Canada's Drug Agency
L'Agence des médicaments du Canada

## CDA-AMC REIMBURSEMENT REVIEW

# Patient and Clinician Group Input

**Qalsody (tofersen)**

(Biogen Canada Inc.)

**Indication:** The treatment of adults with amyotrophic lateral sclerosis (ALS) associated with a mutation in the superoxide dismutase 1 (SOD1) gene.

**March 10, 2025**

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CDA-AMC in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings. **If your group has submitted input that is not reflected within this document, please contact Formulary-Support@cda-amc.ca.**

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CDA-AMC does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no identifying personal information or personal health information is included in the submission. The name of the submitting group and all conflicts of interest information from individuals who contributed to the

# Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: tofersen
Indication: Amyotrophic  lateral sclerosis (ALS)
Name of Patient Group: ALS Action Canada Society
Author of Submission: Rick Zwiep, Board Member, along with a team of other patients and caregivers who contributed to this recommendation.

## 1. About Your Patient Group

Founded in 2020, ALS Action Canada (ALSAC) is Canada's only ALS patient-led charitable organization building a movement to ensure urgent, equitable access to promising therapies for Canadians living with ALS; more and better clinical trials for ALS therapies throughout Canada; and increased federal and provincial investment in ALS research and support for patients, caregivers, and families.

With members from across the country, we are a strong coalition of people living with ALS, their families, and their supporters.

ALS Action Canada is part of a growing, global, patient-led movement dedicated to ending this devastating disease forever.

ALS Action Canada website

## 2. Information Gathering

As a patient led organization, ALSAC has Canadian members who are diagnosed and living with the SOD1 genetic form of the fatal illness ALS. Structured 1 on 1 interviews were conducted with a total of 7 individuals with firsthand lived experience receiving tofersen treatments at Canadian clinics - 5 females, 2 males.

The interviews, conducted in Q3/Q4 of 2024, queried for benefits observed with tofersen, challenges in treatment administration, and its effects on mobility and overall quality of life. We also discussed patient views on key outcomes and their recommendations for considering tofersen's approval and accessibility in Canada.

Additional insights into ALS lived experience were provided by several other patients and caregivers.

## 3. Disease Experience

It is commonly understood that ALS is a progressive illness leading to death anywhere from 1-5 years after diagnosis with a median of 3 years. With that in clear view, most of the other symptoms of ALS although hugely impactful on daily living and overall quality of life, pale in comparison with the unavoidable outcome of death.

ALS presents significant challenges for patients, impacting mobility, strength, daily functionality, and emotional well-being. Common symptoms reported among the interviewees include muscle weakness, difficulty with balance, cramping, and nerve pain, often aggravated by exertion or lack of rest. Mobility issues restrict independence, especially concerning stairs, curbs, and even routine tasks such as carrying groceries or standing for extended periods. Emotional impacts are also evident, with patients expressing fear over disease progression, anxieties related to future independence, and the impact on family members.

- ALS impedes mobility, with many patients experiencing weakness, falls, and difficulty with daily tasks.
- Muscle cramping and nerve pain are recurring issues, impacting sleep and overall comfort.
- Loss of motor function (paralysis in voluntary muscles including the diaphragm)
- Patients experience emotional challenges, balancing the reality of their diagnosis with the desire to maintain independence and quality of life.

Patients identified several critical areas for control within ALS progression to improve their quality of life:

1. **Muscle Weakness:** Restoration or stabilization of muscle strength in the legs and arms is a top priority, as it directly impacts daily functionality and independence.
2. **Cramping and Fasciculations:** Frequent, severe cramping and muscle twitches are sources of significant discomfort, impacting sleep and exacerbating fatigue.
3. **Mobility Maintenance:** Patients prioritize the ability to walk and engage in regular activities, including stair use, driving, and grocery shopping, as part of maintaining an active lifestyle.
4. **Race against the progression:** There is a tremendous physical and mental toll from the continual losses. As muscle functions are lost, they can't be regained. As complete paralysis takes hold, and breathing is impaired or lost the opportunity to halt the progression at an earlier stage is gone forever.
5. **Slowed Disease Progression:** Patients highlighted the need to halt or slow ALS progression to extend their quality of life and delay severe disability.

## 4. Experiences With Currently Available Treatments

In Canada there are only 2 therapies currently available for ALS. One of these, Riluzole has been in market for many years and is available to most patients at little to no cost. Some patients are unable to continue this twice daily pill due to side effects. In spite of its convenience, some patients also simply stop taking it because they believe its efficacy is not well proven or significant enough for the patient to notice any benefit.

The second, newer therapy edaravone (Radicava) is a costly drug (~$10K/mo), typically now self-administered orally 10 days per 28 days. This drug is effectively out of reach for those under 65 with no private insurance, and inaccessible to those who don't meet the strict criteria set by CDA (which ALSAC believes was an inappropriately limiting constraint). Some Canadian clinicians do not prescribe it for their patients. Some patients also simply stop taking it because recent studies have shown results that put the efficacy into question, or because of side effects.

Neither of these therapies are specifically targeting the SOD1 gene mutation variant of ALS.

## 5. Improved Outcomes

Because ALS is progressive and fatal, in general, patients with ALS will pursue all available treatments recommended by their neurologist. Some will also pursue clinical trials where available. Many also use off-label or alternative treatments. We are dying, so we are quite willing to take whatever will help. When a new therapy shows promise in trials, ideally these new treatments would be available quickly, through accelerated programs & compassionate access routes.
Hope is all we have when it comes to this disease. The idea that the progression could be halted, and that those with genetic mutations known to cause ALS could be helped prior to symptom onset is huge.

## 6. Experience With Drug Under Review

### Benefits Observed with Tofersen

Patients reported varying degrees of benefit from tofersen, particularly as dosing protocols were optimized. Many observed stabilizations in their ALS symptoms after transitioning to the 100 mg dosage, resulting in slowed disease progression and maintenance of daily functioning.

**Patient Observations:**

- **Patient-1** and **Patient-2** both noted that switching to a 100 mg dose yielded notable stabilization in their symptoms, allowing them to maintain activities that were previously becoming difficult.

- **Patient-3** and **Patient-4** felt that early intervention with tofersen allowed them to delay noticeable symptoms, giving them hope for longer periods of independence.
- **Patient-5** observed fewer new symptoms since starting the treatment and has been able to sustain her daily activities without further decline.

### Challenges with Treatment Administration

The need for lumbar punctures to administer tofersen has posed logistical and physical challenges. Several patients experienced post-lumbar headaches, nausea, and temporary incapacitation, which limited their ability to resume daily activities post-treatment. Adjustments in the speed of injection (over 2 minutes versus rapid injection) significantly impacted the comfort and severity of side effects for patients.

**Key Challenges:**

- **Travel and Accessibility:** Patients often need to travel long distances to receive tofersen, which is burdensome, especially if adverse effects follow treatment. Relocation of administration to local clinics, where possible, would alleviate this strain.
- **Injection Protocols:** Consistent, slow injections could reduce adverse effects. Patients highlighted the need for a standard protocol to ensure that each site adheres to best practices.

### Impact of Treatment on Daily Life and Mobility

For many, tofersen has provided stabilization, allowing them to engage in daily life with reduced fear of rapid deterioration. Many patients felt a renewed sense of control and confidence in maintaining an active lifestyle. This improvement in life quality underscores the value tofersen may offer to those affected by ALS.

**Patient Reflections:**

- **Patient-1** and **Patient-2** expressed gratitude for the slower progression and the freedom to remain involved in family and social activities.
- **Patient-3** and **Patient-4** are hopeful that early intervention will prevent more severe symptoms, allowing them to remain independent longer.
- **Patient-5** felt that maintaining stability has helped her continue her work and hobbies, reinforcing her sense of independence.

## 7. Companion Diagnostic Test

In our survey we did not question the patients about these clinical details. It is well understood that biomarkers for ALS are still an area of much study, so it's reasonable to believe that some of the patient CSF could be used to check NfL or other biomarkers during each injection period.

## 8. Anything Else?

Recommendations

**Accessibility:** ALS patients face progressive loss of muscle function, impairing mobility and independence, and inevitably resulting in premature death. Tofersen has emerged as a potentially transformative treatment, offering patients hope for slowing or stabilizing disease progression, thereby prolonging their life, as well as allowing them to maintain daily functioning, and have improved quality of life. Tofersen is the first treatment for ALS that has been developed to target a known specific pathological mechanism and is the first drug to interfere with the effects of a genetic cause of ALS, in those patients who carry the defective Superoxide Dismutase gene (SOD1). Tofersen is therefore justifiably regarded as a breakthrough medication and will undoubtedly be seen as a landmark in the development of further drugs targeting specific mechanisms underlying this complex disease. Since tofersen has been approved by Health Canada as effective and safe for the treatment of ALS caused by the SOD1 genetic mutation. **ALS Action Canada urges the Canadian Drug Agency to recommend its reimbursement under provincial drug benefit plans, to all patients without any restrictions other than confirmation of a SOD1 mutation.**

**Standardized Administration Practices:** Standardizing slow injection protocols and offering lumbar punctures at local clinics where feasible may reduce side effects, improve patient experience, and increase access.

**Facilitating Genetic Testing:** Early genetic testing access is essential for patients with family histories of ALS, allowing for prompt intervention with tofersen or other treatments that may emerge in the future.

## Appendix: Patient Group Conflict of Interest Declaration

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3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

### Table 1: Financial Disclosures

**Check Appropriate Dollar Range With an X. Add additional rows if necessary.**

| Company | $0 to 5,000 | $5,001 to 10,000 | $10,001 to 50,000 | In Excess of $50,000 |
|---|---|---|---|---|
| BIOGEN | | $10K | | |
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I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

**Name: Rick Zwiep**
**Position: Board Member and person living with ALS**
**Patient Group: ALS Action Canada Society**
**Date**: 10 March, 2025

CADTH

# Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: TBC - tofersen
Indication: Amyotrophic  lateral sclerosis (ALS)
Name of Patient Group: ALS Society of Alberta
Author of Submission: Leslie Ring Adams

## 1. About Your Patient Group

The ALS Society of Alberta is dedicated to making each day the best possible for Albertans living with and affected by ALS. We achieve this by providing high-quality care, support services, and essential equipment to individuals and families, while also investing in research and advocacy efforts to improve outcomes and drive progress toward a future without ALS.

For more information, please visit ALS Society of Alberta website.

## 2. Information Gathering

In February 2025, an email was sent to six clients in Alberta who are currently using Tofersen, as well as one caregiver whose spouse had used Tofersen, to gather feedback. In addition to the email responses, follow-up phone interviews and email exchanges were conducted with three of the clients to gain further insights. This approach combined written feedback and direct conversations, providing a more comprehensive understanding of their experiences. A total of five respondents participated, all of whom are currently using Tofersen, with 3 (60%) identifying as male and 2 (40%) identifying as female.

## 3. Disease Experience

Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease that affects nerve cells in the brain and spinal cord, gradually leading to the loss of muscle control. As the disease advances, individuals experience increasing difficulty with movement, speech, swallowing, and eventually breathing. Most people die within 2 to 5 years of diagnosis, and there is no known cure for ALS.

The core of ALS is the deterioration of motor neurons—nerve cells responsible for transmitting signals from the brain to the muscles. As these neurons weaken and die, the brain loses its ability to control voluntary movements. Over time, this leads to:

**Muscle Weakness & Paralysis**: Symptoms typically begin in one area, such as the hands, legs, or speech muscles, and progressively spread throughout the body.

**Difficulty Speaking & Swallowing**: Speech may become slurred, and swallowing becomes increasingly challenging, heightening the risk of choking and malnutrition.

**Breathing Problems**: As the muscles that control respiration weaken, individuals may require ventilatory support.

Despite the physical challenges, those living with ALS continue to find ways to maintain dignity and quality of life, adapting to each stage of progression with the support of loved ones, caregivers, and medical professionals.

An ALS diagnosis is life-changing, not only for the individual diagnosed but also for their family and support network. Clients often experience profound emotional distress, moving through the stages of grief—denial, anger, bargaining, depression, and acceptance—as they come to terms with their diagnosis. The loss of independence and the knowledge of their prognosis can be overwhelming, leading to depression, anxiety, and feelings of isolation.

As ALS progresses, social connections can become increasingly difficult to maintain. Communication challenges and physical limitations may strain relationships, and clients often feel disconnected from their communities. However, with adaptive communication devices, support groups, and efforts to promote social inclusion, meaningful connections can be preserved.

While ALS presents profound challenges, those living with the disease can find strength in support systems, assistive technology, and medical care that enhance their quality of life.

Caring for a loved one with ALS is an evolving and demanding responsibility, requiring physical, emotional, and financial sacrifices. Caregivers—often spouses, children, or close family members—take on an increasing role in managing daily needs, medical care, and emotional support.

The physical demands of caregiving can be exhausting. Caregivers assist with mobility, feeding, bathing, dressing, and managing medical equipment such as non-invasive ventilators and feeding tubes. Lifting and repositioning a loved one can lead to musculoskeletal strain, chronic fatigue, and burnout, making self-care an essential yet often neglected priority.

The emotional toll of caregiving is profound. Witnessing a loved one's decline can bring feelings of helplessness, grief, and emotional exhaustion. Many caregivers experience stress, anxiety, and depression as they navigate the unpredictable nature of the disease. The constant demands of caregiving can also result in burnout and compassion fatigue, particularly when adequate support systems are lacking. Finding moments of respite, leaning on support networks, and seeking professional counseling can help caregivers maintain their own well-being.

The financial burden of ALS is significant. The costs of medical equipment, home modifications, and professional caregiving services can be overwhelming. Many caregivers are forced to reduce their working hours or leave their jobs entirely to provide full-time care, leading to lost income and financial instability. Without financial assistance or access to resources, the strain can be immense.

Despite these challenges, caregiving is also an act of deep love and dedication. Access to support services, respite care, and financial resources can help caregivers navigate this journey while ensuring the best possible care for their loved ones.

Living with ALS affects not just the person diagnosed but their entire support network. While the journey is marked by immense challenges, access to compassionate care, loaned equipment, assistive technologies, and strong social and emotional support systems can make a meaningful difference in the lives of those impacted by the disease.

While most cases of ALS occur sporadically with no known family history, approximately 10% of ALS cases are classified as familial. Familial ALS is inherited, meaning it is passed down through generations due to genetic mutations. Over 40 genes have been linked to ALS, with some mutations contributing to more aggressive disease progression.

One of the most well-known genetic causes of ALS is mutations in the SOD1 gene, which account for approximately 15-20% of familial ALS cases. In North America, certain SOD1 mutations are associated with an earlier age of onset and a more rapid disease progression, leading to significantly shorter survival times. This makes SOD1-linked ALS an especially aggressive form of an already devastating disease.

Genetic testing can help identify mutations linked to familial ALS, allowing at-risk family members to assess their likelihood of developing the disease. While no cure exists, research into gene-targeted therapies is offering hope for those with genetic ALS. These therapies aim to reduce the toxic effects of mutated genes and slow disease progression.

As research advances, understanding the genetic underpinnings of ALS is critical to developing more effective treatments, supporting affected families, and ultimately finding a cure.

## 4. Experiences With Currently Available Treatments

Currently available treatments for ALS are limited, with no cure at this time. The only medications approved by Health Canada to extend survival by a few months are Riluzole and Edaravone. Some respondents using Tofersen are also taking Riluzole and Edaravone, and some had previously been on Albrioza before it was withdrawn from the market.

Clients report that while these treatments may provide some benefit, they do not significantly alter the disease progression. Riluzole is generally well-tolerated but may cause fatigue and liver enzyme elevations, requiring ongoing monitoring. Edaravone, administered via infusion, can be burdensome due to the frequent visits required for treatment and the associated logistical challenges such as travel, time off work, and caregiver support.

Due to the terminal nature of ALS and the limited effectiveness of approved treatments, many clients are willing to try experimental or off-label medications. Access to new therapies is critical, as current options fall short in meaningfully altering the course of the disease.

## 5. Improved Outcomes

When evaluating new therapies for ALS, clients and caregivers emphasize the need for treatments that offer more than just a few months of survival. They are seeking meaningful improvements in quality of life, disease progression, and functional ability—improvements that would allow them to spend more time with loved ones and maintain independence for as long as possible.

One client shared, "I want the opportunity to create more memories with my grandkids." This reflects a common sentiment among those living with ALS: the desire to remain present and engaged with family, rather than focusing solely on survival statistics.

For families affected by SOD1-ALS, the genetic nature of the disease carries additional weight. Many clients not only face their own diagnosis but also live with the fear that their children may inherit ALS. One respondent expressed appreciation for research into targeted therapies, saying, "I value that they are working on something that will help my children in the future... something with a measurable change instead of just hoping." This underscores the need for treatments that can slow or halt progression—providing hope for the next generation.

Currently, clients and caregivers are often willing to accept significant trade-offs, including the challenges of frequent infusions, side effects, or high costs, in exchange for a treatment that offers real improvement. While some challenges exist, respondents expressed appreciation for the support they have received in accessing treatment. One client noted, "As I live about an hour from Calgary, I needed to travel there to have testing done. Access and setting up the testing were easy for me as it was all taken care of by the ALS Clinic in Calgary. Testing was covered by healthcare, leaving me with only the expense of fuel and my wife's time off work." A therapy that slows functional decline, preserves independence, and reduces symptom burden would not only benefit those living with ALS today but could transform the future for families affected by genetic ALS.

## 6. Experience With Drug Under Review

All respondents accessed Tofersen through the Special Access Program and reported significant benefits compared to their previous rate of decline. Many described the drug as life-changing, helping to slow or even halt progression, preserve independence, and, in some cases, improve strength and dexterity.

One respondent, who had been experiencing rapid decline, shared, "Once my symptoms started, I was in a rapid decline with extremely high light chain counts. Tofersen immediately brought those numbers down, slowing my decline and allowing me to maintain much of my independence. Without it, at the original rate of decline, I wonder if I would still be here (opting for MAID)."

For another, Tofersen provided tangible functional improvements: "It is the miracle I needed. It is slowing or stopping progression for me in my lower body where my nerve damage is the worst. I am able to still walk and stay independent. I have even gained back strength in my hands. My dexterity is improving and I can open twist caps on most items. I feel like I have hope for an improved future."

A common theme among respondents was the contrast between their own experience on Tofersen and that of relatives who were unable to access the treatment. One participant highlighted, "Once I was on Tofersen, my symptoms slowed quite drastically. Without Tofersen, I feel I would not be writing this submission, as one of my relatives was diagnosed shortly after me with the same SOD1 gene and was not accepted into the trial due to exclusions. He passed 11 months after diagnosis."

Respondents also pointed to a stark difference in disease progression compared to family members who had the same genetic mutation: "It's doing some good because I'm not progressing in the same manner that my mom did." Many expressed deep gratitude for the opportunity to try something that previous generations of their family never had a chance to access. The knowledge that they are benefiting from advancements in treatment—something their parents or other loved ones never had—was profoundly meaningful.

Respondents reported no significant side effects while using Tofersen. One individual noted, "The only side effect I have experienced is very minor soreness at the injection site, which clears up in a couple of days." Overall, the treatment was described as well-tolerated and manageable, especially compared to the severe impact of ALS itself.

Tofersen is addressing an urgent, unmet need for people with SOD1-ALS, a rapidly progressing and devastating disease. Clients value that it is helping to slow or stop disease progression, preserving function and independence. The potential for improved quality of life and hope for the future is critical, particularly given the genetic nature of SOD1-ALS and its impact on families.

For many, this treatment represents more than just a medical breakthrough—it offers a chance to rewrite the future for families affected by SOD1-ALS. Clients recognize that their ability to access Tofersen is something their loved ones never had, and they hope that ongoing research will continue to improve outcomes for future generations. Compared to other ALS therapies, which offer only minimal survival benefits, Tofersen is providing real, measurable improvements—offering not just more time, but a better quality of life during that time.

## 7. Companion Diagnostic Test

Once an ALS diagnosis is confirmed, the standard of care includes genetic testing to determine whether there is a genetic component to the disease. This is particularly important for identifying mutations such as SOD1, which may indicate eligibility for targeted therapies like the drug under review.

Ultimately, genetic testing is a critical step in guiding treatment decisions and ensuring that those who may benefit from targeted therapies can do so as quickly as possible. Improving accessibility and minimizing delays in testing will be essential to optimizing care for individuals with ALS.

## 8. Anything Else?

Respondents emphasized that without access to Tofersen, their disease progression would likely accelerate, drastically affecting both their quality of life and time with loved ones. One respondent shared, "If Tofersen is rejected, I would be unable to access the treatment, and therefore I suspect I would pass quickly, as my recent relative did."

Beyond the physical impact, ALS takes an emotional and financial toll on families. A client noted, "Without Tofersen, my family and I won't be able to do many activities together. Not being able to spend the same time with them affects me, and I feel alone sometimes." Another added, "ALS has also had an impact on our family financially, as I am unable to work. This has caused us to miss out on things we once enjoyed, like travel and entertainment."

Access to this treatment is not just about prolonging life, but about preserving independence, dignity, and the ability to engage in meaningful moments with loved ones—things that past generations of ALS clients with the same genetic mutation never had the chance to experience.

## Appendix: Patient Group Conflict of Interest Declaration

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| Biogen Canada | x | | | |
| | | | | |
| | | | | |

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

**Name: Leslie Ring Adams**
**Position: Executive Director**
**Patient Group: ALS Society of Alberta**
**Date**: March 7, 2025

CADTH

# Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: TBC - Tofersen
Indication: Amyotrophic lateral sclerosis (ALS)
Name of Patient Group: ALS Society of British Columbia (ALSBC)
Author of Submission: Donald Miyazaki (Executive Director)

## 1. About Your Patient Group

The Amyotrophic Lateral Sclerosis Society of British Columbia (ALSBC) was founded in 1981 by renowned neurologist Dr. Andrew Eisen in benefit of patients and family members affected by ALS in British Columbia and the Yukon to meet their physical and emotional needs.

Based in Richmond, British Columbia, the organization provides services such an equipment loan program, psychological support, conducts fundraising events, funding research and advocating for those affected by ALS.

ALSBC's vision is a world free of ALS. For more information about our organization, please visit www.alsbc.ca

## 2. Information Gathering

To the best of the society's knowledge, there are four (4) individuals in British Columbia who are living with ALS that are currently using Tofersen as a form of treatment. Through the work of one of our dedicated volunteers, feedback on the treatment program has been sought given a majority of these individuals take part in joint treatments on a scheduled monthly schedule. Together with their caregivers and family members, feedback to gather experiences has been sought to gain further insight on a comprehensive understanding standpoint of their experiences.

## 3. Disease Experience

ALS is a progressive neurodegenerative disease that affects nerve cells in the brain and spinal cord, gradually leading to the loss of muscle control. As the disease advances, individuals experience increasing difficulty with movement, speech, swallowing, and eventually breathing. Most people die within 2 to 5 years of diagnosis, and there is no known cure for ALS.

The core of ALS is the deterioration of motor neurons - nerve cells responsible for transmitting signals from the brain to the muscles. As these neurons weaken and die, the brain loses its ability to control voluntary movements. Over time, this leads to:

**Muscle Weakness & Paralysis**: Symptoms typically begin in one area, such as the hands, legs, or speech muscles, and progressively spread throughout the body.

**Difficulty Speaking & Swallowing**: Speech may become slurred, and swallowing becomes increasingly challenging, heightening the risk of choking and malnutrition.

**Breathing Problems**: As the muscles that control respiration weaken, individuals may require ventilatory support.

Despite the physical challenges, those living with ALS continue to find ways to maintain dignity and quality of life, adapting to each stage of progression with the support of loved ones, caregivers, and medical professionals.

An ALS diagnosis is life-changing, not only for the individual diagnosed but also for their family and support network. Patients often experience profound emotional distress, moving through the stages of grief—denial, anger, bargaining, depression, and

acceptance—as they come to terms with their diagnosis. The loss of independence and the knowledge of their prognosis can be overwhelming, leading to depression, anxiety, and feelings of isolation.

As ALS progresses, social connections can become increasingly difficult to maintain. Communication challenges and physical limitations may strain relationships, and patients often feel disconnected from their communities. However, with adaptive communication devices, support groups, and efforts to promote social inclusion, meaningful connections can be preserved.

While ALS presents profound challenges, those living with the disease can find strength in support systems, assistive technology, and medical care that enhance their quality of life.

Caring for a loved one with ALS is an evolving and demanding responsibility, requiring physical, emotional, and financial sacrifices. Caregivers—often spouses, children, or close family members—take on an increasing role in managing daily needs, medical care, and emotional support.

The physical demands of caregiving can be exhausting. Caregivers assist with mobility, feeding, bathing, dressing, and managing medical equipment such as non-invasive ventilators and feeding tubes. Lifting and repositioning a loved one can lead to musculoskeletal strain, chronic fatigue, and burnout, making self-care an essential yet often neglected priority.

The emotional toll of caregiving is profound. Witnessing a loved one's decline can bring feelings of helplessness, grief, and emotional exhaustion. Many caregivers experience stress, anxiety, and depression as they navigate the unpredictable nature of the disease. The constant demands of caregiving can also result in burnout and compassion fatigue, particularly when adequate support systems are lacking. Finding moments of respite, leaning on support networks, and seeking professional counseling can help caregivers maintain their own well-being.

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Despite these challenges, caregiving is also an act of deep love and dedication. Access to support services, respite care, and financial resources can help caregivers navigate this journey while ensuring the best possible care for their loved ones.

Living with ALS affects not just the person diagnosed but their entire support network. While the journey is marked by immense challenges, access to compassionate care, loaned equipment, assistive technologies, and strong social and emotional support systems can make a meaningful difference in the lives of those impacted by the disease.

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One of the most well-known genetic causes of ALS is mutations in the SOD1 gene, which account for approximately 15-20% of familial ALS cases. In North America, certain SOD1 mutations are associated with an earlier age of onset and a more rapid disease progression, leading to significantly shorter survival times. This makes SOD1-linked ALS an especially aggressive form of an already devastating disease.

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As research advances, understanding the genetic underpinnings of ALS is critical to developing more effective treatments, supporting affected families, and ultimately finding a cure.

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Due to the terminal nature of ALS and the limited effectiveness of approved treatments, many patients are willing to try experimental or off-label medications. Access to new therapies is critical, as current options fall short in meaningfully altering the course of the disease.

## 5. Improved Outcomes

When evaluating new therapies for ALS, patients and caregivers emphasize the need for treatments that offer more than just a few months of survival. They are seeking meaningful improvements in quality of life, disease progression, and functional ability—improvements that would allow them to spend more time with loved ones and maintain independence for as long as possible.

In recent surveys conducted by ALSBC, respondents from the ALS community in BC have said they most highly desire medications that keep the disease at bay. They heavily value treatments that would enable them to maintain mobility and independence, grant them more time with their family and friends, maintain their professional or school lives, work on their hobbies, and feel like themselves. Given that it's a terminal disease at this stage, prolonging the best possible quality of life has regularly been a common discussion at support groups.

One patient who is currently using Tofersen stated that although they live 4-hours away from Vancouver General Hospital, the spinal infusion works like a "miracle" and they are willing to travel monthly at lengths to ensure they slow the progression of the disease and they feel "fortunate, lucky and blessed" that thanks to Tofersen, they are amongst a rare group of ALS patients that currently has a form of treatment that allows them to prolong their quality of life.

## 6. Experience With Drug Under Review

In interviews conducted with patients who are taking Tofersen, all respondents reported the drug as a form of treatment that is slowing the progression of ALS, while allowing them to uphold or even improve their quality of life.

Three of the four patients in our province are currently having their appointments booked jointly whenever possible, at Vancouver General Hospital. The monthly appointments allow for a mini support group-like environment where their regular interactions allow them to keep in touch and update each other on how they are making out with their treatments.

"I'm thankful for the drug that has slowed down my progression. It has given me belief that it could be a cure or at least, help me prolong quality time with my family before it takes away my ability to walk, to work, and to live my life fully" said one patient.

"I am the fourth person in three generations to have this horrific disease. I am led to believe there are about 400 of us in North America. My birth mother was in the ending stage with genetic SOD1 ALS. I then discovered that my grandfather and uncle also passed from ALS and that it ran in my family. 7 years later, in 2017, I was diagnosed with SOD1 ALS". Discovering this and having Tofersen available as a treatment has been life-altering".

"When I was first diagnosed with ALS, I saw a rapid decline in dexterity. Since the injections, the decline has halted and it has given me hope as I feel I have control of my life again".

As far as side effects of Tofersen, interviewees have reported none to date.

## 7. Companion Diagnostic Test

Once an ALS diagnosis is confirmed, the standard of care includes genetic testing to determine whether there is a genetic component to the disease. This is particularly important for identifying mutations such as SOD1, which may indicate eligibility for targeted therapies like the drug under review.

Ultimately, genetic testing is a critical step in guiding treatment decisions and ensuring that those who may benefit from targeted therapies can do so as quickly as possible. Improving accessibility and minimizing delays in testing will be essential to optimizing care for individuals with ALS.

## 8. Anything Else?

Although they understand that it only affects a small portion of the ALS Community, interviewed patients emphasized the urgent need to ensure that this treatment is available to those who qualify. Closing remarks in interviews include:

“It has done wonders for my quality of life and at times, I feel like the luckiest of the unlucky who have been diagnosed with ALS since there is a treatment that is working to slow down its progression”.

“Hoping that Tofersen is potentially going to be available for a prolonged period of time gives my family hope as it could be something that is passed down for generations”

“We are passionate about being part of the machine that hopefully will one day find a cure for this horrific disease and giving back to the ALS community that has supported us during my journey with ALS”

## Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   No

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   No

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

### Table 1: Financial Disclosures

**Check Appropriate Dollar Range With an X. Add additional rows if necessary.**

| Company | $0 to 5,000 | $5,001 to 10,000 | $10,001 to 50,000 | In Excess of $50,000 |
|---|---|---|---|---|
| Biogen Canada | x | | | |
| | | | | |

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I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

**Name: Donald Miyazaki**
**Position: Executive Director**
**Patient Group: ALS Society of British Columbia**
**Date**: March 9, 2025

CADTH

# Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: **Tofersen**
Indication: **Treatment of adults with amyotrophic lateral sclerosis (ALS) associated with a mutation in the superoxide dismutase 1 (SOD1) gene**
Name of Patient Group: **ALS Society of Canada**
Author of Submission: **Ilayda Ulgenalp**

## 1. About Your Patient Group

Founded in 1977, the ALS Society of Canada (ALS Canada) is working to change what it means to live with ALS. Grounded in and informed by the Canadian ALS community, we respond to the urgent unmet need for life-changing treatments by investing in high-quality research that will fuel scientific discovery and by engaging industry, supporting increased clinical capacity, and advocating for equitable, affordable, and timely access to proven therapies. Responding to the tremendous need for current and credible ALS knowledge, awareness, and education, we empower Canadians affected by ALS to navigate the current realities of ALS, be informed consumers of ALS information, and advocate effectively for change. In Ontario, we provide direct community services to help people navigate ALS. Our work is powered by generous donors who share our vision of a world free of ALS.

## 2. Information Gathering

The following submission reflects data that ALS Canada gathered through an online survey and focus group interviews. All the data was contributed anonymously.

ALS Canada developed and administered a 20-minute online survey disseminated in English and French. Survey respondents were recruited by ALS Canada through promotion via email, social media, and ALS Canada's website, with the following populations invited to take part: people living with ALS ("patients") and their caregivers and family members ("caregivers/family members"). The responses were collected from January 15 and February 14, 2025.

598 patients and caregivers responded to the English and French online surveys. Almost all respondents were from Canada (primarily Ontario and Quebec), with less than 1% participating from the U.S. and France. More than 75% of respondents are, or were, caregivers/family members of someone diagnosed with ALS. The remainder are currently living with ALS. Among the respondents living with the disease, approximately 65% indicated they had been diagnosed with ALS between six months and two years ago, with the rest having received their diagnosis more than 3 years ago. More than half of respondents were 55 years of age or older. At the time of the survey, of the 175 respondents who are living people living with ALS, only 12 had direct experience with tofersen.

In February 2025, ALS Canada supplemented the information gathered through the survey by conducting semi-structured virtual focus group interviews with 3 patients and 1 caregiver, all of whom had direct experience with tofersen.

Their demographics are summarized in the chart below, and specific treatment experience can be found in Section 6:

| Name | Patient/Caregiver | Gender | Age | Type of ALS | Diagnosis Date | Location |
|---|---|---|---|---|---|---|
| **PT** | Patient | Female | 43 | SOD1 | February 2016 | Saskatchewan (Canada) |
| **TB** | Patient | Male | 50 | SOD1 | April 2018 | Alberta (Canada) |
| **TA** | Patient | Male | 28 | SOD1 | July 2020 | Saskatchewan (Canada) |
| **KS** | Bereaved Caregiver | Female | 41 | SOD1 A5V | June 2019 | Alberta (Canada) |

## 3. Disease Experience

Amyotrophic lateral sclerosis (ALS) is a terminal disease that gradually paralyzes people because the brain is no longer able to communicate with the muscles of the body that we are typically able to move at will. As the connection with muscles of the body breaks down, someone living with ALS will lose the ability to walk, talk, eat, swallow, and eventually breathe. Of those who receive an ALS diagnosis, 80% will die within two to five years of diagnosis. There are currently about 4,000 people living with ALS in Canada. Every year, approximately 1,000 Canadians die of ALS and a similar number are diagnosed.

For the 90 to 95% of people living with ALS without an obvious family history, traditionally referred to as “sporadic”, it is estimated that between 11 to 16% of cases are caused by known ALS variants. To date, many genes have been identified that when altered, can contribute to ALS. The four most common genetic causes of ALS are due to variants in four genes: C9orf72, SOD1, FUS, and TARDBP. Approximately 5 to 10% of people living with ALS will have a family history of the disease. A family history means multiple family members were affected by the disease due to a hereditary variant in a gene related to ALS.

87% of the survey respondents indicated no family history of ALS.

A diagnosis of ALS and the realities of living with the disease have a profound and pervasive effect on the lives of not only those who are struck by this devastating disease but also anyone who loves and cares for them. The following is a summary of the key themes that emerged from the respondents of this survey – people living with ALS, caregivers and family of those who are living or have lived with the disease – on its impact on their lives.

### Symptoms

With respect to a wide range of symptoms patients experience due to ALS, among the most severe are difficulty with mobility (i.e. walking, standing), decreased muscle tone, difficulty communicating verbally, muscle stiffness and fatigue. These symptoms were also among the most important to control for people living with ALS, in addition to difficulties breathing, choking episodes, pain and muscle cramping or twitching.

### Impact on Quality of Life

When asked how living with ALS has negatively affected their quality of life, **patients** indicated that their social life, family life, ability to pursue hobbies and emotional well-being had suffered the most. When asked the same questions, **caregivers/family members** indicated that their family life, intimate relationships, and emotional well-being suffered the most.

Below are a few examples of answers from **patients** and **caregivers/family members** when asked to describe in their own words how ALS has impacted their quality of life.

*"ALS has stopped life as I knew it."*

*"I lost the ability to enjoy nature and life fully."*

*"The future as planned and foreseen has been lost, retirement plans have been lost, friends have been lost. The ability to share certain memories has been lost."*

*"Struggles with my faith and spiritual well-being."*

*"I live half the week at my mom's place and hardly see my husband anymore. I struggle with back and joint problems due to caregiving-related injuries."*

*"I have not hugged anyone in months."*

*"I miss the little things like being able to fully enjoy a glass of wine."*

*"I feel I am living in an ALS world which is very narrow and focused instead of the real outside world where I existed before."*

*"Several years after my partner's death, I am still recovering physically and mentally from the complete exhaustion."*

*"Je ne peux plus manger avec des personnes pour boire un peu et jaser entre amis(es) et membres de la famille. Je suis presque forcé d'etre isolé."*

The majority of **patients** indicated that they started needing assistance with eating, drinking, transitioning from lying to sitting, walking, speaking and bathing within a year after their diagnosis, with more than 60% of the respondents receiving 5 to 20 hours of assistance per week from caregivers/family members to perform activities of daily living. Approximately 60% of **caregiver/family members** respondents indicated needing assistance with these aspects of daily living "completely changed" their daily life.

Assistive devices are a critical aspect of the care of people living with ALS as well. Of the **caregivers/family members** surveyed, approximately 60% noted the need for specialized bathroom equipment, followed by hospital bed/mattress, walker, non-invasive ventilation support, standard/power wheelchairs and communications devices.

*"My life is now basically restricted to 4 rooms in our house."*

*"For the past 6 months, most of the time, I stay at home and don't do anything."*

*"Living with ALS has made me totally vulnerable and dependent of my family. I need their support all the time."*

*"I still have to work full time (on site), so my day starts at 5 am to get him [person living with ALS] up, toileted, and partly dressed and into his wheelchair. Put lunch and drinks in an accessible place. Get medications ready for the majority of the day. Get myself ready. Head to work at about 6 am until about 3 pm (unless he has to call me home to use the bathroom or for other urgent needs). Get home, do physio, do housework, cook meals and prep lunches for the next day. Showering occurs twice a week and takes about an hour. Overall, I feel like I never stop and don't have much time to myself."*

*"I don't want to be a burden, so I push myself, but many days I find keeping up a facade of functioning well is exhausting."*

*"I went from being the sole income earner of a family of four, to being 100% dependent in less than a year."*

*"I went from being capable and independent to being almost completely dependent on others and unable to do simple things, like prepare a sandwich, for yourself."*

*"I had no life outside of caring for my husband. It consumed me. I couldn't leave the house. Friends disappeared."*

*"Life—walking alongside the one suffering and losing all their motor abilities, and mostly their capacity to breathe—is nothing short of a nightmare."*

*"Caregiving took 100% of my time and effort. I operated on adrenaline and was exhausted by the end of each day."*

*"Need for a scooter or wheelchair limits ability to travel even locally."*

## Disease Experience for Familial ALS

Given that this submission is specifically for a drug that targets a genetic form of ALS, it is important to provide context on the experiences of people with familial ALS. Their journey is shaped by both the presence of ALS in their family and the knowledge that they may one day face the same diagnosis. For people with familial ALS, the disease experience is often deeply personal. Many have witnessed firsthand how ALS has impacted their parents, siblings, or other relatives, creating an ongoing emotional and psychological burden.

*"I have assisted in care for members of my family with ALS since I was able to walk. That's how I learned how to walk, pushing wheelchairs for people that needed it. I learned how to read by reading the paper to them because they couldn't hold the paper properly. It shaped who I am."*

*"We grow up with the knowledge that this is the way we are going to die. You just wait till you get it, and we deal with it the best we can."*

*"I had members of family who started showing symptoms when they are in their late 20s, early 30s that ended up dead before their 45$^{th}$ birthday."*

Unlike sporadic ALS, where the diagnosis often comes as a shock, people with familial ALS or a genetic predisposition may spend years anticipating the possibility of developing symptoms. This often leads to heightened anxiety and vigilance, impacting all areas of their lives. When a diagnosis is confirmed, it is often met with a profound sense of inevitability yet also an acute awareness of how quickly the disease can progress based on their family history.

| | |
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| *"For most people, hurting your knee, hurting your shoulder when you're 30 years old is not a concern. But for me, the first thing that runs through my mind is, what if it's ALS? What if it's coming for me? It's constant anxiety, and you just can't stop."* | *"I saw my dad's side of family completely get decimated by ALS, so I knew what I was in for when I got my diagnosis. I knew what it would take for me. No ignorance. Just the weight of knowing exactly what was going to happen."*<br><br>*"I felt like I was always waiting for the other shoe to drop. Everything felt like a warning sign that I couldn't just brush off."* |

Many grapple with the reality that their children, siblings, or extended family members may also be at risk. This adds another layer of complexity to decision-making, particularly regarding genetic testing, reproductive choices, and the emotional weight of potentially passing on the mutation.

| | |
|---|---|
| *"The part that people seem to forget is how the children proceed with our lives. Do we test or not test? Is it worth it to find out and try solving it now, or do we wait for our fate? Imagine staring down the barrel of a gun and playing Russian roulette - only this time, there's two chambers and not ten. These are our odds of having a death sentence that can arrive at any point."* | *"As a mother, there's a lot of guilt that I felt that here I am passing this disease on to my kids. They don't deserve to see me go down like this, and they don't deserve to get this disease, either."*<br><br>*"When you have a genetic form of ALS every conversation about the future comes with extra weight. Do I tell them upfront? Do I wait? What if I want kids – do I risk passing it on?"* |

## 4. Experiences With Currently Available Treatments

Currently there are two available treatments for people living with ALS in Canada.

### Rilutek (riluzole)

72% of **patient** respondents indicated that they are taking/have taken Rilutek (riluzole). 52% of **caregivers/family members** respondents indicated that they support/supported a person living with ALS who used/had used Rilutek.

When asked about the benefits they may observe or have observed from Rilutek and the importance of these benefits, both **patients** and **caregiver/family members** identified slowing disease progression, maintaining ability and increased survival as being very important to them. However, while these outcomes are considered important, several **patients** and **caregivers/family members** indicated they could not definitively say they had observed these benefits.

**Caregiver/family members** were also asked about the benefits they have personally experienced as a result of the person they care/cared for taking Rilutek. Most respondents indicated that they did not experience any significant personal benefit from the treatment. Among those who did, the most commonly reported benefit was having more time with their loved ones due to delayed disease progression.

Most **patients** and **caregivers/family members** reported not experiencing or observing any significant side effects while taking Rilutek, but among those who did, the most significant to manage were tiredness, weakness, drowsiness and nausea. Rilutek is administered orally, which was not an issue for most patients. However, some patients with swallowing difficulties (a common symptom of ALS) reported challenges with administration.

Most of the **patients** and **caregivers/family members** indicated they had not faced difficulty accessing Rilutek. However, some patients indicated difficulty due to a lack of private coverage, strict public funding criteria, out-of-pocket costs and supply shortages.

### Radicava (edaravone)

43% of patient respondents indicated that they are taking/have taken Radicava (edaravone). 20% of **caregiver/family members** respondents indicated that they support/supported a person living with ALS who used/had used Radicava.

When asked about the benefits they may observe or have observed from Radicava and the importance of these benefits, both **patients** and **caregiver/family members** identified slowing disease progression, maintaining ability and increased survival as being very important to them. However, several respondents indicated they could not definitively say they had observed these benefits.

**Caregivers/family members** were also asked about the benefits they have personally experienced as a result of the person they care/cared for taking Radicava, and the majority of respondents indicated that they did not experience any significant personal benefit from the treatment. Among those who did, the most commonly reported benefits were having more time with their loved ones due to delayed disease progression and increased independence for the person they care for, allowing for some reduction in caregiving demands.

**Patients** and **caregivers/family members** reported not experiencing or observing any significant side effects while on Radicava. Radicava can be administered both intravenously and orally, with IV infusions being phased out in favour of the oral formulation. The oral formulation was well tolerated by most patients, though some respondents with swallowing difficulties reported challenges in taking the medication. The shift to oral administration has been generally viewed as a positive change, reducing the travel to infusion clinics and not having to schedule daily activities around their infusion schedule.

Most **patients** and **caregivers/family members** indicated they have not had difficulty accessing Radicava.

### Other Treatments

**Patient** and **caregivers/family member** respondents reported using a variety of additional treatments other than Rilutek, Radicava and tofersen.

Many had previously taken Albrioza, which was previously available in Canada but is no longer accessible following the company's decision to withdraw the therapy after the PHOENIX trial results.

Some respondents mentioned symptom management medication, including Baclofen, mexiletine, gabapentin and pregabalin. Supplements and alternative treatments such as Vitamin B12, probiotics, Omega-3, ashwagandha and magnesium were also mentioned.

Others reported participating in clinical trials for investigational ALS treatments including studies for ibudilast and other experimental treatments.

## 5. Improved Outcomes

Patients and caregiver/family members respondents expressed strong preferences for treatment improvements that go beyond what is currently achieved with currently approved therapies – Rilutek and Radicava. When asked what they would like to see in a new treatment for ALS that is not currently achieved, most patients and caregivers/family members identified the following as improvements they would like to see in future treatments:

- Symptom reversal
- Maintaining function and independence
- Slowing disease progression
- Increased survival

Patient and caregiver/family member respondents expressed a strong desire for treatments that extend survival while maintaining quality of life – with a preference for therapies that not only slow ALS but also restore loss of function whenever possible. Most importantly, respondents emphasized the desire for more time with their loved ones in a way that allows them to continue actively participating in life.

Below are a few examples of answers from **patients** when asked to describe how their quality of life/daily life might be different if those desired improvements were achieved with a new treatment:

*"I would feel more like my old self and do all the thing I used to do. I would feel whole again."*

*"You don't know what you've got til it's gone. I badly would like to walk normally again, work around the*

*"If there was symptom reversal, I would be able to be an active person again and enjoy being outdoors and having a better social life and home life."*

| | |
|---|---|
| *garden, eat without fear of choking, sleep without a mask and on and on the list goes."* | *"Je pourrais continuer de profiter de la vie avec l'amour de ma vie."* |
| *"My kids would see me as "dad" not the guy in the wheelchair who can't even hug or talk to them."* | *"I would regain my independence, be able to look after myself, be less of a burden, be able to look forward with hope."* |

Below are a few examples of answers from **caregivers/family members** when asked to describe how their quality of life/daily life might be or might have been different if those desired improvements were achieved with a new treatment:

| | |
|---|---|
| *"Reversal of symptoms is the dream. I would give anything, other than my children, to still have my husband with me. It's too hard to even think about it, knowing that it can't be."* | *"It would lift a huge emotional and physical burden from caregivers. I get choked up thinking about all the positive impacts these improvements could provide."* |
| *"I would have had more time, and more quality time, with my mom. She spent so much time managing her symptoms, that she needed assistance with much in her life. She would have loved to have more time with her family -- particularly her grandson, in her last year."* | *"We both would feel more in control of our lives. Instead of us taking control of the illness, it took control over our lives and eventually took my husband away."* |
| *"I would give anything to have had even one of those improvements be a possibility."* | *"Ce serait le jour et la nuit. Un traitement qui inverserait les symptômes permettrait de guérir les patients finalement, de sauver les familles d'une grande détresse et de libérer les aidants."* |

When considering trade-offs in choosing a therapy, **patient** and **caregivers/family member** respondents are willing to accept some side effects if the treatment offers clear benefits in maintaining function, slowing progression, or improving survival. However, respondents noted that treatment's accessibility and affordability remain key considerations.

## 6. Experience With Drug Under Review

The drug under review is specifically indicated for people living with ALS who have a pathogenic variant (also known as a mutation) in the superoxide dismutase 1 (SOD1) gene. SOD1 variant accounts for approximately 20% of familial ALS cases and about 2% of all ALS cases overall.

12 survey respondents indicated having accessed tofersen. All participants accessed the therapy through the clinical trial. To better understand the impact of this therapy, 4 individuals with direct experience were interviewed. Their specific treatment experience is summarized in the chart below, and their demographic can be found in Section 2:

| Name | Patient/Caregiver | Diagnosis Date | Drug Access Method | Period on Tofersen |
|---|---|---|---|---|
| **PT** | Patient | February 2016 | Clinical Trial | 2016 – Present |
| **TB** | Patient | April 2018 | Clinical Trial | 2019 - Present |
| **TA** | Patient | July 2020 | Clinical Trial | 2020 - Present |
| **KS** | Bereaved Caregiver | June 2019 | Clinical Trial | 2019 – 2023 |

**Patient** and **caregiver/family members** reported some side effects, though most were manageable. The most cited side effect was migraine, which some experienced in varying frequency. 2 individuals reported more severe side effects, including idiopathic intracranial hypertension and papilledema. However, these were monitored and managed effectively with prescription medication. When asked about the trade-offs between side effects and potential benefits of tofersen, respondents overwhelmingly expressed that the benefits far outweighed the challenges. 2 **patients** who experienced migraines and papilledema spoke directly about these challenges:

*"The side effects are 100% worth the benefit. Everything is pretty minor. Even if I lost my eyesight because of papilledema, I can still be alive. I'd rather be alive."*

*"There is no side effect serious enough that would make me decide not to be on tofersen because then the decision is that I'm going to be stuck in a wheelchair, I'm going to progress, and I'm not going to be here at all. So, I don't think a migraine for a couple of days is a big deal."*

Through interviews and survey responses, 3 treatment outcomes from tofersen emerged as the most meaningful to patients and caregivers. The following outcomes not only shaped their experiences with the therapy but also reflected the values they see as most important in any ALS therapy:

1) Delaying Progression
2) Having more time with loved ones
3) Improving quality of life

Many described their disease progression as slowing or halting, allowing them to preserve function far longer than expected. Others emphasized how stability meant more time with their families while still being able to communicate, engage and remain independent. This also contributed to increased quality of life and improvements in certain functions, such as breathing and mobility. These values are deeply intertwined.

Delayed progression means more time, more time means more opportunities to be present with loved ones, and maintaining function preserves independence and quality of life.

Below are the experiences of patients and caregivers that illustrate the meaningful impact of tofersen in these key areas:

### 1) Delaying Progression

When **PT** got diagnosed with ALS at the age of 34, she was told to go home and get her affairs in order. Having seen 26 members of her family die from ALS, she did not expect to be alive in 2025. She was experiencing muscle wasting, issues with mobility in her ankles and significant cramping that would last 8 hours straight. She started accessing tofersen 8 months after her diagnosis and remained on it ever since. She experienced significant changes in her symptoms, where her speech improved, she started feeling stronger, had less muscle cramping and fasciculations. She could stand on her toes and hold her heels up in the air. In 2023, **PT** developed pneumonia – a condition that is typically detrimental for people living with ALS due to its impact on respiratory function. She expected to see a decline in her breathing abilities. However, when she underwent a breathing test to assess any decline, the results showed that her respiratory function had not declined at all. She says, *"It has been like a miracle for me and my whole family to see finally how well I am doing, improving and maintaining."*

Prior to accessing tofersen in 2019, **TB** participated in multiple clinical trials and did not experience any significant benefit, and his progression continued. At the time of his diagnosis, symptoms were initially confined to his right leg, but the disease progressed quickly to his leg before he started accessing tofersen. However, since accessing tofersen in 2019, **TB** saw his progression stabilize completely and has not experienced any further progression of ALS. He says, *"I think it is like night and day what tofersen is doing to me rather than when I was on trial for Pimozide or when I was prescribed Radicava or Albrioza."*

**TA** accessed tofersen just days after his ALS diagnosis in 2020 at the age of 23. At that time, his symptoms were relatively mild, including cramping and fasciculations. He also struggled with foot-related issues and needed a back brace for support. Through his participation in the clinical trial, he not only avoided progression but saw improvements. His lung function has increased over time, and he no longer uses a back brace or experiences foot-related issues.

**KS** shared the experience of her husband, who accessed tofersen shortly after his ALS diagnosis in 2019. At the time of his diagnosis, he had already experienced some progression, primarily in his dominant right hand, with noticeable atrophy in his hand and forearm. Her husband had the SOD1 A4V/A5V variant, which is a very aggressive form of familial ALS. Given his prognosis, they expected a rapid decline, but his experience with the treatment was dramatically different. Once he started tofersen, his disease progression slowed significantly in his arm and hand and stopped everywhere else. His neurologist had initially prepared them for the likelihood that he would lose shoulder function and struggle to lift his arm. However, for 4.5 years, none of these expected losses occurred. His shoulder function remained intact, and outside of the original weakness in his right hand and forearm, he showed no further progression for the first nine months of the treatment. Unfortunately, as time went on, new symptoms did begin to emerge, and he developed a droop in his smile and some difficulty with swallowing. Yet, his strength remained. Though he ultimately

passed away, he lived far beyond what was expected for his form of familial ALS, where his 2 uncles and dad all died within 9 months of diagnosis. **KS** says, "*He wasn't so progressed to the point where ALS dominated every moment of our existence in a sense. For my kids, he was Dad. Dad couldn't smile or eventually couldn't make jokes. But he was there, and he was very, very present".*

### 2) More Time with Loved Ones

**KS** says, "*The greatest gift tofersen gave my family was time. My husband was diagnosed with ALS when our daughter was just 4 years old. Tofersen allowed him to live 4.5 more years, which made all the difference for our daughter. Instead of only knowing her father through pictures and videos, she was able to have real, concrete memories of him, memories of time spent together, of moments they shared, and of who he was as a person. It wasn't the magic bullet that we all hoped it would be, but short of that, it gave us more time to make memories".*

When **TB** received his ALS diagnosis, he was told to go home and prepare to die. His biggest concern was his children – how much time he would have left with them and whether he would get to see them grow up. But instead of watching this time run out, tofersen allowed him to spend more years with his family, making new memories and being present in his children's lives, who are now 20 and 17. He has been able to witness their milestones, something that once seemed impossible.

### 3) Improving Quality of Life

Being diagnosed with ALS at just 23 years old was devastating for **TA**. But despite that, he still gets to do everything he loves – things most people his age take for granted, like playing volleyball, boating and driving. He continues to work 16-hour days on a farm. TB says, *"If I didn't have access to tofersen, I wouldn't be alive right now for all I know, or maybe in a wheelchair. I would have ended up on disability, not be able to make a living or still be living on my own. I'm still able to pay taxes and be a functioning member of society and that means a lot to me."*

**PT** and **TB** spoke about how they are still able to do things they love, giving them a sense of normalcy and fulfillment. Whether it's golfing, running, hiking, playing hockey or simply spending time with their kids, they can still do the things that bring them joy. They also both talked about the importance of being able to continue to work and contribute to society, maintaining their independence and sense of purpose.

For **PT**, this ability to remain present in her children's lives carries even more profound meaning. Having grown up with a parent who had ALS, she knows firsthand what it is like to take on the role of a caregiver at a young age. She reflects on that experience with gratitude, recognizing that she is still here, still able to be present for her children in a way that ensures they can have a childhood.

**KS** and her family were able to make memories together, not consumed by all the things they were losing. Her husband remained engaged and active throughout this diagnosis, and he was still able to play hockey with their kids, run around outside with them and continue working full-time. KS says *"Short of being the magic bullet, tofersen is keeping people alive and giving them a better quality of life. And isn't that the purpose of any medication?"*

### Public Reimbursement

All **patient** and **caregiver/family members** respondents who have direct experience with tofersen agreed that the drug should be publicly funded and accessible in Canada. Given the rapid progression of ALS, timely access to treatment is critical. Many people with familial ALS have watched their family members navigate the disease with no treatment options and they first understand how devastating the lack of available treatments can be. The idea that a treatment now exists yet may remain out of reach due to cost or reimbursement criteria is deeply concerning.

*"The obvious and undisputable right thing to do is to give people access to this medication through, coverage by the government because it not only saved my husband's life for all those years, but it also made him a lot less expensive to the healthcare system."* **– KS**

*"Tofersen getting publicly funded is a matter of life or death for me and you can't put a price on life."* **- TB**

*"If the drug was not reimbursed, I would never ever be able to get another treatment because of how cost prohibitive it is and that means I'm going to get die a lot quicker."* **- TA**

*"Public reimbursement means we can keep contributing to the society and not just be a burden to the system."* **- PT**

## 7. Companion Diagnostic Test

Genetic testing confirming a pathogenic variant in the SOD1 gene is required for this therapy. Among survey respondents, 56% of **patients** reported that they had accessed genetic testing for the most common ALS-related genes, including SOD1.

Overall, **patients** and **caregivers/family members** shared that the process of getting genetic testing was seamless. Both those interviewed and survey respondents noted that the process was efficient with results provided in a timely manner. Testing was covered for most participants, meaning cost was not a barrier to access. Only 2 participants reported having to pay for genetic testing, which was done out of the country.

While the logistical aspects (cost of testing, accessing the facility, etc.) of genetic testing were generally smooth, the emotional and psychological impact of receiving a test result was significant. Many participants described the stress and anxiety that came with waiting for results. For participants who have children, the results carried even greater weight. Some spoke about the emotional difficulty of knowing they may have passed the variant to their children, while others grappled with the uncertainty of whether their other relatives would eventually face the same diagnosis. Another layer of complexity arose in families where not all members had undergone genetic testing. Some participants described the challenge of being the only one in their family who tested, leaving them with difficult conversations about whether their siblings, children or other family members should also pursue testing.

At the same time, many participants also shared that while waiting for results was difficult, having a definitive answer brought a sense of clarity and control. For some, it validated what they already suspected, while for others, it meant they could start making informed decisions about their future, including discussing treatment options ahead of time. Instead of living in uncertainty, a confirmed diagnosis allowed them to plan.

| | |
|---|---|
| *"When my dad was diagnosed with SOD1 ALS, there was nothing. No treatment, no options, just the knowledge that we had to watch it happen. Now I can get genetic testing and knowing there is an option like tofersen. I can plan, take action and figure out what's next"* | *"For me, getting genetic testing is not about just confirming but it's also about having a path forward. I can make informed decisions and actually do something about it and access a treatment that didn't exist for my grandpa, uncles and cousins."* |

Overall, while access to genetic testing itself was straightforward, coping with the results and their implications was much more complex, with many expressing the need for ongoing emotional support, clear information and resources to help navigate these difficult realities for themselves and their families.

We acknowledge that discrepancies exist in access to genetic testing across Canada. ALS Canada and the Canadian ALS Research Network (CALS), network of clinicians across Canada specializing in ALS research and clinical care, are committed to working together to improve access to genetic testing for ALS, ensuring every person with a SOD1 variant receives the necessary care and treatment. As part of these efforts, ALS Canada launched a pilot project to introduce Canada's first national genetic counsellor dedicated to supporting people affected by ALS. This initiative aims to expand access to genetic counselling services through virtual care, helping individuals understand their genetic risk, navigate testing and explore potential treatment options.

## 8. Anything Else?

When asked if there was anything else respondents wanted to share about their experience with ALS or tofersen that they feel would be important for CDA reviewers to know, **patients** and **caregiver/family members** said:

- *"My life is basically in your hands with this decision. This is my reality. The choice you make will determine whether I have a chance to keep living and spending time with the people I love."*
- *"My dad lost his mother, and 2/3 siblings from this disease. He never got the testing because he didn't have any ability to change the outcome. Drugs were out there but didn't have the necessary improvements on the disease to make him get the testing. To read the stories of tofersen approval elsewhere has given us an amount of hope that is unquantifiable. The potential for there to be something, should that dreadful day ever arrive, is quite literally life changing. We've already lost so much so young, please give us the chance our parents never had in being able to fight this fight."*

- *"I have the polymorphism/mutation of SOD1 but am currently symptom free. My son has the mutation but is currently symptom free. Availability of treatment is very important as this disease has had a great impact not just for the loved one, I cared for but for our entire family."*
- *"Patients and families just want some hope and more quality time together. This disease rips everything away from you, other than your relationships with those you love and who love you and those relationships. There is no luxury of time as a person with ALS. Potential treatments need to be provided as quickly as possible."*
- *"The financial implications of ALS are terrible and if this medication can keep people functioning it is well worth the cost. I have seen people on Tofersen thrive! It is amazing!"*
- *"Premier médicament ayant un effet notoire pour la SLA. Devrait être accessible rapidement étant donné la vitesse à laquelle progresse la SLA. Peut faire une réelle différence pour les gens qui ont la forme génétique SOD1."*
- *"Living with this disease, knowing there is no cure, is an incredibly hopeless and isolating experience. For my mom, it was a slow and heartbreaking withering away, and it's something I wouldn't wish on anyone."*
- *"As my wife died from ALS and had the SOD-1 mutation, I am beyond thrilled that this drug may help my children and grandchildren if they inherit this disease."*
- *"It has been shown that Tofersen greatly slow the progression of people with the SOD1 mutation. There should be no question or reason why this drug should not be available in Canada."*
- *"L'accès au Tofersen a changé ma perception de la maladie et m'a redonné espoir. Avec l'annonce du diagnostic, je préparais ma mort. Maintenant, je fais des projets et j'ose croire que je verrai ma fille grandir. C'était ce qui était le plus douloureux pour moi. Je vis cependant avec la crainte que ma fille hérite de la maladie. Je vis également avec la crainte de ne plus avoir accès au Tofersen. Parce que sans le Tofersen, je meurs. Avec le Tofersen, j'ai l'espoir de vivre plus longtemps et avec une meilleure qualité de vie."*
- *"Tofersen is a hard-fought miracle for families like mine and it's doing exactly what everybody in best case scenarios hoped it would do. It's time for this disease to stop just decimating families the way it has ours."*

Additionally, a **caregiver/family member** respondent, who indicated that they were the primary study coordinator for the therapy's clinical development program, from 2015 until July 2022, from Phase 1, through to completion of VALOR, and oversight of the ongoing open-label extension at one of the Canadian trial sites, shared the following:

- *"Through my involvement on the tofersen clinical trial programs, I have first-hand experience in observing the undeniable, clinically meaningful benefit people living with SOD1-ALS have experienced when treated with tofersen. Tofersen is the first time (and to this day still the only time) in*

*my almost 15-year career working in ALS, where my patients were not dying of ALS, but rather living with ALS. Clinically, my first-hand experience mirrors what the extended combined VALOR + OLE data is telling us: that tofersen has a better effect when initiated early, and there can be both stabilization and improvements across ALSFRS-R, breathing capacity, and quantitative measures of muscle strength. But what does this mean practically, in the real world? Study participants I cared for have gone back to work full-time, coming off of disability; they now ride bikes with their children; walkers are getting dusty in closets, no longer needed; parents are walking their children down the aisle at their wedding. These are all examples of living life, because of tofersen, that patients have shared with me, or that I have seen first-hand. Tofersen is the first truly transformational, disease modifying treatment for ALS, one which undeniably should be offered to, and covered for, every individual with SOD1-ALS."*

## Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   No.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   No.

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

   The companies listed below have sponsored ALS Canada signature events, the ALS Canada Research Forum scientific conference, and provided general donations.

## Table 1: Financial Disclosures

**Check Appropriate Dollar Range With an X. Add additional rows if necessary.**

| Company | $0 to 5,000 | $5,001 to 10,000 | $10,001 to 50,000 | In Excess of $50,000 |
|---|---|---|---|---|
| Amylyx Pharmaceuticals | | | | X |
| Biogen Canada | | | X | |
| Cytokinetics Inc. | | | X | |
| Ionis Pharmaceuticals Inc | X | | | |

| | | | | |
|---|---|---|---|---|
| Mitsubishi Tanabe Pharma | | | | X |
| Innovative Medicines Canada | X | | | |

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

**Name: Ilayda Ulgenalp**
**Position: Senior Manager, Advocacy and Stakeholder Relations**
**Patient Group: ALS Society of Canada**
**Date**: **March 7, 2025**

CADTH

# CADTH Reimbursement Review

## Clinician Group Input

| | |
|---|---|
| CADTH Project Number: | SR0883-000 |
| Generic Drug Name (Brand Name): | tofersen (QALSODY™) |
| Indication: | Treatment for amyotrophic lateral sclerosis (ALS) |
| Name of Clinician Group: | The Canadian ALS Research Network (CALS) |
| Author of Submission: | Rami Massie, MD<br>Associate Professor of Neurology at McGill University, Neurologist at the Montreal Neurological Institute and Montreal General Hospital Neuropathy Clinic |

### 1. About Your Clinician Group

The Canadian ALS Research Network (CALS) is a national network of clinicians at academic healthcare centers across Canada who specialize in ALS research and clinical care. Established in 2008, CALS has earned a strong reputation within Canada and internationally for its ability to rapidly and effectively recruit participants and complete clinical studies, making it a trusted partner in global clinical trials for Canadians living with ALS. CALS's mission is to connect ALS clinical research centers across Canada, enhance participation in clinical research for both patients and clinics, and expand access to innovative treatments and trials. Through its collaborative approach, CALS strengthens Canada's position as a global leader in ALS clinical research and provides hope for a future with improved treatments and care for those living with ALS.

### 2. Information Gathering

All members of CALS were invited to participate in a Zoom meeting to discuss key questions related to this submission. This Zoom meeting took place on Thursday, January 30, 2025, and included 8 CALS members from across Canada. Each question was discussed until consensus was reached regarding the wording of responses to the template questions. The CALS Manager (Colleen Doyle, MSc; Director of Canadian Research, ALS Canada) was engaged to work with Dr. Rami Massie to prepare a draft for circulation to all members of CALS. Where appropriate, revisions based on feedback were incorporated into the final draft. In addition, the following key references were used for background information and to describe the current standard of care for ALS:


1. Shoesmith, C., Abrahao, A., Benstead, T., et al. (2020). Canadian best practice recommendations for the management of amyotrophic lateral sclerosis. *Canadian Medical Association Journal*, 192(46), E1453–E1468.
2. Miller, T., Cudkowicz, M., Shaw, P., et al. (2020). Phase 1–2 trial of antisense oligonucleotide tofersen for SOD1 ALS. *New England Journal of Medicine*, 383(2), 109–119.
3. Miller, T. M., Cudkowicz, M. E., Genge, A., et al. (2022). Trial of antisense oligonucleotide tofersen for SOD1 ALS. *New England Journal of Medicine*, 387(12), 1099–1110.
4. Miller, T. M., Cudkowicz, M. E., Genge, A., et al. (2022, June 3). Evaluating efficacy and safety of tofersen in adults with SOD1-ALS: Results from the Phase 3 VALOR trial and open-label extension. Presentation at the European Network to Cure ALS (ENCALS) Meeting, Edinburgh, Scotland.

5. Weishaupt, J. H., Meurer, W., Eßer, P., et al. (2023). Effects of tofersen treatment in patients with SOD1-ALS in a "real-world" setting – A 12-month multicenter cohort study from the German early access program. *eClinicalMedicine,* 58, Article 101920.

6. Meyer, T., Schumann, P., Weydt, P., et al. (2023). Neurofilament light-chain response during therapy with antisense oligonucleotide tofersen in SOD1-related ALS: Treatment experience in clinical practice. *Muscle & Nerve*, 67(6), 515–521.

7. Sabatelli, M., Cerri, F., Zuccarino, R., et al. (2024). Long-term treatment of SOD1 ALS with tofersen: A multicentre experience in 17 patients. *Journal of Neurology*, 271(8), 5177–5186.

8. Smith, S.E., McCoy-Gross, K., Malcolm, A., et al. (2025). Tofersen treatment leads to sustained stabilization of disease in SOD1 ALS in a "real-world" setting. *Ann Clin Transl Neurol*. 2025 Jan 9. doi: 10.1002/acn3.52264. Epub ahead of print.

9. Joint Nordic HTA-Bodies. (2025). Health technology assessment report: Qalsody (tofersen) solution for injection. Published January 17, 2025.

## 3. Current Treatments and Treatment Goals

Amyotrophic lateral sclerosis (ALS) is a debilitating and progressive disease characterized by the degeneration of motor neurons in the brain and spinal cord (1). Over time, patients experience severe weakness in limb, bulbar, and respiratory muscles, leading to loss of autonomy and reliance on assistive devices such as wheelchairs, gastrostomy feeding tubes, and noninvasive ventilatory support. Death due to respiratory failure typically occurs within five years of diagnosis. For the estimated 4,000 Canadians living with ALS, treatment options remain extremely limited.

The cause of ALS remains unknown in the vast majority of patients. Approximately 85-90% of patients have no family history and no identified genetic mutation. They are considered to have sporadic ALS. However, about 10-15% of cases are found to have a hereditary etiology. More than 40 genes have been associated with ALS, but mutations in four of them – SOD1, C9ORF72, TARDBP, and FUS – represent the main causes of autosomal dominant ALS.

Currently, the only disease-modifying treatments available in Canada include riluzole, intravenous (IV) edaravone, and oral edaravone. Riluzole, which inhibits excessive motor neuron firing by targeting glutamate, extends survival by a median duration of three months. IV edaravone reduces oxidative stress and has been shown to slow the rate of clinical decline by 33% in a select group of patients with preserved respiratory function and a disease duration of less than two years. More recently, oral formulation of edaravone has been developed and shown to have similar pharmacokinetics and bioequivalence to the IV formulation. In June 2022, Health Canada approved AMX0035 (marketed as Albrioza) for the treatment of ALS. However, in April 2024, the manufacturer announced its intention to withdraw Albrioza from the Canadian market due to the failure of a key Phase 3 clinical trial, and it is no longer available in Canada. The therapies currently available to Canadians living with ALS provide only modest benefits, underscoring the urgent need for new treatment options. There are no specific treatments for hereditary ALS that have been approved.

While symptom management and quality-of-life optimization remain priorities in patient care, as emphasized in the Canadian Best Practice Recommendations (1), this submission focuses on disease-modifying therapies aimed at slowing disease progression. An ideal treatment would prevent or delay disease progression (i.e., motor neuron degeneration), slow decline in lung capacity, reduce severity of symptoms, minimize adverse events, reduce loss of cognition, improve health-related quality of life, and ultimately increase patients' ability to continue to work, reduce the burden on caregivers, and prolong life. An ideal treatment would also target the root causes of ALS and given ALS's heterogeneity, be personalized to meet the unique needs of each patient.

## 4. Treatment Gaps (unmet needs)

### 4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Currently, the mainstay of care for patients diagnosed with ALS consists of interventions and supports to manage symptoms, such as nasogastric feeding, prevention of aspiration, and ventilatory support. There are no approved treatments to reverse the disease or arrest the progression of neurological decline. Currently approved treatments have only shown very modest benefits in slowing disease progression. Riluzole confers a survival benefit of roughly 3 months, while IV (and possibly oral) edaravone slow disease progression by about 33% in a select patient population.

It is clear to clinicians treating ALS patients that the development of new neuroprotective treatments is required to provide a multimodal approach to address the various mechanisms of action of the disease. There is an urgent need for more personalized, disease-modifying treatments that target the root causes of ALS and provide lasting benefits. The advancement of precision medicine and personalized care plans will be crucial in improving the lives of Canadians living with ALS.

## 5. Place in Therapy

### 5.1. How would the drug under review fit into the current treatment paradigm?

Tofersen, an antisense oligonucleotide therapy targeting SOD1 mRNA, is a potentially transformative treatment for individuals with ALS caused by mutations in the SOD1 gene (15–25% of familial cases and 1-2% of ALS cases overall). More than 200 pathogenic or likely pathogenic mutations in SOD1 have been identified. Tofersen is the first therapy directly addressing a well elucidated pathophysiologic mechanism of disease in ALS.

Tofersen is delivered intrathecally and works by reducing the production of the toxic SOD1 protein, which is implicated in ALS progression. In a Phase 1/2 ascending-dose trial, the highest dose (100 mg) reduced CSF SOD1 concentration by 33% compared to placebo (2). Exploratory outcomes suggested a trend toward slowing decline in the ALS Functional Rating Scale–Revised (ALSFRS-R) score, slow vital capacity, and handheld dynamometry.

In the follow-up Phase 3 VALOR trial, the 100 mg dose of tofersen was tested. Although the study included a pre-defined balance of faster-progressing and slower-progressing participants, the primary analysis population was adults with faster-progressing SOD1 ALS. The study did not show statistical significance for the primary end point (change from baseline to week 28 in the total score on the ALSFRS-R in this subpopulation) (3). Given the lack of difference in the primary outcome variable, differences in secondary outcomes were considered nonsignificant per study protocol. However, SOD1 CSF concentrations were reduced by 29% from baseline in the faster progressing group (as compared to an increase by 16% for those who received placebo) and reduced by 40% in the slower progressing group (as compared to a reduction of 20% for those receiving placebo). In the faster-progressing groups, plasma neurofilament light chain (NfL) decreased by 60% in the tofersen group compared with a 20% increase in the placebo group. Both the SOD1 CSF concentration and the serum plasma NfL levels were prespecified secondary endpoints. Exploratory outcomes also showed potential positive effects on motor function, respiratory function, muscle strength, and quality of life.

A prespecified analysis of the data from VALOR and the open-label extension (OLE) after 52 weeks was performed and showed more robust effects in patients who started tofersen earlier, “early-start,” compared to those who started later, “delayed-start” (3,4). SOD1 levels remained reduced, and the early-start group showed significant improvements in ALSFRS-R, respiratory function, muscle strength, and quality of life after 12 months. The delayed-start group also showed improvements in NfL levels, with trends towards stabilized or improved function. A 12-month German cohort study from the tofersen early access program corroborated these findings, showing reductions in NfL serum levels (5). Further studies investigating long-term treatment of SOD1-ALS with tofersen and NfL treatment response support the notion of tofersen having disease-modifying activity (6,7,8,9).

These significant differences in outcome measures observed in the 12-month OLE population suggests that the 28-week study duration may not have been long enough to capture the full clinical benefits, as SOD1 levels take time to decrease (with a half-life of approximately 30 days in humans, and a reduction in SOD1 protein concentration most apparent after 57 days) (2). As a result, subsequent decreases in NfL and clinical benefits are expected to be delayed. Furthermore, the strategy of including only fast-progressors in the primary endpoint analysis in order to enrich the dataset failed as their progression was 3 times slower in the placebo group of this study compared to their progression in the phase 1/2 study.

Tofersen is generally well-tolerated, although lumbar puncture-related adverse events were common. The mechanism of action of tofersen complements existing therapies, which aim to slow disease progression through different mechanisms. Tofersen would be used in combination with these therapies for individuals with SOD1-ALS, offering a more comprehensive treatment approach by targeting multiple pathophysiologic mechanisms.

There is no rationale for a specific treatment order in ALS, as current therapies are not curative, and there are no reliable biomarkers for treatment success on an individual level. Patients should not be required to "fail" on one therapy before starting another, as this would subject them to irreversible progression. The concept of "failure" is not applicable in ALS, as the disease is terminal, and existing treatments slow but do not prevent progression.

## 5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Tofersen is best suited for all individuals who carry pathogenic or likely pathogenic variants in the SOD1 gene, and display weakness felt to be related to ALS by an ALS specialist. This specific subset of ALS patients (1-2% of all ALS cases) is most likely to benefit from treatment, as tofersen targets an underlying genetic cause of the disease by reducing the production of toxic SOD1 protein. One may also consider treating patients with variants of uncertain significance, if they seem to segregate with the disease. The drug has not been demonstrated to be suitable for individuals with ALS caused by other genetic mutations or non-genetic forms of ALS.

Patients must first display weakness related to ALS, for which no specific diagnostic biomarker exists. As such, the diagnosis is made based on a patient's history, physical examination, electrodiagnostic examination, and exclusion of alternative diagnoses. All patients diagnosed with ALS should undergo genetic testing for, at minimum, the most common ALS-related genes, including SOD1. Once an SOD1 mutation is confirmed through genetic testing, patients should be considered for the drug under review immediately.

Although the randomized controlled trial separated patients in fast-progressors and others, both groups are likely to benefit from the drug, as shown by the reductions in SOD1 levels in the CSF and neurofilament levels in the serum for the two patient groups. However, CSF SOD1 levels and serum neurofilament levels are not tests performed routinely in clinical practice, nor are they available across all provinces, and should not be used to assess a patient’s response on an individual level. Patients with very advanced stages of ALS, particularly those who are dependent on ventilatory support and have no residual motor function in the limbs, may be less likely to benefit from treatment, as they may not have any residual motor neurons to salvage. However, OLE data demonstrated improving respiratory function in the early start cohort, suggesting that people with poor respiratory function (i.e. FVC/SVC < 50%) are still likely to benefit from treatment.

Since access to genetic testing is variable based on the province in which the patient lives, genetic testing for SOD1 gene mutations may be delayed in some areas, which will affect eligibility of the patient for this treatment. Coverage by Biogen of this companion genetic test in provinces where access is difficult would be helpful.

The term “treatment response” for ALS cannot be strictly defined, as the goals of treatment are to slow the degeneration of motor neurons. Disease progression is individual, and monitoring for outcomes (such as slowing disease progression) is not feasible on an individual basis due to disease heterogeneity (hence the reliance on clinical trial results). As such, a reasonable treatment strategy should consist of starting the drug and following the patient at regular intervals until a time when the patient’s goals of care change (to a less interventional/more palliative approach), or the patient and his/her physician decide to discontinue the drug because of an unfavorable risk/benefits ratio.

## 5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

As noted above, a “treatment response” for ALS cannot be strictly defined, as the goals of treatment are to slow the degeneration of motor neurons. Furthermore, the rate of disease progression varies between individuals, and as of yet, there are no biomarkers to discern how a treatment is "working" within a single patient. Therefore, current standard of care involves monitoring the patient at regular intervals, assessing parameters such as physical, functional, emotional, and quality-of-life status. Due to the relentlessly progressive nature of ALS, a patient's clinical status is routinely monitored every 3 to 4 months, as per the Canadian best practice

guidelines, although some patients with slow progression are seen in clinic only once a year (1). At these visits, patients' tolerance for the drug under review, as well as their goals of care, should be explored.

### 5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

It is important for patients to have regularly scheduled visits with their ALS care team to review their clinical status, benefits, and goals of treatment. As the disease progresses and the patient becomes severely disabled, it is reasonable to expect that treatment goals will change. While there is no evidence suggesting that the drug will not provide benefit beyond a specific endpoint, the drug could be continued until the focus of care shifts to palliative and supportive treatment. Once the patient requires total care and near-continuous ventilation, indicating that few motor neurons remain, it would be logical to stop the drug, as it would no longer provide benefit. The patient's goals of care should be prioritized in this decision.

### 5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

The drug under review should be prescribed by a neurologist or physiatrist with experience in the care of patients with ALS.

## 6. Additional Information

The authors of this submission acknowledge the pressures on Canada's publicly funded healthcare system and the need to rationalize resources. However, we are confident that both physicians treating patients with ALS and the patients themselves will be able to make informed decisions to ensure that the drug under review is used for those who stand to benefit the most. Therefore, we believe that tofersen should be recommended for public reimbursement in Canada.

## 7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   The CALS Manager (Colleen Doyle, MSc; Director of Canadian Research, ALS Canada) was engaged to work with Dr. Rami Massie to prepare a draft for circulation to all members of CALS. Where appropriate, revisions based on feedback were incorporated into the final draft.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

## Declaration for Clinician 1

**Name:** Dr. Rami Massie
**Position:** Associate professor of neurology
**Date:** 18-02-2025

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

**Table 1: Conflict of Interest Declaration for Clinician 1**

| | Check appropriate dollar range* | | | |
|---|---|---|---|---|
| **Company** | **$0 to $5,000** | **$5,001 to $10,000** | **$10,001 to $50,000** | **In excess of $50,000** |
| Biogen | X | | | |
| Mitsubishi Tanabe Pharma | X | | | |
| Amylyx | X | | | |

* Place an X in the appropriate dollar range cells for each company.

## Declaration for Clinician 2

Name: Dr. Christen Shoesmith
Position: Neurologist, Medical Director of the ALS Clinic at London Health Sciences Centre
Date: 01-03-2025

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

**Table 2: Conflict of Interest Declaration for Clinician 2**

| | Check appropriate dollar range* | | | |
|---|---|---|---|---|
| **Company** | **$0 to $5,000** | **$5,001 to $10,000** | **$10,001 to $50,000** | **In excess of $50,000** |
| No relevant disclosures | | | | |

* Place an X in the appropriate dollar range cells for each company.

## Declaration for Clinician 3

Name: Dr. Gordon Jewett
Position: Neuromuscular neurologist and Assistant professor, University of Calgary
Date: 21-02-2025

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

**Table 3: Conflict of Interest Declaration for Clinician 3**

| | Check appropriate dollar range* | | | |
|---|---|---|---|---|
| **Company** | **$0 to $5,000** | **$5,001 to $10,000** | **$10,001 to $50,000** | **In excess of $50,000** |
| Argenx Pharmaceuticals | X | | | |
| Amylyx Pharmaceuticals | X | | | |

* Place an X in the appropriate dollar range cells for each company.

## Declaration for Clinician 4

Name: Dr. Nicolas Dupré
Position: Neurologist
Date: 20-02-2025

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

**Table 4: Conflict of Interest Declaration for Clinician 4**

| | Check appropriate dollar range* | | | |
|---|---|---|---|---|
| **Company** | **$0 to $5,000** | **$5,001 to $10,000** | **$10,001 to $50,000** | **In excess of $50,000** |
| No relevant disclosures | | | | |

* Place an X in the appropriate dollar range cells for each company.

## Declaration for Clinician 5

Name: Dr. Lorne Zinman
Position: Professor of Neurology, University of Toronto
Date: 03-03-2025

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

**Table 5: Conflict of Interest Declaration for Clinician 5**

| | Check appropriate dollar range* | | | |
|---|---|---|---|---|
| **Company** | **$0 to $5,000** | **$5,001 to $10,000** | **$10,001 to $50,000** | **In excess of $50,000** |

| | | | | |
|---|---|---|---|---|
| Biogen | X | | | |
| Mitsubishi Tanabe Pharma | | X | | |
| Cytokinetics | X | | | |

* Place an X in the appropriate dollar range cells for each company.

## Declaration for Clinician 6

Name: Dr. Agessandro Abrahao Jr
Position: Assistant Professor and Neurologist, University of Toronto
Date: 03-03-2025

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

**Table 6: Conflict of Interest Declaration for Clinician 6**

| | Check appropriate dollar range* | | | |
|---|---|---|---|---|
| **Company** | **$0 to $5,000** | **$5,001 to $10,000** | **$10,001 to $50,000** | **In excess of $50,000** |
| Mitsubishi Tanabe Pharma Canada | | X | | |
| Amylyx | | X | | |

* Place an X in the appropriate dollar range cells for each company.

## Declaration for Clinician 7

Name: Dr. Peter Dobrowolski
Position: Assistant Clinical Professor of Neurology
Date: 03-03-2025

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

**Table 7: Conflict of Interest Declaration for Clinician 7**

| | Check appropriate dollar range* | | | |
|---|---|---|---|---|
| **Company** | **$0 to $5,000** | **$5,001 to $10,000** | **$10,001 to $50,000** | **In excess of $50,000** |
| No relevant disclosures | | | | |

* Place an X in the appropriate dollar range cells for each company.

## Declaration for Clinician 8

Name: Dr. Oliver Blanchard
Position: Neuromuscular Neurologist
Date: 26-02-2025

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

**Table 8: Conflict of Interest Declaration for Clinician 8**

| | Check appropriate dollar range* | | | |
|---|---|---|---|---|
| **Company** | **$0 to $5,000** | **$5,001 to $10,000** | **$10,001 to $50,000** | **In excess of $50,000** |
| Quralis | X | | | |
| Amylyx | X | | | |
| Biogen | X | | | |
| Corcept Therapeutics | X | | | |
| Verge Genomics | X | | | |
| UCB Pharma | | X | | |
| Johnson and Johnson | | X | | |
| argenx | | X | | |
| Alexion Canada | X | | | |

* Place an X in the appropriate dollar range cells for each company.

## Declaration for Clinician 9

Name: Dr. Grayson Beecher
Position: Assistant Professor, Division of Neurology, Department of Medicine, University of Alberta
Date: 03-03-2025

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

**Table 9: Conflict of Interest Declaration for Clinician 9**

| | Check appropriate dollar range* | | | |
|---|---|---|---|---|
| **Company** | **$0 to $5,000** | **$5,001 to $10,000** | **$10,001 to $50,000** | **In excess of $50,000** |
| argenx | X | | | |

* Place an X in the appropriate dollar range cells for each company.

## Declaration for Clinician 10

**Name:** Dr. Theo Mobach
**Position:** Neuromuscular Neurology, ALS Clinic Directory Calgary
**Date:** 05-03-2025

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

**Table 10: Conflict of Interest Declaration for Clinician 10**

| Company | Check appropriate dollar range* | | | |
|---|---|---|---|---|
| | $0 to $5,000 | $5,001 to $10,000 | $10,001 to $50,000 | In excess of $50,000 |
| Biogen | | X | | |
| Amylyx | X | | | |
| Quralis | | X | | |

* Place an X in the appropriate dollar range cells for each company.

## Declaration for Clinician 11

**Name:** Dr. Jocelyn Zwicker
**Position:** Neurologist
**Date:** 05-03-2025

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

**Table 11: Conflict of Interest Declaration for Clinician 11**

| Company | Check appropriate dollar range* | | | |
|---|---|---|---|---|
| | $0 to $5,000 | $5,001 to $10,000 | $10,001 to $50,000 | In excess of $50,000 |
| Amylyx | X | | | |
| Mitsubishi Tanabe Pharma | X | | | |
| ALS Canada Discovery Grant | | | | X |

* Place an X in the appropriate dollar range cells for each company.

## Declaration for Clinician 12

Name: Dr. Ari Breiner
Position: Assistant Professor, University of Ottawa
Date: 05-03-2025

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

**Table 12: Conflict of Interest Declaration for Clinician 12**

| | Check appropriate dollar range* | | | |
|---|---|---|---|---|
| **Company** | **$0 to $5,000** | **$5,001 to $10,000** | **$10,001 to $50,000** | **In excess of $50,000** |
| No relevant disclosures | | | | |

* Place an X in the appropriate dollar range cells for each company.

## Declaration for Clinician 13

Name: Dr. Vincent Picher-Martel
Position: Assistant professor and Neurologist
Date: 06-03-2025

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

**Table 13: Conflict of Interest Declaration for Clinician 13**

| | Check appropriate dollar range* | | | |
|---|---|---|---|---|
| **Company** | **$0 to $5,000** | **$5,001 to $10,000** | **$10,001 to $50,000** | **In excess of $50,000** |
| Alexion | X | | | |

* Place an X in the appropriate dollar range cells for each company.

## Declaration for Clinician 14

Name: Dr. Colleen O'Connell
Position: Medical Director, Stan Cassidy Centre for Rehabilitation
Date: 06-03-2025

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

**Table 14: Conflict of Interest Declaration for Clinician 14**

| | Check appropriate dollar range* | | | |
|---|---|---|---|---|
| **Company** | **$0 to $5,000** | **$5,001 to $10,000** | **$10,001 to $50,000** | **In excess of $50,000** |

| | | | | |
|---|---|---|---|---|
| Biogen | X | | Clinical trial paid to institution | |
| Mitsubishi Tanabe Pharma | | X | | |

* Place an X in the appropriate dollar range cells for each company.