials to monitor functional decline patients over time and recommended as part of the EMA and FDA Guidance for ALS drug development, although survival is still often measured as a secondary endpoint and EMA considers it a critical part of assessment of efficacy."

The prespecified primary analysis population (n=60, mITT) had a slow vital capacity (SVC) of 65 percent or greater of predicted value and met prognostic enrichment criteria for rapid disease progression, defined based on their pre-randomization ALS Functional Rating Scale–Revised (ALSFRS-R) decline slope and SOD1 mutation type. The non-

mITT population (n=48) had a SVC of 50 percent or greater of predicted value and did not meet the enrichment criteria for rapid disease progression.

Baseline disease characteristics in the overall ITT population (combined mITT and non-mITT population) were generally similar in individuals treated with Qalsody and individuals who received placebo, with slightly shorter time from symptom onset and higher plasma NfL at baseline in the Qalsody group. At baseline, 62 percent of individuals were taking riluzole, and 8 percent of individuals were taking edaravone. Mean baseline ALSFRS-R score was 36.9 (5.9) in the Qalsody treatment group and 37.3 (5.8) in the placebo group. Median time from symptom onset was 11.4 months in the Qalsody treatment group and 14.6 months in the placebo group.

The primary efficacy analysis was the change from baseline to Week 28 in the ALSFRS-R total score in the mITT population, analyzed using the joint rank test to account for mortality in conjunction with multiple imputation (MI) to account for missing data for withdrawals other than death. Individuals treated with Qalsody experienced less decline from baseline in the ALSFRS-R compared to placebo, but the results were not statistically significant (Qalsody-placebo adjusted mean difference [95 percent CI]: 1.2 [−3.2, 5.5]). Other clinical secondary outcomes also did not reach statistical significance. Secondary endpoints of change from baseline at Week 28 in plasma NfL and CSF SOD1 protein were nominally statistically significant. NfL reduction was consistently observed for all subgroups based on sex, disease duration since symptom onset, site of onset, and riluzole/edaravone use.

The accelerated approval from the FDA was based on the statistically and clinically questionable reduction of plasma NfL levels and CSF SOD1 levels in individuals treated with tofersen (Qalsody) versus individuals treated with placebo. These were secondary endpoints for the clinical trial. The primary endpoint of change from baseline to 28 weeks in the ALSFRS-R total scores did decline less in the mITT population treated with tofersen (Qalsody) versus the group treated with placebo, but the change did not reach a level of statistical significance and the clinical significance of any measurable observed differences among experimental and control groups were not addressed and cannot be elucidated upon independently through reliable evidence. Few studies from the peer-reviewed literature can be located that provide details regarding levels of NfL in plasma as a potential measure of neuroaxonal injury in individuals with ALS; however, there is no consensus as to why the levels of NfL decrease later in the course of ALS and the clinical implications of these observations from limited data. The levels can vary widely in individuals with ALS. High-quality clinical investigations have not demonstrated that treatments for which decrease in the NfL levels have been reported also result in a decrease in the disease progression rate or increased survival for the individual with ALS.

The FDA's continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trial(s), since the primary endpoint representing a definitive and objective outcome was not achieved. The current FDA approval is based on nominal results of NfL, which was a secondary endpoint in seminal work so far. There is lack of direct, consistent, and unequivocal clinical evidence that demonstrates that decreasing the levels of NfL results in a decrease in the disease progression rate, improved quality of life, clinically meaningful physiological improvements, and progression-free or overall survival. The evidence is insufficient to determine that treatment with tofersen (Qalsody) results in improvements in relevant health outcomes of individuals with ALS.

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Coding

Inclusion of a code in this table does not imply reimbursement. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

The codes listed below are updated on a regular basis, in accordance with nationally accepted coding guidelines. Therefore, this policy applies to any and all future applicable coding changes, revisions, or updates.

In order to ensure optimal reimbursement, all health care services, devices, and pharmaceuticals should be reported using the billing codes and modifiers that most accurately represent the services rendered, unless otherwise directed by the Company.

The Coding Table lists any CPT, ICD-10, and HCPCS billing codes related only to the specific policy in which they appear.

CPT Procedure Code Number(s)
N/A

ICD - 10 Procedure Code Number(s)
N/A

ICD - 10 Diagnosis Code Number(s)
N/A

HCPCS Level II Code Number(s)
J1304 Injection, tofersen, 1 mg

Revenue Code Number(s)
N/A

FirstChoice VIP CARE
by Select Health of South Carolina

Policy History

MA08.162a

05/07/2024	The following new policy has been developed to communicate the Company's coverage criteria for tofersen (Qalsody).

Version Effective Date:
05/07/2024
Version Issued Date:
05/07/2024
Version Reissued Date:
N/A