CADTH

Patient Input Template for CADTH CDR and pCODR Programs

Name of the Drug and Indication	**Radicava (edaravone) for amyotrophic lateral sclerosis (ALS)**
Name of the Patient Group	**ALS Society of Canada**

1. About Your Patient Group

Founded in 1977, the ALS Society of Canada (ALS Canada) and its provincial partners are dedicated to supporting Canadians living with ALS and investing in research to achieve a future without ALS. We are a registered charity that receives no government funding – all of our services and research are funded through the generosity of donors. ALS Canada advocates federally, provincially and locally for better government support and access within the healthcare system for people touched by ALS.

2. Information Gathering

To better understand the experiences of the ALS community, ALS Canada in coordination with ALS Societies across Canada circulated a survey about patient and caregiver experiences with the disease, current treatment options, and experience with or expectations of Radicava (edaravone) in both English and French from June 11-24, 2018. There were a total of 574 responses: 432 in English and 142 in French. Of the total responses, 208 (36.2%) were from people living with ALS (hereby referred to as patients), 181 (31.5%) were from caregivers, and 200 (34.8%) were from people who lost a loved one to ALS. (Please note that some respondents brought more than one perspective to the survey.)

Among the respondents who chose to identify their gender, 385 respondents (67.1%) were female and 186 (32.4%) were male. Respondents spanned many ages: younger than 15 (1 respondent or 0.2%), between 15-25 years old (20 or 3.5%), between 25-35 (54 or 9.4%), between 36-45 (81 or 14.1%), between 46-55 (129 or 22.5%), between 56-65 (153 or 26.7%) and older than 65 (136 or 23.7%).

Of the respondents, 26 patients had experience with edaravone and an additional 20 were current and former caregivers for someone living with ALS who had experience with edaravone. This is not entirely unexpected as there have been no clinical trials of edaravone in Canada and those who had experience with the medication had to access edaravone from outside Canada. It is most common for patients to access the generic form of the drug – or potentially the Japanese brand version, Radicut. As such, this submission uses the term “edaravone” throughout.

ALS Canada also held two focus groups with a combined 22 people in English and one focus group of 2 people in French. One participant noted: *“Few of us participating are early enough in our progression to benefit from eventual approval in a year or so, and many of us won’t live long enough to see it happen. Yet we all participated with hope — hope that we might help others avoid the ’loss of living’ that is ALS.”*

3. Disease Experience

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. Every year, ALS kills approximately 1,000 Canadians and a similar number are diagnosed. There are currently about 3,000 people living with ALS in Canada. There is no cure and in Canada, only one treatment option currently exists (riluzole), with minimal impact on disease course. The

impact of the disease on patients and their families is astounding: *"ALS changes everything"* and *"took over my life."* Another described it as *"like running full speed on a treadmill but still moving backwards."*

A diagnosis of ALS and the realities of living with the disease profoundly affect people's lives. Just over half (54.3%) of patients and 191 (79.9%) of caregivers reported that family life is significantly negatively affected or completely changed. In particular, one caregiver described the enduring impact of intensively caring for their mother, who had passed away: *"Taking care of my [m]other and seeing her get weaker so fast has mentally and physically taken a huge impact on myself. I burnt myself out taking care of her and 1 1/2 years after her death I'm still not back to myself.… I've been told [by others] that they miss the old me."*

For many respondents (72 or 41.6% of patients and 148 or 62.9% of caregivers), the relationship between the patient and their caregiver, spouse and/or partner was significantly negatively impacted or completely changed. Much of this is due to the intense and sustained efforts of providing care during the course of ALS. Work or school life was also significantly affected for 111 patients (65.7%) and 153 caregivers (65.9%), including job reassignments for some: [translation] *"I am less physically strong so I get tired more quickly and in my job as a police officer had to be re-assigned to a light-duty office worker."*

Patients and caregivers also reported a major negative impact or complete change in other aspects of their lives including: travel options (120 or 84.4% of patients; 182 or 75.8% of caregivers), hobbies (126 or 72.4% of patients; 151 or 65.7% of caregivers), their intimate relationships and sex life (109 or 63.4% of patients; 128 or 56.6% of caregivers), and their social life (107 or 61.5% of patients; 167 or 70.2% of caregivers).

People living with ALS experience a wide variety of symptoms, which progress over time as they become increasingly paralyzed. Patients, their families and caregivers must constantly adjust to additional losses of function. As a caregiver stated: the *"[d]isease progressed rapidly. Literally one day [my loved one] could swallow [and the] next day couldn't. [We had n]o chance to get [a] feeding tube."* One patient noted: *"Every day I find something else I cannot do and I mourn the loss."* For another patient, ALS is like *"…living on the edge of a precipice. I do not know when will be the last time I will be able to walk, or play with my son."* Another described the experience as *"[s]lowly being imprisoned in a non-functioning body."*

Out of 175 patient respondents, 101 (57.7%) experienced difficulty **breathing**. Patients also told us that they experienced cramping and weakness in their diaphragm. **Choking** episodes were experienced by 102 patients (58.3%) and 123 (70.3%) experienced **excess saliva or dry mouth**. These symptoms have a significant impact on patients' lives: they are *"losing autonomy bit by bit. Humiliated in public by the drooling and inability to eat properly and drink. Get thirsty but difficult to drink. Inability to prepare, cook and bake because of the drooling."*

Eighty-four patients (48.0%) reported experiencing reduced **food intake and weight loss**. To eat and drink properly, 81 (46.3%), patients require assistance with eating, 58 (33.1%) drinking, 133 (76.0%) preparing food and 65 (37.1%) feeding themselves. The assistance required by patients also affects the lives of caregivers, who stated that their day-to-day lives were significantly negatively affected or completely changed by providing assistance to eat (143 or 59.3%), drink (132 or 54.8%), prepare food (156 or 64.7%), and for those who could not feed themselves (147 or 61%). The use of feeding tubes also affected caregivers and families: *"[f]amily dinners changed and I had a hard time eating at the table enjoying a delicious meal while he was fed through a tube. His empty chair at the dinner table was an emptiness like no other – even though he was just in the other room."*

Losing control of one's bladder or bowels is a difficult but surprisingly common experience for patients (100 patients or 57.1%). As a result, patients often require assistance with self-care, including using the toilet (78 or 44.6%) and bathing (109 or 62.3%). In providing this care, caregivers' daily lives are significantly negatively affected or completely changed when the person they are caring for needs assistance to use the toilet (151 or 62.7%) or bathe (169 or 70.1%). As one patient shared: *"I have community care three times a day to get me up and toileted and sitting in the chair; fed at the middle of my day and either up from a nap or down for a nap and toileted; and at bedtime to get me toileted and dressed [for] bed. I have diapers / pull-ups on all the time as my control is variable and it involves what and when I eat…. I've eliminated a number of foods that can either promote relaxing of my bowels or overwhelming of my bladder."* Caregivers often have to plan their day around such needs: *"I am unable to leave the house freely anymore. Even to go grocery shopping or other necessary errands places stress*

on me because he is unable to toilet himself .... For now, I need to plan the timing of outings and make them [as] quick as possible."

As ALS causes motor neurons to stop communicating with the muscles in the body, muscles begin to atrophy from disuse. Consequently, **muscle fatigue and discomfort** are ever-present, with 168 patients (96.0%) experiencing decreased muscle tone, which affects daily life for patients and caregivers: "*I cannot lift my arms above my chest, so [that makes it difficult to do] all hygiene, showering, dressing, [and my] hair."* **Muscle cramps and twitches** were experienced by 167 patients (95.4%) and 159 patients (90.9%) experienced muscle stiffness or rigidity. These symptoms made it difficult to grip or hold things for 156 patients (89.1%) and muscle exhaustion caused fatigue for 171 patients (97.7%*): "I have no arm strength so I can't even carry a coffee in one hand. I can't hold a knife properly so all my food has to be cut into bite-size pieces. It feels like going through life with a 25-pound weight on each arm. Even trying to get my glasses on and off is exhausting."* Several respondents noted that one of the daily impacts of ALS is the **increased time and effort** that it takes people to do things that were once simple for them. Other fatigue affected 150 patients (85.7%), however despite greater fatigue, the discomfort brought on by ALS can negatively affects sleep, with 129 patients (73.7%) experiencing insomnia caused by discomfort. They also experienced headaches, stomach problems and itchiness. Not least of all, 134 patients (76.6%) experienced pain (muscle and nerve).

The disease's effect on muscles resulted in **joint discomfort and stiffness** for 152 patients (86.9%) and the inability to move around also affected circulation and resulted in **leg and foot swelling** for 108 patients (61.7%). However, 123 patients (70.3%) needed assistance with exercise and therapy, which 161 (66.8%) of caregivers noted significantly affected or completely changed their lives. Care and assistance for walking (126 or 72.0%), transitions from sitting to standing (96 or 54.9%) and from lying to sitting (91 or 40.6%) significantly negatively affected or completely changed the daily lives of 182 (75.5%), 160 (66.4%), and 153 (63.5%) of caregivers respectively.

As ALS progresses, people have greater difficulty **communicating,** with 118 patients (67.4%) having difficulty forming words or projecting their voice and 95 patients (54.3%) having difficulty communicating verbally. To address this, 78 patients (44.6%) received assistance to speak and 87 (49.7%) to type or write, which significantly affected or completely changed the daily lives of 140 (58.1%) and 149 (61.8%) caregivers, respectively. One respondent noted the significance of diminished communication, including their *"inability to call friends and family members[,] to attend dinners and parties with friends and to take part in group discussions."* As ALS progresses and patients lose the ability to speak, it is difficult for the patients and their families: [translation] *"I cannot even express myself with that slow, serious voice that is mine now."* Patients and their families and caregivers must constantly adjust to additional losses of function.

In terms of the **emotional and mood** impacts of ALS, 111 patients (63.4%) experienced apathy or depressive behaviour, 120 (68.6%) experienced a lack of ability to control their emotions, 72 (41.1%) sometimes experienced inattention, 44 (25.1%) sometimes experienced obsessive or unusual behaviour, and 36 (20.6%) experienced mood changes or frontotemporal dementia symptoms. ALS causes *"emotional distress"* and *"big stress"*, has had a *"major impact on their faith and beliefs"*, and has *"completely changed"* some patients' mental health.

Caregivers' mental health is also affected, with some developing major anxiety and depression or finding *"depression and anxiety about the future [are] ever present"*. One caregiver said *"[m]entally I was in mourning for my [m]other starting with her diagnosis. … I know what it's like to not have hope."* Caregivers *"felt [we weren't] doing enough"* and found it *"so hard on the family to watch [our loved one] deteriorate".* The lack of options made some caregivers feel *"helpless"* and *"hopeless"* and the *"[l]evel of psychological distress was palpable […] financial and psychological impact and burden are unbelievable with a diagnosis of ALS."* Other caregivers shared the impact of ALS on their mental health*: "[taking care of a family member with ALS] brought forth guilt, anxiety, loss of self-worth [and] grief"* and *"[d]aily care, anxiety and fatigue were at their peak. I had no social life, I was exhausted and I had insomnia. Fear and misunderstanding were always present, which prevented me from going about my business headlong. My family life has been upset and we feel trapped ..."* On a day-to-day basis, it was *"like living on eggshells"* - caregivers were *"always on alert for the next thing to happen"* and were *"worried about the effects of the disease, how [they] were going to manage it all, educating [them]selves, securing assistive devices, [and] research[ing a] care home when the time came."*

ALS also affects **finances**. The average cost of ALS to a family is between $150,000-$250,000.[1] The financial situations of 86 (49.1%) patients and 129 (54.4%) caregivers were significantly negatively affected or completely changed. One patient described the impact: *"I am in more debt [than] I care to admit and that's just from having to buy medical equipment. Not accounting for home modifications and transportation methods [and g]as for appointments that are out of town."* For others, the impact is more dire: *"[I c]an't afford anything"*; *"often go hungry"*; had my *"car repossessed"*; and *"lost my home 'cause I couldn't afford it."* Many patients and caregivers are unable to work in order to cope with the demands of the disease, while others have to adjust their work schedule or hours.

4. Experiences With Currently Available Treatments

There is no cure for ALS and at this time the only medicine that has received market authorization from Health Canada to extend survival for those with ALS is riluzole. Due to the lack of drugs that modify the disease or delay its progression, the survey responses suggest that many patients are accessing a variety of experimental or off-label medications from outside Canada because there are no other options available.

In particular, of 163 patient respondents, 77 (49.8%) used riluzole to treat their ALS and 2 patients (1.2%) reported their physicians are considering prescribing it to them. Out of 203 caregiver respondents, 73 (36.0%) said the person they are or were caring for used riluzole. Of those who described their experiences with riluzole, some patients noted their mood improved and they had more energy. Another noted it is easy to take while others said they had not seen any improvements. One caregiver reported that the person being cared for declined to take it because they were told it would only be effective within a certain window of symptoms appearing (not at diagnosis). Patients did report some negative experiences with riluzole. One patient noted it caused cramps; another that it caused diarrhea; two others noted it made them feel sick; one noted the regime is *"a little restrictive,"* one patient discontinued its use due to high levels of liver enzymes; and another found it caused heartburn which later subsided.

Given the lack of disease-modifying treatment options, many patients take a host of other medications to manage ALS symptoms, including: antidepressants; anti-anxiety and sleeping medications; prescription and over-the-counter muscle relaxants and anti-spasmodics; concentration medications; prescription and over-the-counter pain and anti-inflammatory medications; saliva medications; medications to address gastrointestinal upset; respiratory medications; medications to counteract dizziness; medications to improve control over one's bladder/bowels; laxatives; anti-allergic medications; skin medications; anti-fatigue medications; anti-nauseants; and medications to treat fluid build-up. Some patient respondents also indicated through comments that they use medical cannabis to address pain, spasms, sleep and other issues; natural health products, Chinese tea and turmeric; and vitamins, antioxidants and minerals. Others reported using off-label drugs, drugs not marketed in Canada (such as Nuedexta or tirasemtiv) or stem cell treatments. Of the 163 patients who responded, 46 commented they are not taking any medications.

Many respondents reported experiencing benefits from the medications they take to address the many symptoms of ALS, yet one patient noted that *"there is really nothing that has worked effectively to control the symptoms without causing another symptom."* One respondent noted a lot of sleepiness from their *"cocktail"* of medications. Others noted diarrhea, constipation, fatigue, and mood changes; no improvements in fasciculations; tinnitus; erectile dysfunction; headaches; extreme dry mouth and double vision resulting from the different medications they took. Another noted that they are taking the maximum daily doses of some medications and continue to have muscle spasms; however, if they increase the doses, they become too sleepy. It is also important to note that some medication is also difficult to swallow for ALS patients.

Out of 163 patient respondents, 91 (55.8%) somewhat disagreed/disagreed/strongly disagreed with the statement: "My current treatments are able to control my ALS symptoms" while 35 (21.5%) neither agreed nor disagreed and 37 (22.7%) somewhat agreed/agreed/strongly agreed. When asked to explain their responses, patients noted that *"because they do not slow down the progression of the disease, the*

[1] Gladman, M., Dharamshi, C., and Zinman, L., Economic burden of amyotrophic lateral sclerosis: A Canadian study of out-of-pocket expenses, *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, 2014 Sep;15(5-6):426-32. doi: 10.3109/21678421.2014.932382. Please note that the out-of-pocket expenses cited in this paper include lost income from patients/caregivers having to quit/leave their jobs.

symptoms of ALS only increase", that *"the disease continues to do its damage"* and that they are *"still wasting away."* Others noted that specific symptoms have not improved on their current treatments or that they weren't sure that their current treatments were helping.

While specialty or interdisciplinary care is very accessible to people diagnosed with ALS (149 or 91.4% of patient respondents had access to an ALS specialist or neurologist and 79 or 48.5% to a multidisciplinary care clinic), respondents had mixed success accessing their care and treatment(s) overall, with 74 (45.4%) finding it easy/very easy. Access to family physicians is challenging for many in the ALS community as is travelling to clinics. Caregivers noted that transportation to clinic visits is challenging because of the distance, especially when their loved one is in a wheelchair or suffers from fatigue. That said, many were happy with the care they received from their neurologist and care team.

For those who receive help from speech therapists, occupational therapists, and physiotherapists, these were found to have improved their functioning. Other exercises (such as aquatic exercise) and devices were helpful. Among the challenges described by patients are: delays in accessing equipment and devices (which is exacerbated when ALS progresses faster than wait lists), allied health services (e.g., physiotherapy) and home care; and changes to government-funded programs that leave them without the service.

Due to the progressive nature of ALS, patients rely on assistance from care providers to perform activities of daily living (ADLs). Most patients (127 or 72.6%) receive 5 or fewer hours per week of government-funded assistance and 130 (82.8%) pay directly for 5 or fewer hours per week. When it comes to assistance provided by informal caregivers (including family and friends), 63 patients (36.0%) receive 5 or fewer hours per week, while 44 (25.1%) receive between 6 and 15 hours per week, 54 (30.9%) receive between 16-100 hours per week and 14 (8.0%) receive more than 100 hours per week of informal care.

Many patients rely on a suite of assistive devices, which they must constantly upgrade as ALS progresses to live as fully as possible. In terms of supporting mobility, 64 (39.3%) use a power wheelchair while 59 (36.2%) a standard wheelchair, 61 (37.4%) a walker, 42 (25.8%) a cane and 34 (20.9%) a wheelchair-accessible van. To enable mobility around the home, 95 (58.3%) of patient respondents use specialized bathroom equipment; 50 (30.7%) a hospital bed and mattress; 42 (25.8%) a lift chair and 25 (15.3%) a lift attached to the ceiling (e.g., Hoyer lift); 19 (11.7%) a porch lift and 13 (8.0%) a stair lift. To support breathing and eating, 49 (30.1%) of patient respondents use non-invasive ventilation support (e.g., a BiPAP machine) while 1 (0.6%) rely on invasive ventilation support and 27 (16.6%) use a feeding tube. Only 25 (15.3%) of patient respondents reported not using any assistive devices.

5. Improved Outcomes

With the exception of a cure for this *"horrible", "sad", "terrifying", "tiring", "awful", "unmanageable", "consuming", "horrendous", "isolating", "exhausting",* and *"incurable"* disease, survey respondents from the ALS community 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: one patient with limb-onset ALS noted: *"[i]t has been 6 months since I hugged anyone."*

Symptoms that affect mobility; communication; muscle weakness, stiffness and atrophy; swallowing; and nerve pain were specifically identified as important symptoms that would ideally be controlled by a medication. Due to fatigue and potentially far distances to travel to a clinic or hospital, many patients and caregivers indicated that edaravone infusions administered by nurses through home care was desired.

Even when a medicine does not reverse symptoms or cure the underlying malfunction, it ultimately gives people a break from increasing disability and an uncertain future. Slower progression of ALS would enable some to *"continue riding, walking, playing gol[f], traveling, living my life!!!", "get back to doing the things I enjoy doing", "go out more",* ultimately have their *"quality of life erode less quickly"* and allow them to *"think more about the future as currently [they] have no idea how long [they] will be mobile or able to eat or breath[e]."* They would *"be relieved"* and their *"family might not be so freaked out by [their] declining health."*

When asked specifically what delayed progression of ALS would mean for them, patients responded that it would *"reduce depression and anxiety", "provide some level of mobility", "mean more time with my children" and "seeing my kid grow up",* result in *"less financial hardship",* help them *"regain some…*

independence", and *"stay at home longer"*. It would mean they would *"have longer to live a normal life"* and *"would be able to be more active in the house".* One patient noted that "*to maintain [their] current condition as long as possible [would be a v]ictory!"* For others it would mean *"more self-reliance; delayed need for more invasive treatments; delayed increasing disability"*, and they would *"feel like there was a point to staying alive."*

Others noted that if it didn't restore function, it would *"just prolong life"* and for many – particularly those with advanced progression – that was not an appealing option: *"it would draw this living hell out even longer".* For others, hope is precious: *"It would be amazing, it would give me a little hope"* and it would *"give me hope that I might live until a cure is found"* or "*give hope that a substantial treatment is on the horizon."*

6. Experience With Drug Under Review

Among survey respondents, 26 patient respondents (16.0%) and 20 caregivers (9.9%) had experience with edaravone. When asked how they accessed it, 16 respondents (76.2%) said it was ordered through the mail or a courier, 2 asked someone to pick it up for them while out of the country and another 2 used the MTPC Edaravone Canadian Supply Programme. Patients have also accessed edaravone through their doctor and by travelling to China or Japan and directly purchasing it. In the focus groups, 5 people had experience with this treatment.

Eighteen of the patients who had tried edaravone (69.2%) somewhat agreed/agreed/strongly agreed that it *"better controlled [their] ALS symptoms than any other treatment [they] used"* while 6 (23.1%) neither agreed nor disagreed with this statement and 2 (7.7%) somewhat disagreed/disagreed/strongly disagreed. When asked whether edaravone "improved daily life compared to other treatments", 15 patients (57.7%) agreed/strongly agreed while 8 (30.8%) neither agreed nor disagreed and 3 (11.5%) disagreed/strongly disagreed. When caregivers were asked whether it improved their day-to-day lives, there was almost an even split (10 caregivers or 52.6% agreed and 9 or 47.4% did not). Some respondents also noted that they would not know how to compare the impact of edaravone on their loved one versus the person not using it.

When patients who had taken it were asked whether they would "recommend that edaravone be made available to people with ALS", 21 of 26 (80.1%) agreed it should be made available "to all people with ALS" while 4 (15.4%) thought it should be made available to those "likely to benefit" and only one patient (3.8%) responded that they would not recommend it. In particular, one patient noted *"[o]n the limited evidence I have I would conclude that it has slowed my rate of decline. I would wish the same for all other ALS patients."* Another said *"Everyone deserves to have access to all possible medications in order to slow or prevent progression of ALS."*

Overall, patients who used edaravone reported experiencing a variety of benefits. In particular, they reported more energy, better mood, greater strength, less muscle twitching and stiffness, less pain in arms and legs, clearer speech, more easily projected voice, regained bladder control and one patient noted *"I feel more like my old self".* One caregiver noted it appeared to increase her adult child's upper body strength. Five patients felt it was or might be slowing the progression of their ALS. On the other hand, 2 patients noted in the survey that they discontinued it after not finding any benefits and 3 others said they were not sure they were experiencing any benefits. Similar findings were also mentioned by some caregivers, with five independently noting they did not see an improvement.

Most patients (15 of 26 or 57.7%) receive edaravone infusions at home, 5 (19.2%) receive infusions at the hospital, 4 (15.4%) at a combination of the hospital or outpatient clinic and at home and 2 (7.7%) in another (unspecified) location. Several caregivers highlighted the difficulty in accessing nurses to administer the infusion and distance traveled to do so. Six patients noted in the survey that accessing the infusions is *"very inconvenient"* and expensive, with 2 paying privately to do so. One caregiver noted that it was *"hard to administer, costly to administer, [and] time consuming to administer."* Those who are working must schedule business trips around the infusion schedule.

Many patients reported that infusions must be started by a clinic or hospital while the family and caregivers are trained to administer the infusions. Some patients and caregivers report that while nurses in their province are permitted by their regulatory colleges to administer edaravone, they are not always insured when doing so and thus refuse to administer it. Without nurses to administer it and train family,

patients are not able to use the medicine even if they have purchased it. Infusions administered at a private clinic cost $200-250 per infusion. In Alberta, edaravone infusions are reportedly not administered in hospital and patients usually seek out a private clinic. For a private home care company to administer edaravone in Ontario, the cost is reportedly $125 per treatment.

For the infusions, some patients access a PICC line or portacath for the duration of the infusion schedule. Of those who have used edaravone and participated in the focus group, one used an IV line that was inserted and removed for each infusion cycle; another used a PICC line, which was flushed regularly; and another who received the infusions from his nurse spouse at home, had a portacath, from which the line was disconnected following infusion cycles and was challenging to keep dry. One caregiver noted that the daily IV was *"a deterrent to daily activities if you wanted to go away"* and another said that the daily infusions, the PICC line and the portacath all *"interfere with daily life."*

In addition to the medication, supplies are necessary. One BC patient receives these free of charge from the clinic and this diminishes the burden but does not completely eliminate it: *"[e]very day requires a new line, an infusion bag, two vials of edaravone, sterile wipes for the line, 4 flush syringes, the actual sterile needle and a flush of heparin. We haul a couple of boxes of supplies every week. ... Then of course there's also a box where the used needles are kept. …This is no small project!"*

Not all patients followed the standard infusion schedule. Nine patients out of 25 responded that they deviated from the infusion schedule while 16 did not. Some patients found that during the 14 days without the infusion, their symptoms reappeared. Participants in the focus group who used or had experience with edaravone described neurologist-recommended infusion schedules that differed from the standard infusion cycle. For example, while on this schedule, one person lost bladder control but after following neurologist advice to take the infusion for 5 days followed by 2 off, regained control of the bladder after 4 weeks. This patient's bladder control diminished when on a 10-day holiday (without edaravone), but returned to 80% control after five weeks of resuming it. The patient's spouse noticed decreased energy levels during a 5-day holiday that returned to normal when infusions were resumed. Out of convenience, another patient received infusions for 7 days, followed by 7 days without the infusion but reverted to the 14-day schedule for holidays or travel. This patient described his neurologist being *"very surprised"* with the lack of progression of his disease and finds edaravone *"extremely helpful"* and that it reduces muscle twitching and cramping, which is more comfortable, and does not take pain relievers during the time they are receiving infusions.

When patients were asked whether they would be willing to tolerate daily infusions for 10-14 days followed by a 14-day period without infusions, 99 of 129 patients (76.7%) responded "yes". Some patients noted that anything that decreases the impact of the disease – or stops it altogether – was *"worth it."* One patient noted they *"already have a PICC line"* and another that *"I need to rest in bed much of the day anyway."* Other patients noted that the treatment is time-consuming, they live far away from health facilities, if it would involve more people coming to their home they *"might resist it,"* there is "*no reason to introduce another unknown,"* they don't have enough energy for such a schedule, and that they have "*no money [and] no transportation."*

Of the 26 patients who reported using edaravone, 22 (84.6%) said they experienced no side effects and 12 of 17 of caregivers (70.6%) reported that they saw no side effects in their loved one. It was sometimes difficult to determine whether some symptoms of ALS (e.g., weakness, changes from walking gait, etc.) were side effects of edaravone and they were managed as they otherwise would have been (e.g., BiPAP for headaches, assistive devices for mobility, etc.). Skin inflammation or rash were reported by 3 patients (11.5%) and 2 caregivers (11.8%). Infusion site redness / swelling / bruising / pressure / pain were reported by 2 patients (7.7%) and 1 caregiver (5.9%); bruising by 1 patient (3.8%) and 1 caregiver (5.9%); and respiratory disorder, hypoxia and glycosuria were each reported by 1 caregiver (5.9%).

Patients were also asked whether they would be willing to tolerate the side effects of edaravone if it were to delay the progression of their ALS. Of 122 patients, 94 (77.0%) are willing to tolerate bruising, 91 (74.6%) are willing to tolerate redness/bruising/inflammation/pain/pressure at the infusion site, 69 (56.6%) skin inflammation or rash, 51 (41.8%) headaches, 44 (36.1%) eczema and/or fungal infections, and 43 (35.2%) glycosuria. However, only 15 (12.3%) were willing to tolerate respiratory disorder and 13 (10.7%) respiratory failure and/or hypoxia.

When asked whether they would try Radicava (edaravone) if it were offered to them, 105 out of 129 patients (81.4%) responded that they would, with some patients highlighting that *they "would do anything that would help with this disease"*, others emphasizing the importance of hope, including *"hope that these onset disabling symptoms could be slowed or diminished"* and that *"I am ready to do anything to improve my situation."* One patient commented: *"[t]his disease is debilitating, and fatal … anything I could do to slow this progression down so I can spend more time with my children would be amazing."* Some patients responded that they would want more information about the treatment before taking it, including consultations with their neurologist. Other patients noted that their disease has progressed and they did not expect that edaravone would help them or that their neurologist did not think it would help. Several patients noted that their goal was not to *"prolong"* their lives or their *"suffering"* so would not be interested in accessing edaravone.

Among those who had no experience with edaravone, when asked about their expectations of the medication, 57 of 108 patients (52.8%) expected that it might be an alternative to current treatments, while 10 (9.3%) thought they would use it in addition to other treatments. Nearly a quarter of patients expressed hope that it would slow the progression of ALS and the symptoms patients identified as expecting edaravone to improve reflected the suite of symptoms they experienced as their ALS progressed. In terms of side effects, 68 of 111 patient respondents (61.3%) expected that it would or might have side effects. As well, some patients commented that they expected the medication cost to be a challenge and 2 commented they are expecting an oral formulation in future.

Family caregivers in the focus group who had no experience with edaravone highlighted that they would be concerned about administering the infusion to their loved one because they would be very anxious about doing something wrong and hurting them. One caregiver commented in a focus group that they decided against it at a later stage of progression out of fear it would worsen symptoms, saying it is *"a lot to ask of families"* on top of the daily challenges of caring for their loved one and dealing with the emotional impact of the disease.

When people were asked what it would mean to them if Radicava (edaravone) were able to delay the progression of ALS, several words reappeared many times among respondents: *"more time", "everything", "priceless"* and *"the world".* Caregivers noted they would like to see improvements in all symptoms of ALS, often focusing on the ones that affected their loved ones. For one caregiver whose loved one's disease had progressed, *"[i]t would have meant a great deal if it could have slowed the progression. Everything was so rapid, there was no time to plan in advance and every accommodation was quickly out-stripped by need."* Another caregiver noted that slower progression "*would have allowed my father a little more time between losses of mobility to accept and grieve the loss of his independence."*

One caregiver responded that it would "*be more family and community time, Christmas, birthdays, camping, helping others with ALS,… more hugs and I love yous … more time to treasure."* For another, "*a future …meant my dad becoming a grandfather"*. Several respondents highlighted the importance of hope for those living with ALS: *"Hope…is the best thing when your loved one is terminal. You don't know what hope means until you have none."*

7. Anything Else?

In nearly 20 years, Edaravone is the first drug under Health Canada review to show evidence of slowing the progression of ALS. In the absence of a therapy that modifies the disease and delays the onset of debilitating and progressive symptoms, patients continue to seek out experimental and off-label therapies that offer hope for a better quality of life.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH CDR and pCODR programs, 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.

   ALS Canada completed the submission independently in partnership with provincial ALS Societies and with external support from a public affairs agency who was hired by ALS Canada on a fee-for-service basis.

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.

   As noted above, a public affairs agency supported data collection and analysis along with internal resources.

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.

   The companies listed below have sponsored the ALS Canada Research Forum scientific conference.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
MT Pharma		X		
Cytokinetics (annual contribution over each of the last 2 yrs)		X		
Innovative Medicines Canada	X			
AB Science	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: Lisa Marchitto
Position: Director, Marketing and Communications
Patient Group: ALS Canada
Date: July 16, 2018