CADTH REIMBURSEMENT REVIEW

Patient and Clinician Group Input

omaveloxolone (TBC)

(Biogen Canada Inc.)

Indication: For the treatment of Friedreich's ataxia (FA) in adults and adolescents aged 16 years and older.

October 7, 2024

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CADTH 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.

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CADTH

Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: Omaveloxolone
Indication: For the treatment of Friedrich's ataxia (FA) in adults and adolescents aged 16 years and older.
Name of Patient Group: Ataxia Canada- Association canadienne des ataxies familiales
Author of Submission: François-Olivier Théberge

1. About Your Patient Group

Ataxia Canada – Claude-St-Jean Foundation is first and foremost a community of women, men, adults, teenagers, and children suffering from a hundred forms of ataxia, in all corners of the country. Ataxia is a degenerative neuromuscular disease that affects hundreds of young and old people in Canada and is incurable to date

In 1972, Claude St-Jean, following an evaluation of his symptoms by Dr. Barbeau (a prominent person in the neurological field), was condemned to death. He did not accept it and in response to this diagnosis decided to create a scientific committee to begin medical research on the disease named "Friedreich's ataxia". During this era, doctors knew almost nothing about the disease and their interest in research was nonexistent. The same year, Claude founded our foundation. he holding of fundraisers was necessary to assure the financing of eventual medical research as well as to support a potential group of people presenting the same symptoms.

For over 50 years now, our mission is to improve the well-being of people with familial ataxia and to support research.

https://lacaf.org/en/

2. Information Gathering

We are a small charity, and we are close with our patient group and caregivers, with 3 out of 4 employees are or were caregivers. The information we have gathered about Canadian patient and caregivers was done via a combination of interviews, a survey comprising of 85 responders and personal experience. Our patient survey was done in August of 2024, with 85 responders from every Canadian province and one (1) from the northwest territories. Only 2 patients have experience with the drug in review, they were from the original participants of the clinical trial and were traveling to UCLA, Los Angeles

From our survey, most patients (72%) have a disease onset before the age of 15yo. 50% of total patients are diagnosed between the age of 8 and 15. They typically become fully wheelchair dependent at a median of 11.5yold (Predictors of loss of ambulation in Friedreich's ataxia, EClinicalMedicine. 2020 Jan; 18: 100213) .The disease progression in FA usually starts with balance issues then gait and walking abnormality and progresses to unsteady movements coordination for the whole body. As coordination worsens, individuals may experience frequent falls and have difficulty standing or moving without support.

According to patient survey, Table 1, the symptoms that impact the quality of life is around mobility (Awkward unsteady movements, impaired muscle coordination, Difficulty walking and poor balance) The disease progression also significantly impacts on fatigue, Slowness and slurring of speech (dysarthria), curving of the spine (scoliosis) and mental health repercussions.

Table 1: Impact of these FA symptoms on the quality of life, according to 85 patients

FA symptoms that have impact on the quality of life	Impact of these symptoms on the quality of life. (1 No impact, 10 severe impact)
Awkward, unsteady movements and impaired muscle coordination	8
Difficulty walking and poor balance	8
Slowness and slurring of speech (dysarthria)	6
Spasticity: abnormal muscle tightness due to prolonged muscle contraction	6
Curving of the spine (scoliosis)	6
Difficulty swallowing	4
Hearing and vision loss	**4**
Cardiac issues	**3**
Diabetes	**1**
Fatigue	**7**
Mental health	**5**

The majority (85%) of patients rely on between 1and 4 different caregivers that spend anywhere between 2 to 4 hours a day to more than 10 hours a day assisting FA patients. As you can see in table 2, most of the care is given by family members vs paid personnel.

Table 2: Hours per day spend by caregivers (family members vs personnel)

Hours spend per day assisting each FA patient	Dailly hours from family members	Dailly hours from family members distribution Percentage	Dailly Hours from personnel	Dailly hours from personnel distribution percentage
None	**5**	6%	35	41%
Under 2 hours	**32**	38%	18	21%
2 to 4 hours	**18**	21%	16	19%
5 to 7 hours	**12**	14%	8	9%
8 to 10 hours	**10**	12%	6	7%
more than 10 hours	**8**	9%	2	2%

About mental health repercussion, nothing impacts more the patient as the constant grief cycle associated with a degenerative neuromuscular disease. They are many causes for the mental strain on FA patients, Loss of independence, autonomy, social Inclusion, Employment and Financial Stability. From our own survey and interviews, its about hope. Hope for a treatment, hope to slow or stop the progression of the disease, hope to regain what was loss. In fact, 97% of patient answers yes when answering the following question Would you be open to trying a new treatment to slow or stop the progression of AF if it is approved by Health Canada? When asked, would you be open to trying a new treatment to slow or stop progression if it were a clinical trial? 95% responded yes. As a patient organization, its hard to convey the daily struggles of these patients and caregivers but we wanted to present the unfiltered patient perspective

Table 3: A sample of direct answers from patient and caregivers on the impact of FA

	Can you describe how AF impacts your daily life and overall well-being?
1	FA has had a devastating impact on my quality of life, specifically loss of mobility, balance, and awkward gait which makes me feel very self-conscious and anxious about my safety. I have also experienced loss of voice, as well as loss of independence. FA has affected my mental health, specifically depression, high anxiety, and loss of confidence in daily living.
2	Sick for 28 years Wheelchair-bound for 8 years Off work for 3 years
3	Impacts every aspect of my life
4	I have a teenager who isolates himself at home because he doesn't want to be judged.
5	Others around me at times have difficulties in understanding me and some just don't converse. Some things I could do one day, I have lost already or slowly losing that ability. I seem to be dropping or spilling things constantly which is so frustrating as well as my coordination.
6	We must help my son with all his daily needs
7	It has impacted on my life, since I'm a girl and everyone is judging my walk pattern, I can't walk straight. My friends do not want to go out with me because I lose my balance and stay behind. There are many things I want to say but it's hard for me to explain.
8	destroys independence, financial poverty, falls, social stigma, strict regimen and training daily, + 60 hours per week dedicated on health involving training, extra sleep, extra time dressing/moving/doing anything, constant appointments, constant when you have friedreich ataxia, you are constantly fighting a war . we need physiotherapy daily, but we cannot afford it
9	There are many things I am unable to participate in which makes it difficult to connect with peers. I am much more tired than most people which impacts my daily activity. These examples and other FA symptoms take a toll on my mental health.
10	Poor hearing to be in a community and ambient noise Loss of car use after loss of leg mobility
11	I had a lot of trouble accepting the disease, I've been on antidepressants for 2-3 years, I feel a lot of fatigue
12	This disease affects the entire autonomy. Difficulties in eating, handling objects, difficulty in making oneself understood, social isolation.
13	AF has a very big impact on my life, AF has ruined my mental health and doesn't let me live like other people my age, which has made me very tired
14	Loss of motivation, loss of meaning in life
15	Isolation because of difficulties in going out which tires a lot. Loss of work therefore decrease in resources which forces us to go out less

16	I don't work anymore. Wheelchair at all times, becoming more and more tired
17	Extremely difficult to live with for me, but also for those around me. I am in very good spirits, but I am aware that I am an exception.
18	To see yourself slowly weakening, losing your vigour…
19	Very difficult to motivate yourself
20	I am not able to live my adolescence like the others. I feel isolated and unmotivated at school. I don't see what the point is because everything is complicated
21	It affects him everything. I can't work, I have trouble making friends or a spouse. I can't use my Ipad anymore. I need constant help with eating, dressing, going to the bathroom, showering, writing, talking, etc.
22	Difficulty moving around and making friends
23	I'm deprived of doing like other young people my age, I'm limited in my activities, and I also often have back pain
24	Use of a wheelchair, difficulty in transfers
25	Isolation, restriction, fatigue, difficulty moving, and many others
26	AF impacts all daily activities; whether it is to get out of bed, get dressed, wash, eat, move. It's impossible to be autonomous because we always have to rely on someone for help for our daily activities. Plus, it's stressful not knowing what the future holds and how the disease will evolve. In the space of only 4 years I have lost my ability to walk and I use a wheelchair. It's also sometimes difficult for morale to stay positive because there are constantly pitfalls to overcome.

4. Experiences With Currently Available Treatments

There is no current available treatment for Friedreich ataxia. Depending on the case certain treatment and drugs are given for the management of certain symptoms. Here are but a few examples.

Anticoagulation for individuals with Friedreich ataxia with permanent, persistent or paroxysmal atrial fibrillation.

Muscle cramps or spasms: Baclofen, Tizanidine, *Benzodiazepines, Dantrolene sodium, Intramuscular botulinum toxin Injection*

It is also recommended to attempts to maintain a normal cardiac rhythm over rate control in individuals with Friedreich ataxia and atrial tachyarrhythmias. Highly symptomatic individuals who are younger require careful consideration regarding intervention. Some consideration should be given for moderate risks of pharmacological intervention versus higher risks with ablation, including prolonged anesthesia.

Ataxia Canada is also deeply concerned that some clinics around the world that are promising stem cell-based treatments for ataxia without oversight and other standard patient protections. They boast stunning rates of cures without scientific evidence to back those claims. In essence the only thing they do provide is cruel health fraud, at an exorbitant price, preying on the desperation that patients and families feel in the face of this untreatable neurological disease. We have cautioned families and continue to do so but we have had many Canadians who have gone to undertake these potentially dangerous treatments because they just must try something. The availability and accessibility to a regulated treatment will help dissuade this endeavor in the future.

5. Improved Outcomes

In our survey 95% of responders would be open to trying a new treatment to slow down or stop the progression of FA if it gets approved by Health Canada. We had an open question where we asked how patients think a new treatment would improve their life? What are your expectations? An overwhelming number of patients are just looking for anything to slow the progression of the disease so they can maintain a certain quality of life. To maintain mobility, autonomy and Independence. Here are just a few examples; the ability to perform daily activities; short supported walks, ability to do wheelchair transfers, personal hygiene, ability to feed yourself. Most of these examples concern specific ataxia symptoms; unsteady movements, coordination, difficulty walking and poor balance.

It is our understanding that these symptoms are measured by the mfars scale by a neurologist and that patients using Omaveloxolone, initially showed a 2.3-point improvement in mFARS versus placebo over 12 weeks (Lynch et al. Annals of Clinical and Translational Neurology 2019). Subsequently, the molecule showed a 2.40-point improvement in mFARS versus placebo over 48 weeks in the 16- to 40-year-old population (Lynch et al. Ann Neurol 2020).

If the disease is slowed, it gives a respite on daily life and quality of life for patients, caregivers, and families. When choosing a therapy, patients can weigh the potential benefits against the trade-off. In this case, Omaveloxolone was well tolerated in the studies.

Table 3: A sample of direct answers from patient and caregivers on new treatment expectations

	How would you like a new treatment to change your FA journey? What are your expectations?
1	I think it's incredibly important to get omaveloxolone out to children who are diagnosed early to prevent from degeneration before it gets very bad. Quality of life improves when symptoms improve.
2	Hope To stop the progression and improve mobility
3	I would hope it would help to slow my progression. It would give me hope for a better life when right now there is no other treatment available
4	slow down symptoms
5	It would be great to slow down the FA for my son to maintain his current quality of life
6	Slow progression and avoid wheelchair
7	Any treatment or therapy to slow down the progression of the disease should be available to those affected. Also, having hope for an improvement does have value.
8	Heard all the positive effects of omaveloxolone from the other patients, yes I am looking forward to have this drug available since all my kids are affected by this disease and I definitely want to try this in order for my kids to get better
9	I would like to slow it down or stop it all together so I could enjoy a bit of life before I die
10	I just want to be healthy and walk like normal person eat like normal person. I just want to have a normal life.
11	HOPE. All I need is something positive.
12	Hope
13	Slow down the progression
14	The biggest piece for me would be slowing progression and helping with fatigue which greatly reduces my quality of life. If I can slow progression, I can continue to do many things independently and it will allow me to believe that my dreams for the future are attainable.

15	I hope the treatment can slow down my symptoms
16	Yes, as long as it is in line with other drugs against arrhythmias. A slight improvement would already be extraordinary.
17	We all dream of being healthy... to live a normal life, so when I see myself in this degenerating state, I cross my fingers and I have a dream
18	For my part, I know that walking again is impossible. But if the other symptoms were controlled, it would give me a new lease of life! Nothing less.
19	Slowing down the progression of the disease will allow me to stay at home.
20	I know that it has no miracle product but if there would be someone to stop, slow down even regain a little better ak my condition would be a big plus
21	Reducing the symptoms of ataxia would bring a better quality of life
22	I want to slow down the progression of AF, so that I am still able to walk with my walker.
23	Already to see that my disease stops progressing would be really great and in the best case to recover from what I have lost
24	I need to have hope that one day a cure can cure me, or at least slow down the effects of the disease. I am willing to try anything to have a positive impact on degeneration.
25	I'm still standing right now. My language is almost unaffected. It would be wonderful if I stayed that way

6. Experience With Drug Under Review

2 Canadian patients accessed the drug omaveloxolone by participating in the original Reata clinical trial at UCLA in Los Angeles. They continue to use the drug through the open-label extension. They have had noted symptoms have progressed less than originally anticipated with no side effects.

Access to omaveloxolone was through a clinical trial, as it is not available in Canada but available in the United States and Europe. The patients has experienced less symptom progression, which has significantly improved quality of life. While side effects were present, they were manageable, and the patient found the drug relatively easy to use compared to the absence of effective treatments for FA.

For subgroups of patients with slower-progressing symptoms or those seeking to delay disease progression, omaveloxolone may be particularly helpful. In terms of therapy sequencing, patients with FA would likely move from symptom management to omaveloxolone once it becomes available.

The key values for patients and caregivers include access to treatments that can slow disease progression, manageable side effects, and a better quality of life with less physical and emotional burden on families.

7. Companion Diagnostic Test

There are 2 tests that are common with a patient journey.

One is the genetic test for the confirmation of the disease by detection of biallelic pathogenic variants in *FXN*. Friedreich ataxia is a trinucleotide **repeat genetic disorder** caused by an abnormal repetition of a sequence of three nucleotides,(GAA trinucleotides) in the DNA. The larger the repeat the faster the disease onset and progression. **Full-penetrance (disease-causing expanded) alleles is** 66 to approximately 1,300 GAA repeats. In our survey, 84% of responders were genetically confirmed.

The other is the mFARS scale depends largely on the assessment of balance and is evaluated in 4 parts by a neurologist.

Bulbar function: The areas of assessment include strength and volume of coughing and clarity of speech, which are assessed by asking patients to repeat specific sentences: **Related daily activities**: swallowing or speaking

Upper limb coordination: This section has a total of 5 different movements that are used to assess tremor (simple shaking) and coordination of the hands and arms. **Related daily activities:** brushing teeth, pointing to an object or reaching out for something, or turning a doorknob

Lower limb coordination: This section assesses coordination of the legs and feet. **Related daily activitie**s: putting on socks and shoes Upright stability.

The largest section in mFARS assesses ability to stand and walk. Sitting posture, upright stability with eyes opened or closed, and stance, among other activities, are measured. **Related daily activities: walking, sitting in a car, standing in line, or showering**. Since this aspect deteriorates especially at the end of adolescence, it is during this period of life that the progression of the disease seems most rapid. Overall, however, the disease progresses slowly, and the scale tends to plateau in patients who are wheelchair dependent. The assessment of upper limb function is limited in scale.

Few clinicians are familiar with the mFARS scale. Those who do would have participated in a Natural History study that we finance or would follow enough patients to keep up with current literature or conferences. As a patient organization, we have a good understanding of neurologist working in our field and they are very few who will have enough patients to allow them to develop expertise with it. In our survey, we could count one hand the number of patients who had an understanding on where they were situated on the mFARS scale.

Since the scale becomes less sensitive to change as patients transfer to a wheelchair, our organization is against this scale being used to include or exclude patients from treatment.

8. Anything Else?

Friedreich's Ataxia (FA) is a progressive, debilitating disease that severely impacts the quality of life for patients and their families. In both the United States and Europe, omaveloxolone has been approved, providing patients with the first-ever treatment option specifically for FA. Following these approvals, it is essential for Canadian patients to have the same access to this treatment to slow disease progression and improve quality of life.

For Canadian families, the wait for a treatment option has been long and filled with challenges, including traveling outside the country to participate in clinical trials. With FA being a rare disease, equitable access to treatments, especially after they have been demonstrated as safe and effective in other regions, should be a priority for Canada. Denying or delaying access to this treatment in Canada would not only put Canadians at a disadvantage compared to patients in other countries, but it would also exacerbate the physical, emotional, and financial burdens that patients and their families already face.

Furthermore, the availability of this treatment could dissuade Canadians from seeking unproven, potentially dangerous therapies abroad. As Canadians have expressed in their patient experiences, this treatment offers hope for a future with better quality of life, autonomy, and reduced caregiver burden. CADTH's recommendation should consider the unique position of FA patients in Canada and ensure that they are not left behind in accessing this therapy.

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 outside help was given to complete this submission

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		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: Francois-Olivier Théberge
Position: General Manager
Patient Group: Ataxia Canada-Association canadienne des ataxies familiales
Date: 2024-09-18

CADTH

Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: Omaveloxolone
Indication: Friedreich's ataxia
Name of Patient Group: Friedreich's Ataxia Research Alliance
Author of Submission: Jen Farmer, CEO; Kellyn Madden, Patient Engagement Manager; Myriam Rai, Director of Global Initiatives

1. About Your Patient Group

The Friedreich's Ataxia Research Alliance (FARA) is a national, public, 501(c)(3), non-profit, organization dedicated to the pursuit of scientific research leading to treatments and a cure for Friedreich's ataxia (FA). Our mission is to marshal and focus the resources and relationships needed to cure FA by raising funds for research, promoting public awareness, and aligning scientists, patients, clinicians, government agencies, pharmaceutical companies and other organizations dedicated to curing FA and related diseases.

2. Information Gathering

FARA regularly seeks feedback from the Friedreich's ataxia (FA) community to understand patient and caregiver views on drug development and preferred potential treatment outcomes. Patient and caregiver viewpoints shared in the "Disease Experience" section are drawn from 1) a white paper detailing the importance of pediatric inclusion in clinical trials published by FARA in 2023, and 2) an Externally Led Patient Focused Drug Development Meeting in 2017. The white paper included the views of a small number of parents of children with FA living in the United States who had previously advocated for pediatric inclusion in clinical trials. The Patient Focused Drug Development Meeting included 145 patients and caregivers, representing 70 families attending in person, along with an additional 200 online participants. Participants were polled about current disease state, experience with different symptoms, and perspectives on future treatments. While the majority of participants resided within the US, 3% lived in Canada. Participants were not asked whether they were taking omaveloxolone (omav) through the clinical trials that were ongoing at this time, however 14% noted they were currently taking experimental medications which may have included omav.

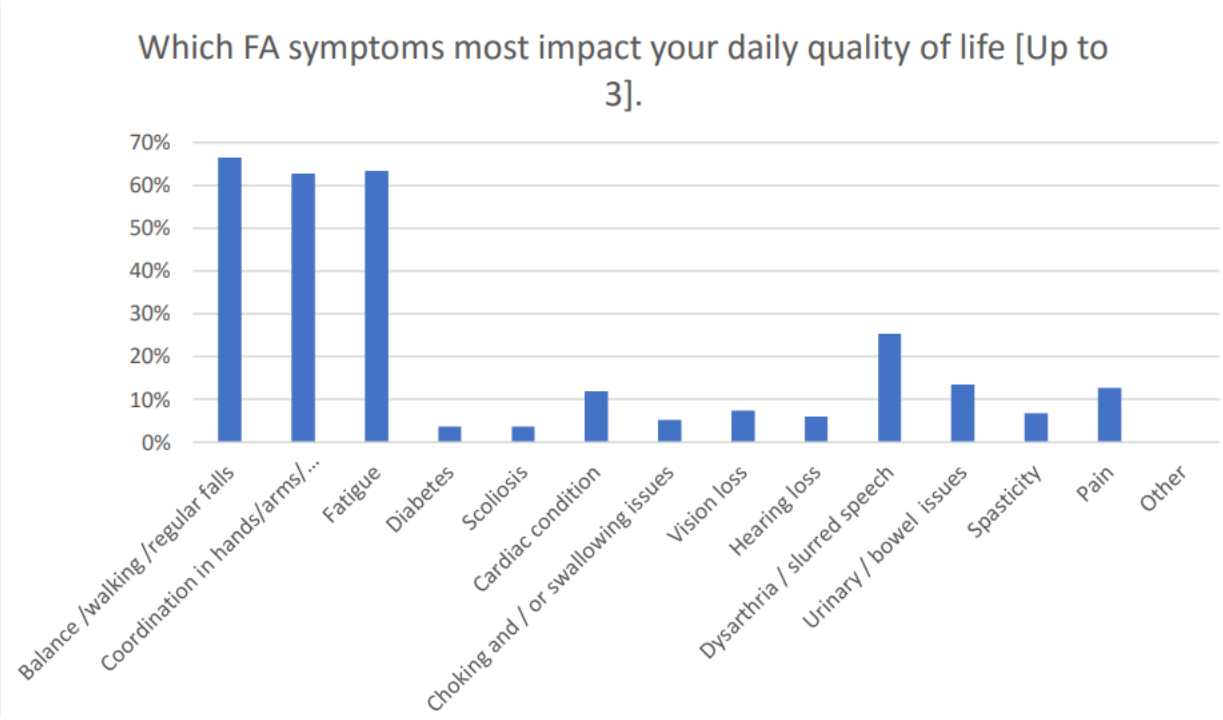
Views shared in the "Experience With Drug Under Review" section were collected by FARA in January of 2021 as part of the FA Community Response Letter which urged the US Food and Drug Administration (FDA) and Reata Pharmaceuticals (subsequently acquired by Biogen in 2023) to consider submission of a New Drug Application (NDA) for omaveloxolone (omav) based on existing evidence from clinical trials. FARA shared the FA Community response letter via our website, email lists, and social media channels. In total 74,070 individuals from 118 countries signed on to this letter, including 3,157 individuals from Canada. 1,924 individuals living with FA and 688 parents of children with FA provided written testimony. Written testimony was provided by individuals and families across the disease spectrum, from recently diagnosed to living with

FA for over 15 years. Among those who provided written testimony, over 70 individuals with FA had experience taking omav through clinical trials (MOXIe trials) and 148 family members had a loved one with FA who had participated in a MOXIe trial.

3. Disease Experience

FA is a devastating, progressive and life-shortening rare genetic condition that affects children and adults. All individuals with FA suffer neurological symptoms which include loss of coordination of movement in the upper and lower limbs, loss of balance and gait ataxia leading to loss of ambulation. Other common symptoms include dysarthria (speech difficulty), fatigue, cardiomyopathy, arrhythmia, diabetes, vision loss, and hearing loss. The average life expectancy for individuals with FA is about 35 years. FA is most often diagnosed between the ages of 5 and 15, and there are approximately 15,000 people living with this disease worldwide.

During the 2017 Patient Focused Drug Development Meeting, patients and caregivers stated that neurological symptoms and fatigue have the most impact on daily quality of life, as shown in the below graph.



Alt text: a bar graph showing symptoms of FA that most impact daily quality of life. 60-70% of respondents ranked neurological symptoms including issues with balance, walking, and falling and coordination of hands and arms as most impactful. About 65% of respondents also ranked fatigue as most impactful.

In FA, ataxia affects every muscle of the body, impairing both gross and fine motor control. The progressive aspect of the disease creates an intense physical, psychological, and financial burden. As neurological symptoms progress, people with FA may transition from using a walker or cane, to a manual wheelchair, to an electric wheelchair. Families and individuals must constantly adapt to the "new normal" as motor skills and mobility are continually lost. As the disease progresses, most individuals will need assistance with every aspect of daily living including eating, writing, dressing, and bathing. Towards the later stages of disease, people with FA experience vision loss, hearing loss, and dysarthria (speech difficulty), impairing their ability to communicate and engage with their loved ones and surroundings. One patient noted:

It took 10 years just accepting myself as wheelchair bound. Now, add not hearing well when I once could, [not] seeing well when I once could, then losing my ability to be understood, and it's a recipe for feeling worthless.

In addition to neurological symptoms, fatigue has a profound impact on people with FA regardless of disease status. As one parent explained:

The fatigue is hard to quantify but plays out in every moment of every day. With a child who is too tired to play, or the lie on the floor while life happens around them, when coloring books and snacks are delivered on trays to a child who is still in bed because they are too tired to get up, you feel a sense of loss as a parent that is unexplainable. Childhood is the time of curiosity, joy, and wonder; but, much of my child's life has been lost to fatigue.

While some individuals with FA can live and work independently, those more severely affected must often sacrifice an independent life and career as their symptoms worsen. Families dedicate countless hours and funds towards caring for their loved one with FA. For these reasons, patients and caregivers rated the slowing or stopping of neurological symptom progression as the most meaningful outcome of a potential treatment during the 2017 Patient Focused Drug Development Meeting.

4. Experiences With Currently Available Treatments

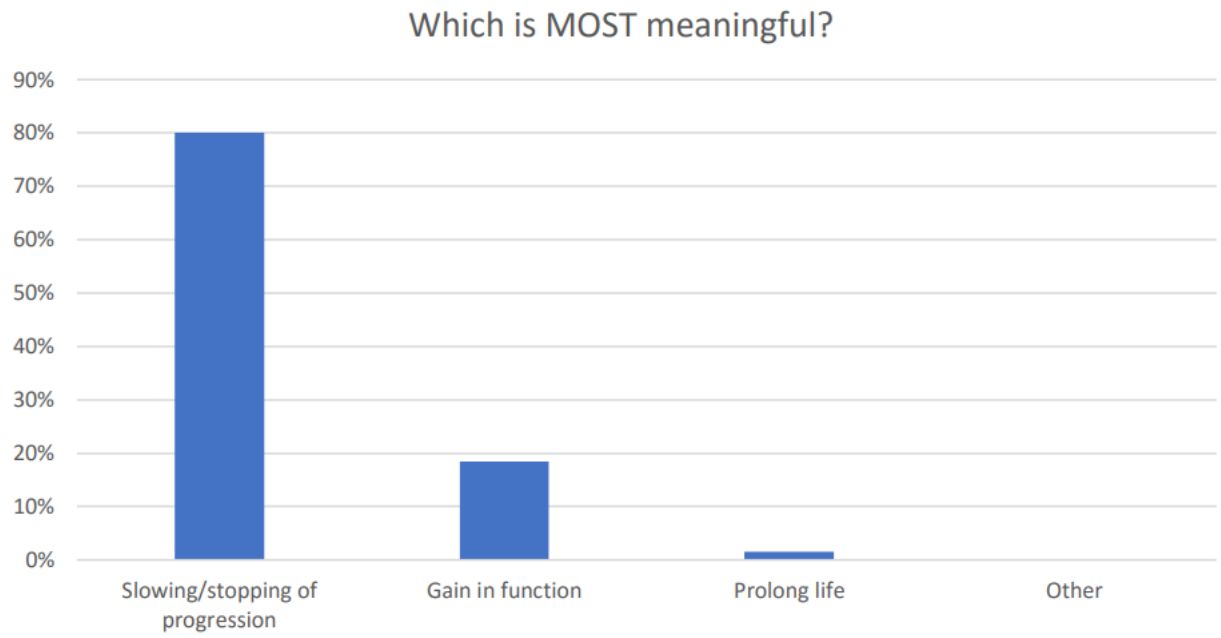
There are currently no approved treatments for FA in Canada. When it was approved by the United States FDA in 2023, omaveloxolone became the first ever approved drug for FA, and most Canadian patients currently do not have access to this therapy.

Patients and families spend countless hours and expense managing FA through symptom-based medications, supplements, physical, occupational, and speech therapies, visits to medical specialists (neurologists, cardiologists, orthopedics, endocrinologists, among others), mobility devices, and modifications to their home, work, and school environments for accessibility. As mentioned previously, many people with FA who are severely affected by the disease must eventually leave the workforce and require daily care and assistance from loved ones or personal care assistants. Symptom management is not enough to fight this disease, as it does nothing to slow disease progression and results in high financial and social burden.

While rare disease drugs, including omav, come with high price tags, the slowing of progression would likely lead to saved expenses in other areas. Slowed progression, or retention of motor function, would allow individuals with FA to remain employed for longer, prevent falls that result in emergency room visits, and prolong individuals' abilities to independently perform activities of daily living, reducing the need for personal care assistants or reliance on family members.

5. Improved Outcomes

During the 2017 Patient Focused Drug Development Meeting, 80% of participants ranked slowing or stopping progression as the most meaningful outcome of a potential treatment short of a cure, as shown in the below graph. The top symptoms or abilities participants wanted treatment for were improved balance or walking and reduced fatigue.



Alt text: a bar graph showing that 80% of patients and caregivers ranked slowing or stopping of progression as the most meaningful outcome from a potential treatment.

One parent stated:

It would be very meaningful to slow progression. If 35 years of progression could be 25 she would still be walking, instead of using a wheelchair."

Besides retention of motor function and independence, slowing or stopping progression would additionally grant individuals with FA the confidence to plan for their futures. One patient explained:

…being able to objectively stop or slow progression would be invaluable to me. I want to plan my life, with confidence; to be able to rely on my current abilities in the future, and without the fear of devastating

complications such as diabetes, stroke, or cardiomyopathy…I can adapt my life to current symptoms to stay active and engaged, but fear of what I know the future holds continues to cripple me, especially on an emotional level.

Along with prolonging motor function and independence and improving patients' outlooks on the future, slowing of progression would likely alleviate some of the expense and hours patients and families dedicate to symptom-based management of FA, as discussed in the prior section.

6. Experience With Drug Under Review

Omaveloxolone (omav) is a small molecule drug that upregulates the Nrf2 pathway, which is involved in mitochondrial biogenesis and has been shown to be downregulated in FA. Clinical trials (MOXIe Part 1, 2, and open label extension) showed that omav is both safe and effective in individuals with FA. A propensity matched analysis using natural history data showed that omav slows progression of FA symptoms by 55%, an incredible result in this relentlessly and uniformly progressive condition. Several patients and caregivers have noted improvements in symptoms beyond slowing of progression, although this was not captured in the clinical trial data.

The FA Community Response Letter included the viewpoints of individuals with FA who had previously or were currently participating in a MOXIe trial, and the viewpoints of parents of individuals who had participated, a sample of which are included below:

- "The main benefits for me have been: coping better with fatigue, being able to stand still (without swaying) for a prolonged period of time, and better/quicker improvement at the gym, better endurance, and better gain in definition of muscle." - *MOXIe trial participant*
- "J. was in the part 2 study and is currently in the open label extension. Omaveloxolone has given us hope. J. has not lost any abilities since starting the open label extension as well as we have seen improvement. People in our small community have noticed a great improvement in his speech and their ability to understand him. Personally, I have noticed that he is walking better behind his walker and more willing to walk. He is standing more upright instead of bent over. Another thing I have noticed that he is not choking as often at mealtimes. We will do whatever it takes to keep J. on Omaveloxolone to keep his FA paused for as long as we can." – *Parent of MOXIe trial participant*
- "I personally feel like omav has made a difference in my daily living, the positive outcome has relieved stress and anxiety in my life of feeling like my body is failing." – *MOXIe trial participant*
- "My symptoms have remained stable for 1 year now. I do not feel like I have progressed. I can still walk with the help of a walker and I have energy to work full time and participate in physical therapy." – *MOXIe trial participant*
- "I feel as if my progression has been extremely slow since I began taking this drug and that has helped me to be successful and not overwhelmed in my college education so far. Pausing and even slowing progression is so important, especially in younger FA patients so that they can continue

performing tasks for as long as possible. Losing physical ability due to FA progression is devastating and frustrating. If OMAV can help fight progression, that is something every FA patient should be able to access." – *MOXIe trial participant*

- "At 10 months [after starting omav] we started to see a calmness in his movements. He is sitting up easier and no longer asking to be moved to a chair that supports his neck. He is eating with more precision. That fork full of rice is getting to his mouth with ease and not spilling. He is sitting at the edge of the bed and changing his clothes by himself. He is way less fatigued because it seems like he is not fighting with his body to stay still… This drug is helping my child! Instead of watching him in a continued state of decline we are seeing progress. My hope is that every FA patient and family can have access to this drug and experience this progress." – *Parent of a MOXIe trial participant*

Side effects of omav were minimal and include transient elevation of liver function enzymes, elevated cholesterol, headache, diarrhea, and nausea. For most patients, these are small tradeoffs for the benefit of slowed progression and longer retention of motor function, especially when there is no other treatment for this disease. While omav is not a cure, it slows progression, the treatment outcome that was most important to patients and caregivers who participated in the 2017 Patient Focused Drug Development Meeting. Slowing progression is relevant for patients across the disease spectrum. Individuals who are still ambulatory may retain the ability to walk for longer. Individuals at the end stages of disease may retain the ability to speak clearly, thus extending the amount of time they are able to communicate with their loved ones. Many individuals taking this medication hope that use of omav will allow them to retain more motor function as they wait for future approved drugs that may stop or reverse progression.

7. Companion Diagnostic Test

Omav clinical trials indicated that this medication may elevate B-type natriuretic peptide (BNP), cholesterol, and transaminase levels in the blood. The FDA label for omav recommends blood tests prior to and during treatment to monitor for potential elevations. There are no barriers to accessing these routine blood tests outside of typical barriers to accessing health care that any patient, even those without rare disease, may face, such as living in a rural area or not having access to adequate transportation.

8. Anything Else?

Since omav's approval in the United States in February 2023, FARA has been contacted by several Canadian FA patients regarding access to this medication. Some have asked if it's possible to access the drug by paying out of pocket, which costs about $350,000 per patient per year. Upon learning that only residents of the U.S. can obtain prescriptions for omav, some individuals have considered moving to the U.S. The Canadian FA community has been desperately awaiting access to this therapy, which is why we are advocating for the approval and reimbursement of omaveloxolone in Canada.

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.

   Several testimonies included in this document were drawn from the 2017 Patient Focused Drug Development Meeting. This meeting was co-hosted by FARA, the Muscular Dystrophy Association, the National Ataxia Foundation, and the Cure FA Foundation.

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
Amgen/Horizon				X
Biogen/Reata Pharmaceuticals				X
Design Therapeutics			X	
Larimar Therapeutics				X
Lexeo Therapeutics				X
PTC Therapeutics				X
Solid Biosciences			X	
Stealth Biotherapeutics				X
Astellas Pharma			X	
Biomarin Pharmaceutical		X		

Fannin		X		
Neurocrine	X			
Prime Therapeutics	X			
Alexion Pharmaceuticals	X			
Takeda Pharmaceuticals				X
Novartis				X
IXICO			X	
Tune Therapeutics	X			
Minoryx Therapeutics	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: Jennifer Farmer
Position: Chief Executive Officer
Patient Group: Friedreich's Ataxia Research Alliance
Date: October 5, 2024

CADTH

CADTH Reimbursement Review Patient Input

Name of the Drug and Indication	**omaveloxolone** **Friedreich ataxia** **SR0864-000**
Name of Patient Group	**Muscular Dystrophy Canada**
Author of Submission	**Homira Osman, PhD**

1. About Your Patient Group

Describe the purpose of your organization. Include a link to your website.

Muscular Dystrophy Canada is registered with CADTH.

Muscular Dystrophy Canada (MDC) supports people affected by muscular dystrophies and related muscle diseases. Together, these rare conditions are referred to as “neuromuscular disorders.” Neuromuscular disorders are a group of diseases that weaken the body’s muscles. The causes, symptoms, age of onset, severity and progression vary depending on the exact diagnosis and the individual.

Since 1954, Muscular Dystrophy Canada has been the leading health charity and voice of the neuromuscular community in Canada. MDC is a sophisticated network of informed professionals, service specialists, and volunteers who deeply understand neuromuscular disorders. MDC represents 30,896 Canadians impacted by neuromuscular disorders including 12,047 persons with neuromuscular disorders, and 19,155 family members/caregivers.

MDC’s mission is to enhance the lives of those impacted by neuromuscular disorders by continually working to provide ongoing support and resources while relentlessly searching for a cure through well-funded research.

MDC has a full spectrum of programs, services, and supports for the thousands of Canadians of all ages living with a neuromuscular disorder that include: systems navigation, education and knowledge translation, access to financial supports for critical life-changing equipment and services to improve quality of life, peer-to-peer networking, emotional support, evidence- based information for new treatments, medical advances, and clinical trials and advocacy. Plus, MDC invests in transformative research to work towards more answers, therapies, and hopefully, potential cures.

Funded by Canadians from coast to coast, our investment in the research community is advancing the development of important new treatments. Our programs and services play a critical role in informing and supporting members of the neuromuscular community by funding equipment to improve daily life; hosting family and caregiver retreats; providing emotional and educational support; and with providing access to vital resources and support systems. Our advocacy efforts focus on enhancing public policy at all levels of government to bring about positive change. We are currently working to bring new treatments and trials to Canada. Advances in medicine have resulted in individuals with neuromuscular disorders living longer but not necessarily living better. As their disorder progresses and changes, so do their needs and financial strains.

Our desire is to provide support through all stages of disease progression by providing the tools, resources and support individuals need to live a full and rich life.

At the MDC, we follow the principle *Nothing About Us Without Us* closely. Individuals with Myasthenia Gravis and their circle of support are actively involved in every aspect of our organization - from leadership and decision-making roles to serving on committees and participating in collaborative research efforts. By integrating the perspectives and experiences of those affected by Myasthenia Gravis, we strive to ensure that our efforts are aligned with the needs and priorities of the patient community

Friedreich ataxia is one of the neuromuscular disorders that falls under MDC's umbrella. There is expected to be approximately 8, 000 patients affected by FA in Canada.

FA is a rare, progressive, and debilitating genetic disorder that primarily affects the nervous system and the heart. It leads to the gradual loss of coordination and muscle strength, impairing a person's ability to walk, speak, and perform daily tasks. FA results from mutations in the FXN gene, causing reduced production of frataxin, a protein essential for mitochondrial function. Without this protein, nerve cells degenerate, particularly in the spinal cord and peripheral nerves, leading to symptoms like poor balance, clumsiness, and fatigue. Over time, it can also cause scoliosis, diabetes, and life-threatening heart conditions such as cardiomyopathy.

FA is typically diagnosed in childhood, and patients progressively lose their independence, often becoming wheelchair users in adolescence. There is currently no cure, and treatment options are extremely limited, focusing only on symptom management rather than addressing the root cause.

Information Gathering

CADTH is interested in hearing from a wide range of patients and caregivers in this patient input submission. Describe how you gathered the perspectives: for example, by interviews, focus groups, or survey; personal experience; or a combination of these. Where possible, include ***when*** *the data were gathered; if data were gathered* ***in Canada*** *or elsewhere; demographics of the respondents; and* ***how many*** *patients, caregivers, and individuals with experience with the drug in review contributed insights. We will use this background to better understand the context of the perspectives shared.*

Muscular Dystrophy Canada has Neuromuscular Service Support Staff in all provinces across Canada. As part of the System Navigation Program, the Neuromuscular Service Support Staff provide front-line support to thousands of Canadians affected by neuromuscular disorders. The program operates on collaboration and patient engagement principles. Neuromuscular Service Support Staff work directly with patients and family members to identify non-medical needs (e.g., housing, transportation, access to equipment, information on clinical trials) and provide them access to the right resources in a personalized customized manner. Neuromuscular Service Support Staff work in partnership with patients and their families to address barriers, network and make connections with others in the community, share education materials and resources, enhance life skills and self-coping strategies, embrace inclusion and ultimately provide supports to help positively improve the overall well-being and quality of life of the patient and their family members.

The Neuromuscular Service Support Staff identified and contacted adults living with FA and parents of children over the age of 16 to participate in a healthcare experience survey (available in English and French) and semi-structured virtual (phone, Zoom) interviews. We shared the survey with members by e-blasts, personalized invites and Canadian patient online groups.

MDC also conducted a FA Canadian Journey Mapping project which was designed to capture the lived experiences of children and adults with FA, focusing on their healthcare journeys, challenges, and the impacts of the disease. We gathered insights on diagnosis delays, gaps in treatment, emotional and social effects, and access to care and support systems.

The following submission reflects data from a total of 86 individuals impacted by FA, all of which have a confirmed diagnosis of FA through clinical reports. The respondents included 40 males and 45 females between ages 16 to 70 from all provinces in Canada.

A qualitative descriptive approach, employing the technique of constant comparison, was used to produce a thematic analysis. We have included patients' quotes to ensure their voices are captured in this report and to provide context for quantitative elements. A report capturing all patient comments is also available for review.

2. Disease Experience

CADTH involves clinical experts in every review to explain disease progression and treatment goals. Here we are interested in understanding the illness from a patient's perspective. Describe how the disease impacts patients' and caregivers' day-to-day life and quality of life. Are there any aspects of the illness that are more important to control than others?

We asked participants to describe how FA affects their daily life and quality of life, as well as which aspects of the condition are more important to manage. Based on the responses, the survey identified 5 key themes that were frequently reported, listed in order of frequency: 1) significant impact on coordination/maintaining balance; 2) significant impact on mobility and scoliosis; 3) significant productivity at work and home; 4) significant impact on independence and social participation; and 5) significant impact on mental health and well-being.

Individuals affected by FA conveyed through their quotes that the impact of FA extends beyond physical symptoms, and that it affects their mental health, quality of life, and the wellbeing of their families.

Significant Impact on Coordination/Balance

"I have had many falls and broken fractures."

"The loss of balance and coordination has been the worst. This led to no longer walking and muscle mass loss in my legs that confined me to a wheelchair."

"Loss of coordination, introduction of slurred speech, penmanship reverted over time, loss of balance and stamina within activities. All of these contributed to day to day losses in walking, talking, activities, friendships, education, and created increasingly significant burden of care requirements on my parents."

"I have bad gait and issues with my balance"

"I had scoliosis and had corrective surgery for it in my 30s. I didn't realize until later that it is a symptom. I wasn't recovering after surgery, losing balance and falling down.

"Balance and gait unsteadiness led to frequent and many broken bones."

"My reaction time became very slow. This led to not being able to drive or do virtually anything on my own."

"I was very clumsy and falling often"

"I was having trouble keeping up with other kids at sports. I was falling and bumping into things."

"I began to lose balance and my gait began to slow me down. Sports were very challenging and even some daily tasks became difficult."

Significant Impact on Mobility & Scoliosis

"I got really tired quickly. I couldn't walk long distances like normal people."

"I had slow handwriting and repetitive movements."

"My most bothersome symptom was losing *the ability to walk safety. I fought using a wheelchair for years."*

Significant Impact on Productivity (at Work and Home)

"I couldn't get a job and could not work. I can't do anything, confined to my wheelchair."

"Fatigue made school work challenging, I would lay on the floor to recover after intense workouts, was unable to complete Military Basic Training."

Significant Impact on Independence & Social Participation

"For me, I always felt that if you cannot run with the pack, they tend to leave you behind. Meaning, at that age, all my friends and throughout high school, they were all doing fun things like going camping, restaurants, walking around downtown, and I tended to be left out a lot of the time. So that was probably my first problem and that was something that lasted throughout. I never felt like I could keep up to what others were doing."

"Difficulty participating in certain sports."

"I felt the lack of independence most with FA. I cannot perform any duties independently."

"It started with not being able to work, then not being able to drive, then not being able to walk without a walker; I couldn't multi-task at all to not do basic tasks for myself."

"Could not climb in playground, never learned to walk stairs correctly, could not participate in sports, was shy around others, refused to join in groups, was tired a lot, had inflammation, had slightly slurred speech, had trouble with fine motor skills and could not put lego together, had to quit piano lessons, was constantly at the doctor's trying to figure out what was happening. My mother never returned to work as an executive since she was busy with issues at school, did physio and doctor's visits."

Significant Impact on Mental Health

"It didn't affect me much physically but mentally I pretty much gave up on everything."

3. Experiences With Currently Available Treatments

CADTH examines the clinical benefit and cost-effectiveness of new drugs compared with currently available treatments. We can use this information to evaluate how well the drug under review might address gaps if current therapies fall short for patients and caregivers.

Describe how well patients and caregivers are managing their illnesses with currently available treatments (please specify treatments). Consider benefits seen, and side effects experienced and their management. Also consider any difficulties accessing treatment (cost, travel to clinic, time off work) and receiving treatment (swallowing pills, infusion lines).

When MDC asked how FA is being managed with available treatments or therapies, three main themes emerged in response:

The majority of respondents (n=61) indicated that they had no prior experience with treatments specifically designed for Friedreich ataxia. However, a significant number reported the use of various supplements, such as Co-enzyme Q10 (Co-Q10) and creatine, in an attempt to manage their condition. Additionally, many patients were prescribed medications aimed at addressing the symptoms and complications of FA, such as beta blockers to support heart function. Notably, three individuals were receiving targeted treatments as part of clinical trial participation, providing them access to experimental therapies aimed directly at FA.

4. Improved Outcomes

CADTH is interested in patients' views on what outcomes we should consider when evaluating new therapies. What improvements would patients and caregivers like to see in a new treatment that is not achieved in currently available treatments? How might daily life and quality of life for patients, caregivers,

and families be different if the new treatment provided those desired improvements? What trade-offs do patients, families, and caregivers consider when choosing therapy?

The responses to what people would want in a treatment for Friedreich's Ataxia (FA) can be grouped into the following key themes:

- **Slowing or Stopping Disease Progression:** The most frequently mentioned wish was for treatments that could slow or halt the progression of FA, with many expressing hopes for a "flatlining" of symptoms or even reversing the progression entirely.

- **Symptom Management and Improvement:** People mentioned a variety of symptoms they wanted improved, including better balance, speech, muscle strength (especially in hands, legs, and arms), vision, and heart function. Many wished for stabilization of their condition so that symptoms like slurred speech or muscle weakness wouldn't worsen.

- **Mobility:** A significant number of responses focused on regaining or preserving mobility. Some hoped to walk again, others wanted to avoid the need for walkers or wheelchairs, and many emphasized the importance of maintaining independence.

- **Energy and Fatigue:** Many respondents expressed a desire for more energy, highlighting how fatigue significantly impacts their daily lives. They hoped for treatments that would increase energy levels and improve overall stamina.

- **Quality of Life and Independence:** There were hopes for improvements that would enhance the ability to perform daily tasks and retain independence, such as better motor function, grip strength, and reduced pain. Enhancing overall quality of life was a common theme.

- **Prevention of Complications:** Respondents expressed a desire for treatments that could prevent further complications or secondary conditions like scoliosis or diabetes, or address heart problems associated with FA.

- **Cure and Reversal:** Several individuals hoped of a complete cure or a treatment that would not only stop progression but reverse the effects of FA, helping them regain full mobility, strength, and coordination.

Some mentioned the importance of making treatments like olaveloxolone/Skyclarys (currently available in the U.S.) accessible in Canada, as patients feel they are waiting too long for approvals.

These themes reflect the urgent need for effective treatments that not only manage symptoms but also slow or stop the progression of FA to improve patient outcomes and quality of life.
There are significant unmet treatment needs for individuals living with FA. Patients with FA also expressed a strong need for better management and control over their condition. They seek treatments that not only minimize the impact of symptoms but also reduce side effects and prevent exacerbations that can severely disrupt their lives. Effective therapies would help patients maintain their independence, reduce the frequency of serious medical interventions or hospitalizations, and ultimately improve their overall quality of life. There is an urgent call for more comprehensive and targeted treatment options that address these critical gaps, ensuring patients can lead fuller, healthier lives with fewer limitations imposed by their condition.

When we asked how people feel about new treatments for FA being available outside of Canada, responses can be summarized into the following key themes:

- Many expressed deep frustration and anger about the delays in Canada, feeling that access to life-changing treatments is unfairly slow. This frustration often stemmed from the knowledge that other countries, particularly the U.S., already have access to treatments like omaveloxolone/Skyclarys, while Canadians are left waiting.

- Some individuals remained hopeful and optimistic, expressing excitement that treatments are on the horizon. They are eager for these therapies to eventually become available in Canada and are hopeful that they could improve their condition or help future generations.

- A common theme was disappointment in the speed of the Canadian healthcare system, with many feeling that drug approval and reimbursement process is too slow. Some respondents also noted the financial burden that comes with treatments not being covered or available through public healthcare.

- Several respondents expressed anxiety about whether they will be able to afford the treatments when they are approved, or if they will come too late to make a meaningful difference in their condition. There is also fear about the ongoing progression of their disease as they wait for new options.

- There was a strong sense of feeling "left out" and the desire for equitable access to treatments available in other countries. Many voiced that they would consider moving to another country or traveling abroad to access treatments if they could afford it.

- Some responses reflected sadness, a sense of helplessness, and even hopelessness, especially among those who feel that treatments may come too late to help them due to the advanced stage of their disease.

- Several individuals expressed a desire to be part of clinical trials or to access new treatments earlier, hoping that even small improvements in their symptoms could enhance their quality of life.

These themes highlight a strong mix of frustration, hope, and desire for more rapid access to life-changing treatments in Canada, with many individuals feeling left behind in the global landscape of FA treatment advancements.

When asked about ‘trade-offs’, the most frequently mentioned concern was the high cost of treatment. Many worry about whether their insurance will cover the medication, with some fearing they would not be able to afford it without financial assistance. This burden often extends to associated expenses like travel and accommodation. Travel to clinics is a significant concern, particularly for those living in remote areas or without accessible transportation. The cost of traveling (e.g., rental cars, flights, hotels) and the lack of accessible spaces in clinics adds to the challenges. Some also noted the need to rely on others for transportation, which further complicates the process. Many anticipate difficulties with swallowing pills as their disease progresses. Concerns about the physical act of receiving treatment, such as handling infusions or injections, and other medical procedures like giving blood or ultrasounds, were raised as well. Taking time off from work or school to attend appointments or receive treatment was frequently cited as a concern. For caregivers, the need to take time off work to accompany family members to appointments was also mentioned, adding another layer of difficulty. The energy required to travel to appointments, manage the logistics, and endure the physical toll of the disease is also seen as a significant barrier, especially for patients whose mobility or energy levels are already limited. A few respondents mentioned the difficulties in navigating the healthcare system, such as the slow approval process for treatments and the red tape involved in getting medications reimbursed or covered by insurance. Despite these challenges, respondents were clear in their resolve: they are willing to endure such effects and trade-offs if it means stabilizing their condition, reducing symptoms, and ultimately improving their health outcomes. The priority is clear—access to treatment that offers the possibility of halting or reversing disease progression is worth any inconvenience or hardship. These individuals are prepared to make sacrifices to regain control over their health and improve their quality of life, underscoring the urgency and necessity of providing access to effective treatments without delay.

5. Experience With Drug Under Review

CADTH will carefully review the relevant scientific literature and clinical studies. We would like to hear from patients about their individual experiences with the new drug. This can help reviewers better understand how the drug under review meets the needs and preferences of patients, caregivers, and families.

How did patients have access to the drug under review (for example, clinical trials, private insurance)? Compared to any previous therapies patients have used, what were the benefits experienced? What were the disadvantages? How did the benefits and disadvantages impact the lives of patients, caregivers, and families? Consider side effects and if they were tolerated or how they were managed. Was the drug easier to use than previous therapies? If so, how? Are there subgroups of patients within this disease state for whom this drug is particularly helpful? In what ways? If applicable, please provide the sequencing of therapies that patients would have used prior to and after in relation to the new drug under review. Please also include a summary statement of the key values that are important to patients and caregivers with respect to the drug under review.

Only one person had received the treatment under consideration:
"I started Skyclarys five years ago when I was already using a wheelchair, and while my condition had progressed significantly by that point, I believe I would have seen even greater improvements had I begun the treatment earlier. Despite this, Skyclarys has helped stabilize my condition, preventing further decline. My family and I noticed benefits. I continue to return to the clinical trial site every six months for follow-ups, and I remain committed to the treatment as long as it remains available to me. The regular monitoring ensures that I stay on track, and I truly believe that this treatment has played a critical role in improving my quality of life."

6. Companion Diagnostic Test

If the drug in review has a companion diagnostic, please comment. Companion diagnostics are laboratory tests that provide information essential for the safe and effective use of particular therapeutic drugs. They work by detecting specific biomarkers that predict more favourable responses to certain drugs. In practice, companion diagnostics can identify patients who are likely to benefit or experience harms from particular therapies, or monitor clinical responses to optimally guide treatment adjustments.

What are patient and caregiver experiences with the biomarker testing (companion diagnostic) associated with regarding the drug under review?

Consider:

- Access to testing: for example, proximity to testing facility, availability of appointment.
- Testing: for example, how was the test done? Did testing delay the treatment from beginning? Were there any adverse effects associated with testing?
- Cost of testing: Who paid for testing? If the cost was out of pocket, what was the impact of having to pay? Were there travel costs involved?
- How patients and caregivers feel about testing: for example, understanding why the test happened, coping with anxiety while waiting for the test result, uncertainty about making a decision given the test result.

Out of 86 responses, the majority confirmed their clinical diagnosis was verified through genetic testing. Specifically, 82.6% (71 out of 86) responded "Yes," while 17.4% (15 out of 86) responded "No." Half of the respondents found the testing process to be easy. When asked about their diagnostic process, many respondents reported that the diagnostic process took a long time, sometimes spanning years, with delays in testing and referrals. Some mentioned a lack of genetic testing availability at the time, while others faced misdiagnoses before getting an accurate result.

The process was often emotionally challenging, with feelings of fear, grief, frustration, and even devastation. Parents and patients alike mentioned the emotional toll of receiving a life-changing diagnosis, especially when they weren't fully prepared by healthcare providers.

Some respondents found certain tests uncomfortable or painful, such as nerve conduction studies and shock therapy. For others, there were logistical challenges, such as lost test results or repeated testing due to errors.

A subset of individuals had a relatively smooth and quick diagnostic experience, often due to knowledgeable doctors who recognized symptoms immediately and quickly ordered the necessary tests, especially when genetic testing was readily available.

Despite the difficulties, many felt relief once they finally received a diagnosis, as it provided clarity and helped explain years of unexplained symptoms. This also helped some patients and families prepare for the future.

In some cases, having a family member already diagnosed with FA made the process easier, as they knew what to look for and could advocate for specific tests. Others shared that they faced dismissal or disbelief from healthcare professionals before receiving the correct diagnosis.

7. Anything Else?

Is there anything else specifically related to this drug review that CADTH reviewers or the expert committee should know?

There's a pressing need for treatment options to address the ongoing challenges faced by FA patients. From our engagement with Canadians affected by FA, there was a clear sense of urgency for treatments and access in Canada, with respondents emphasizing the need for faster drug approvals and better support systems to help those living with FA maintain their quality of life. Many expressed the hope that future generations would have access to treatments sooner than they did.

Appendix: Patient Group Conflict of Interest Declaration

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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 two years AND who may have direct or indirect interest in the drug under review.

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 No funds were directed toward Muscular Dystrophy Canada's operations or staff salaries. All funding received was through sponsorships and grants specifically designated for restricted educational initiatives, with no involvement from Biogen. Examples include the Walk and Roll for Muscular Dystrophy and the Spinal Muscular Atrophy motor function measures workshop.

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: Homira Osman, PhD
Position: VP, Research & Public Policy
Patient Group: Muscular Dystrophy Canada
Date: October 7, 2024

CADTH

Patient Input Letter for CDA/CADTH Reimbursement Reviews

Name of Drug: Omaveloxolone
Indication: Friedreich Ataxia
Name of Patient Group: National Ataxia Foundation
Author of Submission: Dr. Celeste Suart, Patient Engagement Manager

1. About Your Patient Group

The National Ataxia Foundation (NAF) was established in 1957 to help persons with Ataxia and their families. Our mission is to accelerate the development of treatments and a cure while working to improve the lives of those living with Ataxia. NAF's vision of a world without Ataxia will be accomplished through our primary programs of funding Ataxia research, providing vital programs and services for Ataxia families, and partnering with pharmaceutical companies in the search for treatments and a cure. We work closely with the world's leading Ataxia researchers and clinicians, promoting exchanges of ideas and innovation in Ataxia discovery.

We currently have over 16,000 members from around the world, including persons with ataxia, caregivers, and clinicians. We support individuals will all types of Ataxia, including genetic, acquired, and sporadic forms. The National Ataxia Foundation has 738 members living in Canada, 51 of whom have a connection to Friedreich Ataxia.

2. Information Gathering

When the National Ataxia Foundation learned of the opportunity to provide feedback to the CDA on Omaveloxolone, we conducted a survey of our community members with Friedreich Ataxia living in Canada. The data presented in this letter is a combination of this Canadian survey data, personal statements from community members, scientific literature, and data from American NAF members where Omaveloxolone is currently approved for the treatment of Friedreich Ataxia. We will indicate the sources of information as they are used within subsequent sections.

NAF Canadian Friedreich Ataxia Feedback Survey Overview

Our survey was conducted between Friday, August 23 and Friday, September 13, 2024. Survey questions were only available in English, as we were aware that our sister organization Ataxie Canada was conducting a similar patient survey in French.

We received 14 responses from a total of 51 potential respondents (27% response rate). This included 9 individuals with Friedreich Ataxia and 5 caregivers. Table 1 outlines the provinces where respondents live.

Table #1: Location of Respondents

Respondent Type	British Columbia	Manitoba	New Brunswick	Ontario	Quebec
Person with Friedreich Ataxia	2	1	0	6	0
Caregiver	0	0	3	1	1

14% of respondents indicated their Friedreich Ataxia symptoms (or their loved one's symptoms) were first noticed when they were less than 7 years old, with 50% noticing symptoms between ages 8-15, and 36% noticing symptoms after age 25.

3. Disease Experience

Friedreich Ataxia is a recessive neurodegenerative disease caused by biallelic mutations in the *FXN* gene. Friedreich Ataxia is a progressive, debilitating, and life shortening condition. The primary symptoms of Friedreich Ataxia include cerebellar ataxia and sensory neuropathy. Other common symptoms include dysarthria, dysphagia, hypertrophic cardiomyopathy and other cardiac dysfunction, fatigue, vision loss, hearing loss, diabetes, and scoliosis. People with Friedreich Ataxia progressively lose ambulation and independence to accomplish activities of daily living over two to three decades following initial symptom onset. The neurological and cardiac symptoms lead to early mortality, with the average lifespan being 35 years old. Individuals whose symptoms begin in adulthood tend to slowly disease progression that those whose start in childhood or adolescence.

Many people with Friedreich Ataxia must end their careers early, or are never able to work, due to their physical disability. Managing the symptoms of Friedreich Ataxia can be a full-time job. People with Friedreich Ataxia and caregivers spend countless hours with symptom-based therapies and visiting medical specialists (neurologists, cardiologists, orthopedics, and endocrinologists to name a few). Obtaining mobility devices and making modifications to physical spaces (home, work, school) is challenging, expensive, and time consuming.

Moreover, people with Friedreich Ataxia and their caregivers often need to travel to specialist clinics in large city centers to access healthcare and specialized support, as local clinicians are unfamiliar with Friedreich Ataxia or unable to provide the comprehensive care required. As disease progression occurs and symptoms become more severe, travel becomes more challenging for individuals Friedreich Ataxia. Having a caregiver assist with travel can help with access, however, not all caregivers can take the time away from work to attend appointments. Other people with Friedreich Ataxia may not be able to travel for healthcare due to associated costs, particularly if they are unable to work. This creates health disparities between patients who live near ataxia centres or movement disorder clinics and those who do not.

Even with symptomatic treatments, mobility devices, and support from caregivers, Friedreich Ataxia has a large impact on someone's quality of life. Table 2 outlines responses from our Canadian members survey, with people with ataxia rating the impact of Friedreich Ataxia on their life and caregivers rating the impact of Friedreich Ataxia on their loved one's life.

Table 2: Impact of Friedreich Ataxia on Quality of Life

Impact Level	Person with Ataxia Respondents (%)	Caregiver Respondents (%)
No Impact	0%	0%
Minor Impact	0%	0%
Moderate Impact	33%	60%
Major Impact	67%	40%

It is important to note that all respondents indicated that Friedreich Ataxia has a moderate or major impact on their, or their loved one's, quality of life. None selected minor impact or no impact. This is reflective of the high unmet medical need of the Friedreich Ataxia community.

4. Experiences With Currently Available Treatments

There is **currently no approved medication or treatment for Friedreich Ataxia in Canada**. Instead, many people with Friedreich Ataxia rely on symptomatic treatment or supportive therapies. Table 3 outlines the ways in which our Canadian survey respondents manage their symptoms.

Table 3: Current Strategies for Managing Symptoms

Strategy	Person with Ataxia Respondents (%)	Caregiver Respondents (%)
Occupational Therapy	67%	20%
Physiotherapy	78%	80%
Speech Therapy	33%	0%
Exercise or Balance Training	78%	80%
Diet	33%	40%
Symptom-Specific Medications (such as insulin for Friedreich Ataxia related Diabetes)	33%	0%

Though these symptom management strategies can help improve quality of life, they **do not slow the degenerative progression of Friedreich Ataxia**. People using these treatment options will continue to see their symptoms worsen over time. There are also barriers to accessing these treatment options, as many insurance plans do not cover occupational therapy or speech therapy. Furthermore, the way many insurance plans reimburse occupational therapy, physiotherapy, and speech therapy assume treatment is due to an acute injury, which will eventually be recovered from. This means that individuals with incurable, progressive conditions like Friedreich Ataxia will eventually run out of coverage for supportive therapies.

The fact that the current treatment strategies do not slow down the progression of Friedreich Ataxia symptoms is a major limitation to their effectiveness. Table 4 outline how effective respondents from our Canadian survey rated their current strategies for managing Friedreich Ataxia symptoms. All respondents indicated that their current treatment strategies were either somewhat effective, slightly effective, or not at all effective. Of note, caregivers tended to report lower degrees of effectiveness of treatment options than people with Friedreich Ataxia. Overall, this further reinforces the critical need for Friedreich Ataxia-specific therapies which slow progression of disease.

Table 4: Effectiveness Rating of Current Symptoms Management Strategies

Effectiveness Rating	Person with Ataxia Respondents (%)	Caregiver Respondents (%)
Not at all effective	22%	40%
Slightly effective	33%	40%
Somewhat effective	44%	20%
Moderately effective	0%	0%
Extremely Effective	0%	0%

5. Improved Outcomes

If approved, Omaveloxolone would **represent the first approved treatment for Friedreich Ataxia in Canada**. Unlike other currently available symptomatic and supportive therapies, Omaveloxolone has been clinically shown to slow disease progression. We asked our Canadian members with Friedreich Ataxia to share what having access to Omaveloxolone in Canada would mean to them. Here some of their thoughts:

"It would give me hope that there is finally something that is proven to slow the progression of FA." (Person with Friedreich Ataxia)

"Hope of a better life and a slower disease progression." (Person with Friedreich Ataxia)

"I would like to slow down or stop the progression of my FA because I am progressing very fast now (before turned 65, my progression was slower) and I would like to stop or slow down the progression for my remaining years." (Person with Friedreich Ataxia)

"Hopefully improvement in balance, eyesight, heart problems" (Person with Friedreich Ataxia)

"Hope to stop my symptoms to progress." (Person with Friedreich Ataxia)

"It would mean being able to slow progression, which is huge for FAmily." (Person with Friedreich Ataxia)

"Any and all resources would be appreciated, the sooner the better." (Caregiver)

"It would mean the world to have this medication to give my nephew, a chance at a normal life." (Caregiver)

"Hope for slower lost of capacity" (Caregiver)

"Means at least we can try to prolong her remaining abilities maybe even possibly get walking better for a little longer before she's wheelchair bound." (Caregiver)

Data from the MOXIe Open Label Extension trial on Omaveloxolone demonstrated that **Friedreich Ataxia disease progression was slowed by 55% with Omaveloxolone treatment**, as measured by the mFARS clinical assessment scale, [1]. That is an incredible result with tremendous potential impact for individuals with this relentless and uniformly progressive condition. Treatment with Omaveloxolone slows disease progression, giving people with Friedreich Ataxia more time and fewer symptoms in the fight against this disease.

[1]Lynch, D. R., Chin, M. P., Boesch, S., Delatycki, M. B., Giunti, P., Goldsberry, A., Hoyle, J. C., Mariotti, C., Mathews, K. D., Nachbauer, W., O'Grady, M., Perlman, S., Subramony, S. H., Wilmot, G., Zesiewicz, T., & Meyer, C. J. (2023). Efficacy of Omaveloxolone in Friedreich's Ataxia: Delayed-Start Analysis of the MOXIe Extension. *Movement Disorders*, 38(2), 313–320. https://doi.org/10.1002/mds.29286

6. Experience With Drug Under Review

As there are few Canadians who have first-hand experience with Omaveloxolone, we turned to our American members to share their experience with this drug. The following is a statement provided by an American with Friedreich Ataxia provided to the National Ataxia Foundation on September 18, 2024:

> Lealan Sims is 39 years old and diagnosed with Friedreich Ataxia (FA) at age 20. She lives in Atlanta, Georgia, USA and was a patient of the FDA phase II clinical trial for Omaveloxolone in 2015. She has been on Omaveloxolone for 14 months at 150mg, once in the morning on an empty stomach, waiting one hour until breakfast, accessing it through a Medicare prescription plan. Side effects were mild and have since tapered off, but included occasional diarrhea for 6 months and infrequent, rapid heart rate for 6 weeks.

> No other treatment is approved in the US for FA. Given this circumstance, there is literally no comparison, except to not having the drug available. The excitement around trying this drug alleviated any of her negative side effects. In terms of benefits, she sees and feels a stop in neurological symptoms progressing, or a slight reversing, though patient-reported, in movements maintaining balance, writing, swallowing, talking, stamina/energy, and more. She is still wheelchair-bound, but does not have any heart complications. Further, her heart marker has dropped significantly on required bloodwork.
>
> Truly assessing this drug on her quality of life is difficult to describe and understand given it has only been 14 months. However, living with more zest and fervor are leading the way to many impactful positives. Lealan attempts to balance motherhood (2 toddlers!) and volunteerism (patient advocacy, and also with her children's school) while managing FA and maintaining a love for life. Her hope to be a real part of her children's lives has expanded because of Omaveloxolone.

Though this is the experience of only one person, Lealan's story reflects the multitude of stories we have heard from people with Friedreich Ataxia who have had the chance to receive Omaveloxolone. Symptoms are slowed, quality of life improves, and there no other currently available treatment options that provide the same benefits. To borrow a phrase from Lealan, "there is literally no comparison".

7. Companion Diagnostic Test

Before being prescribed Omaveloxolone, individuals will require a genetic diagnosis of Friedreich Ataxia through confirming the presence of biallelic mutations in the *FXN* gene. 71% of respondents indicated that they, or their loved one with Friedreich Ataxia, had no difficultly accessing genetic counseling and genetic testing services. Most provincial and territorial healthcare systems cover the cost of Friedreich Ataxia genetic testing. However, there can be barriers to access regarding proximity to genetic testing facilities and availability of appointments. There can be mixed emotions from receiving genetic testing results, ranging from relief at having an answer to the cause of symptoms to fear about progression of disease. Some caregiving parents also report feeling guilt at passing on the *FXN* gene to their children.

Current prescribing practices in the United States require that physicians obtain alanine aminotransferase, aspartate aminotransferase, bilirubin, B-type natriuretic peptide, and lipid parameters prior to initiating Omaveloxolone and during treatment. The National Ataxia Foundation has had difficulty confirming which of these tests are covered by provincial and territorial healthcare systems. However, some members have shared with us that they already receive these tests as part of their ongoing care from their healthcare team. We have not had specific feedback from our Canadian members about the process of testing, cost of testing or their feelings about testing regarding these measures.

8. Anything Else?

Living with a chronic, progressive disease like Friedreich Ataxia takes a great toll on the mental, emotional, and physical health of people with Friedreich Ataxia and their caregivers. For decades our community had been told there is nothing they can do, no treatments can stop the progress Friedreich Ataxia. But with Omaveloxolone, there is now hope. For the first time, our community can see the possibility of an end to this devastating disease.

Due to how quickly Friedreich Ataxia degeneration occurs, time is of the essence. The National Ataxia Foundation urges CDA/CADTH reviewers and the expert committee to review Omaveloxolone in as timely a manner as possible while abiding by regulations.

> Time is crucial for people living with Friedreich's ataxia. Please, expedite the process to bring Skyclarys to Canada. (Person with Friedreich Ataxia)
>
> My son is only 14. His health is affected and unless we find a way to control this disease, his days are counted. (Caregiver)

CADTH

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.**

   We discussed our submission of this patient input letter with other patient advocacy groups, including Ataxie Canada and the Friedreich Ataxia Research Alliance (FARA), to coordinate our letter writing efforts. We also discussed with submission with Dr. George Wilmont of Emory University to identify NAF members receiving Omaveloxolone who would be willing to share their first-hand experience.

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 outside support was used to collect or analyze the data used in this submission.

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 5: 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 USA Inc / Reata Pharmaceuticals (USA)				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: Dr. Celeste Suart
Position: Patient Engagement Manager
Patient Group: National Ataxia Foundation
Date: October 1, 2024

CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number:
Generic Drug Name (Brand Name): Omaveloxolone
Indication: Friedreich ataxia
Name of Clinician Group: Neuromuscular Disease Network for Canada
Author of Submission: Dr. Massimo Pandolfo MD; and
Dr. Hanns Lochmuller
Dr. Jean Mah
Dr. Colleen O'Connell
Dr. Grace Yoon

1. About Your Clinician Group

Please describe the purpose of your organization. Include a link to your website (if applicable).

The Neuromuscular Disease Network for Canada (NMD4C) is a new pan-Canadian network that brings together the country's leading clinical, scientific, technical, and patient expertise to improve care, research, and collaboration in neuromuscular disease. https://neuromuscularnetwork.ca/

Launched in January 2020 with funding from the Canadian Institutes of Health Research (CIHR) and Muscular Dystrophy Canada (MDC), NMD4C builds on existing national initiatives such as the Canadian Neuromuscular Disease Registry (CNDR), the Canadian Pediatric Neuromuscular Group (CPNG), and the former neuromuscular network CAN-NMD. The mission of NMD4C is to improve the care, research and treatment of NMDs for all Canadians. Its vision is to be a comprehensive, inclusive, open and enduring network through which Canadian stakeholders can share expertise and data and collaborate on joint activities and research for the benefit of Canadian patients.

The network's goals are to:

- Formalize and sustain a network of NMD stakeholders united around a cohesive three-year work plan
- Train and educate the next generation of NMD stakeholders (clinicians, scientists, and patient advocates)
- Raise the standard of care for NMD and access to therapies across Canada
- Strengthen biomedical and clinical infrastructure to build research capacity in Canada

Since its inception, NMD4C has grown to more than 500 members with the majority having expertise in neurology and physical medicine and rehabilitation. NMD4C provides leadership and evidence-based support to improve access to approved novel treatments. We published a Canadian guidance on gene replacement therapy in spinal muscular atrophy (SMA), provided guidance on NMD respiratory care and vaccination during the COVID pandemic, and developed a variety of knowledge translation products.

As NMD4C members and neuromuscular clinicians across Canada with significant clinical expertise in the management of patients with Friedreich ataxia, we are writing to offer our strong support for favorable benefit access for Omaveloxolone as a treatment option in Canada.

2. Information Gathering

Please describe how you gathered the information included in the submission.

Clinicians with experience in managing Friedreich ataxia (FRDA) were asked to contribute to this submission. These expert clinicians contribute to the knowledge of FRDA and its treatments and are involved in clinical and observational research, clinical guidelines development and health technology assessment. The clinicians contributing herein are familiar with the data from clinical trials on treatments for FRDA, and, specifically, for Omaveloxolone. The information presented in this submission was gathered from 1:1 discussions with lead author, Dr. Massimo Pandolfo, and group discussions.

3. Current Treatments and Treatment Goals

Before the FDA approved Omaveloxolone for treating individuals with FRDA over 16, there was no authorized medication for the condition. The European Medicines Agency (EMA) later became the second regulatory body to approve the drug for the same indication.

Specialized care for FRDA remains complex, requiring interdisciplinary management by a team of medical and health professionals. The 2014 and 2022 Clinical Management Guidelines (CMGs) offer recommendations to support best practices. FRDA management addresses not only motor impairment but also associated challenges such as vision and hearing loss, psychological and cognitive issues, cardiomyopathy, diabetes, and skeletal abnormalities. Current treatment focuses on rehabilitation and managing complications.

The primary therapeutic goals are to slow disease progression, preserve or enhance function, extend survival, and improve patient well-being.

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.

Current treatments only partially achieve therapeutic goals. Despite rehabilitation efforts, no effective therapy exists to significantly slow or delay the progression of neurological deficits affecting motor control, communication, and cognition. Life expectancy is variably shortened, with a significant minority of patients succumbing to cardiomyopathy before the age of 30. Others face complications from severe neurological impairment, and in some cases, diabetes mellitus.

5. Place in Therapy

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

Pivotal trial evidence shows that Omaveloxolone improves neurological function and sustains this improvement over time. The trial (MOXIe) was an international, double-blind, randomized, placebo-controlled, phase 2 study conducted at 11 sites in the U.S., Europe, and Australia (NCT02255435, EudraCT2015-002762-23). It included patients aged 16 to 40 with genetically confirmed Friedreich ataxia (FA) and baseline modified Friedreich's Ataxia Rating Scale (mFARS) scores of 20 to 80, where higher scores indicate more severe impairment (range 0–93). A total of 40 patients received 150 mg/day of Omaveloxolone, while 42 were given a placebo. The primary outcome was the change in mFARS score after 48 weeks. Patients on Omaveloxolone showed improvement by three months, sustained throughout the study. In contrast, placebo patients initially improved at three months but then deteriorated at the expected natural progression rate. At 48 weeks, the change in mFARS scores was –1.55 ± 0.69 in the Omaveloxolone group and 0.85 ± 0.64 in the placebo group, with a significant difference of –2.40 ± 0.96 ($p = 0.014$) favoring Omaveloxolone. [1]

The MOXIe trial was followed by an open-label extension (OLE) study lasting up to three years[2]. Patients initially receiving placebo showed improvement and then stabilization, but they never caught up with those originally treated with Omaveloxolone. In the OLE phase, these patients were matched to participants in the natural history study FACOMS, using logistic regression to estimate propensity scores based on sex, baseline age, age of onset, baseline mFARS score, and baseline gait score[3].

The primary efficacy endpoint was the change in mFARS at Year 3, comparing MOXIe extension patients to their FACOMS-matched counterparts using a mixed model repeated measures analysis. Results showed that Omaveloxolone provided sustained benefits over three years. In the primary population (136 patients in each group), FACOMS patients progressed by 6.6 points, while those on Omaveloxolone progressed by 3 points (difference = –3.6; nominal p = 0.0001). This benefit was driven by early stabilization of mFARS in the Omaveloxolone group, followed by a gradual return to progression. It remains unclear whether, over a longer period, the progression rates between the two groups would further diverge or remain parallel.

Based on these findings, Omaveloxolone is poised to be incorporated into the current treatment paradigm to significantly delay ataxia progression in individuals with FRDA over age 16. Secondary outcomes from the MOXIe trial confirm that improvements in mFARS scores translate into functional gains, as reflected by the Activities of Daily Living (ADL) component of the full FARS. This supports both a meaningful functional improvement and a delay in functional decline.

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?

Which patients are most likely to respond to treatment with drug under review? While no definitive data exists, most participants in the MOXIe trial were ambulatory, and the analysis excluded those with severe pes cavus, a deformity common in individuals with earlier onset and more severe disease. This suggests that patients with milder symptoms and earlier stages of the disease may benefit the most. However, the greatest improvement was seen in the mFARS subscale for upper limb coordination, a function that continues to deteriorate even after loss of ambulation. This indicates that patients with more advanced disease may also benefit from Omaveloxolone treatment. Longer follow-up of Omaveloxolone-treated patients is likely to provide more reliable information.

Which patients are most in need of an intervention? All patients with FRDA would benefit from an intervention to slow disease progression.

Would this differ based on any disease characteristics (e.g., presence or absence of certain symptoms, stage of disease)? The need applies to ambulatory patients, who may extend their ability to walk, and to non-ambulatory patients, who could maintain upper limb function, speech, and the ability to transfer for a longer period.

How would patients best suited for treatment with drug under review be identified (e.g., clinician examination/judgement, laboratory tests (specify), diagnostic tools (specify)) The current expert opinion, as integrated in an update to the 2022 CMGs, is to propose treatment to all patients with FRDA above the age of 16. This age limit may change as new pediatric trials are carried out. Longer experience with the drug may eventually provide criteria to identify patients best suited for treatment.

Are there any issues related to diagnosis? The diagnosis is established via molecular genetic testing, which is available in many academic and commercial laboratories.

Is a companion diagnostic test required? No, all individuals with a positive molecular diagnosis are candidates for this treatment.

Is it likely that misdiagnosis occurs in clinical practice (e.g., underdiagnosis)? It is possible that underdiagnosis occurs in clinical practice, as molecular genetic testing is only performed when there is clinical suspicion of the diagnosis. While in the past diagnosis was commonly delayed by many years after symptoms onset, such delay is decreasing thanks to increased awareness of the condition among medical professionals. There are no immediate plans to introduce generalized newborn screening for this condition.

Is it possible to identify those patients who are most likely to exhibit a response to treatment with drug under review? As discussed above, there is nothing clear at this point that predicts those patients who are most likely to respond. Even the extent of differences in response is not yet known. Long-term experience with this drug is expected to provide guidance.

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?

Are outcomes used in clinical practice aligned with the outcomes typically used in clinical trials? Most FRDA patients are treated in specialized centers familiar with ataxia rating scales used in clinical trials. However, not all clinicians routinely use these scales in regular assessments. Nonetheless, it is entirely feasible to regularly assess patients on Omaveloxolone using key outcome measures like mFARS and FARS ADL. These are standardized versions of tests commonly used in neurological exams (mFARS) and functional assessments (ADL). Adding some simple clinician- and patient-related outcomes like Global Impression of Change is also recommended. The systematic use of these measures after starting Omaveloxolone will be crucial for supporting post-marketing (phase IV) studies. Regular evaluations—at least every six months in the first year, then at least annually—are both reasonable and practical.

What would be considered a clinically meaningful response to treatment? Consider the magnitude of the response to treatment. Is this likely to vary across physicians? A clinically meaningful response to treatment should improve patient function and well-being. However, how this improvement is reflected in a rating scale like mFARS remains a topic of debate. For ambulatory patients, even a 1-point improvement in the upright stability score is significant, indicating better balance in the short term and predicting delayed loss of ambulation. Similarly, a 1-point change in speech or upper limb function could mean the difference between being able to type or eat independently or being asked to repeat words occasionally instead of often. The strong correlation between mFARS and ADL scores supports the clinical relevance of these changes.

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

The drug may be discontinued due to lack of efficacy or side effects. For lack of efficacy, a reasonable approach is to try the drug for at least one year, before making a decision. Because of the noisy nature of the outcome measures like mFARS, decision to discontinue should be based on the clinician's and patient's global impression of change (CGI-C and PGI-C) rather than on scale scores. This is even more important if discontinuation is considered at a later time, when progression, though delayed, resumed in treated individuals in the OLE study[2,3]. The most common side effects in the MOXIe trial[1] and OLE[2,3] were transient increases in aminotransferases without bilirubin changes and transient increases in NT-ProBNP without evidence of heart failure, which do not require discontinuation. . However, sustained increases with evidence of organ dysfunction may require discontinuation. This is best left to the judgement off the prescribing clinician. Increases in LDL cholesterol have also been common with Omaveloxolone treatment, but prescribing a statin and managing cardiovascular risk factors is recommended over stopping the drug.

5.5 What settings are appropriate for treatment with Omaveloxolone? Is a specialist required to diagnose, treat, and monitor patients who might receive Omaveloxolone?

Ideally, FRDA patients should be treated at specialized centers that offer comprehensive interdisciplinary care, regardless of Omaveloxolone treatment. For patients without easy access to such centers, care should be managed by a neurologist knowledgeable about the disease and its management. Equipping these providers with the necessary educational tools for prescribing and monitoring the drug will be crucial for ensuring effective treatment.

6. Additional Information

In closing, we **strongly endorse access to Omaveloxolone** as a treatment option in Canada. We thank CADTH for the opportunity to provide clinician input on the Omaveloxolone submission. My colleagues and I would be pleased to provide additional information and/or clarification.

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.

   None

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.

   None

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: Massimo Pandolfo
Position: Clinical Professor
Date: 06-10-2024

☒ **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	
Design Therapeutics	X			
Larimar		X		
Solid Bio	X			

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

Declaration for Clinician 2

Name: Hanns Lochmuller
Position: Neurologist and Clinical Academic
Date: 01-10-2024

☒ **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 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**
Add company name				
Add company name				
Add or remove rows as required				

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

I have no conflicts of interest to declare.

Declaration for Clinician 3

Name: Jean K. Mah
Position: Pediatric Neurologist
Date: 01-10-2024

☒ **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 3

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

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

I have no conflicts of interest to declare.

Declaration for Clinician 4

Name: Colleen O'Connell
Position: Physical Medicine and Rehabilitation Physician and Medical Director, Stan Cassidy Centre for Rehabilitation
Date: 07-10-2024

☒ **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 4

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Roche	x			
Biogen	x			

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

Table 1: Conflict of Interest Declaration for Clinician 5

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

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

I have no conflicts of interest to declare.

References

1. Lynch DR, Chin MP, Delatycki MB, Subramony SH, Corti M, Hoyle JC, Boesch S, Nachbauer W, Mariotti C, Mathews KD, Giunti P, Wilmot G, Zesiewicz T, Perlman S, Goldsberry A, O'Grady M, Meyer CJ. Safety and Efficacy of Omaveloxolone in Friedreich Ataxia (MOXIe Study). Ann Neurol. 2021 Feb;89(2):212-225.
2. Lynch DR, Chin MP, Boesch S, Delatycki MB, Giunti P, Goldsberry A, Hoyle JC, Mariotti C, Mathews KD, Nachbauer W, O'Grady M, Perlman S, Subramony SH, Wilmot G, Zesiewicz T, Meyer CJ. Efficacy of Omaveloxolone in Friedreich's Ataxia: Delayed-Start Analysis of the MOXIe Extension. Mov Disord. 2023 Feb;38(2):313-320.
3. Propensity matched comparison of Omaveloxolone treatment to Friedreich ataxia natural history data. Lynch DR, Goldsberry A, Rummey C, Farmer J, Boesch S, Delatycki MB, Giunti P, Hoyle JC, Mariotti C, Mathews KD, Nachbauer W, Perlman S, Subramony SH, Wilmot G, Zesiewicz T, Weissfeld L, Meyer C. Ann Clin Transl Neurol. 2024 Jan;11(1):4-16.