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Reimbursement Recommendation

Omaveloxolone (Skyclarys)

Indication: For the treatment of Friedreich's ataxia in patients 16 years of age and older

Sponsor: Biogen Canada Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Skyclarys?

Canada's Drug Agency (CDA-AMC) recommends that Skyclarys be reimbursed by public drug plans for the treatment of Friedreich's ataxia (FA) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Skyclarys should only be covered to treat patients aged 16 years and older, who have a confirmed genetic diagnosis of FA, and a score between 20 and 80 on the modified Friedreich's Ataxia Rating Scale (mFARS). The mFARS scale measures how the disease affects bulbar function, coordination of the arms and legs, and balance.

What Are the Conditions for Reimbursement?

Skyclarys should only be reimbursed if the patient is under the care of a clinician experienced in treating ataxias and if the cost of Skyclarys is reduced. Treatment with Skyclarys should be stopped if the patient's mFARS score increases by more than 2 points in a year, or if their score increases to more than 80.

Why Did CDA-AMC Make This Recommendation?

- Evidence from a clinical trial demonstrated that after 48 weeks, treatment with Skyclarys may have slowed down the worsening of nerve and movement issues in people with FA compared to those who received a placebo. Some progression in daily activities was observed, but there were no clear improvements in arm movement, walking, or fall frequency.
- Patients and clinicians noted that FA has a serious impact on daily life and that there are no treatments that can slow down or stop the disease. Patients say that even slowing the disease could help them stay independent longer. While Skyclarys seems to help with some symptoms, there is still uncertainty about how meaningful the improvements really are.
- Based on the CDA-AMC assessment of the health economic evidence, Skyclarys does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Skyclarys is estimated to cost the public drug plans approximately $225 million over the next 3 years. However, the actual budget impact is uncertain.

Summary

Additional Information

What Is FA?

FA is a rare inherited disease that affects the nervous system and muscles. FA usually begins in childhood or the teenage years. The first signs are often trouble with walking and balance. Over time, people may also have slurred speech, difficulty swallowing, nerve damage, vision and hearing problems, and trouble with coordination. Many people with FA also develop heart problems. FA shortens life expectancy, mainly due to heart complications. On average, people with FA live to about 37 years old. In Canada, it is estimated that between 300 and 1,000 people live with FA.

Unmet Needs in FA

Patients indicated that there is a need for a treatment that can cure or reverse FA. Patients are also hoping for a therapy that can slow down or stop the disease, better manage symptoms, help maintain or improve mobility and energy, and improve health-related quality of life (HRQoL). There is a high unmet need for a disease-modifying treatment for FA, which is a rare, debilitating condition with no approved alternatives.

How Much Does Skyclarys Cost?

Treatment with Skyclarys is expected to cost approximately $399,180 per patient per year.

Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that omaveloxolone be reimbursed for the treatment of Friedreich's ataxia (FA) in patients aged 16 years and older, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

FA is a rare, inherited, degenerative disease that causes damage to the nervous system, resulting in difficulties with coordination, balance and movement, fatigue, and difficulty speaking. CDEC emphasized that there is a need for effective therapies for patients with FA.

Evidence from 1 phase II randomized, double-blind, placebo-controlled trial (MOXIe Part 2) (N = 103) demonstrated that at week 48, treatment with omaveloxolone likely results in a slower progression of neurologic decline in patients with FA compared with placebo. In the full analysis set, patients receiving omaveloxolone experienced a mean improvement (a decrease) in modified Friedreich's Ataxia Rating Scale (mFARS) score of 1.45 points versus a worsening (increase) of 0.90 points in the placebo group — yielding an estimated mean difference of −2.40 points (95% confidence interval [CI], −4.31 to −0.50; P = 0.0141). In addition, improvements in activities of daily living (ADL) were observed (mean difference = −1.30 points), and secondary end points (upper limb function, mobility, and fall frequency) did not show significant differences. Importantly, there is a high unmet need for a disease-modifying treatment in FA, which is a rare, debilitating condition with no approved alternatives.

Input from patient groups and clinical experts underscore the severe burden of FA, the profound impact on quality of life, and the absence of effective disease-modifying therapies. Patients report that even slowing of disease progression could help preserve function and independence. CDEC acknowledges that while omaveloxolone appears to meet some patient needs (e.g., stabilization of mFARS and ADL), uncertainty remains due to the lack of an estimated meaningful improvement difference (MID) estimate.

Using the sponsor-submitted price for omaveloxolone and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for omaveloxolone plus standard of care (SOC) was $1,534,503 per quality-adjusted life-year (QALY) gained compared with SOC alone (health care payer perspective). At this ICER, omaveloxolone plus SOC is not cost-effective at a $50,000 per QALY willingness-to-pay threshold for patients aged 16 years and older with FA. A price reduction is required for omaveloxolone plus SOC to be considered cost-effective at a $50,000 per QALY threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Adults and adolescents aged 16 years and older as per the following criteria: 1.1. genetically confirmed FA 1.2. mFARS score ≥ 20 and ≤ 80.	The MOXIe Part 2 trial provided evidence of safety and efficacy for the use of omaveloxolone in patients with genetically confirmed FA aged 16 years and older with a baseline mFARS score ≥ 20 and ≤ 80.	The clinical experts noted to CDEC that diagnosis of FA should be based on confirmed presence of biallelic mutations of the *FXN* gene. CDEC recommends that the sponsor be required to cover the cost of the training and/or the resources required for the administration of the mFARS score.
2. The maximum duration of initial authorization is 12 months.	The MOXIe Part 2 trial assessed the primary end point at week 48.	—
Discontinuation		
3. Treatment with omaveloxolone should be discontinued if the patient's mFARS score increases by more than 2 points at the annual assessment compared to the previous year, or if the patient's mFARS score exceeds 80.	There is a lack of evidence that omaveloxolone would benefit patients with an mFARS score of more than 80. The MOXIe Part 2 trial demonstrated that patients who benefited from omaveloxolone exhibited a stabilization of the disease at 48 weeks of the study. Considering the nature of the disease and the large unmet need, clinical experts and patient groups suggested that disease stabilization or slowing disease progression can be considered meaningful.	—
Prescribing		
4. The patients must be under the care of a clinician experienced in treating ataxias.	Accurate diagnosis and management of patients with FA are important to ensure that omaveloxolone treatment is prescribed to appropriate patients.	—
Pricing		
5. A reduction in price.	The ICER for omaveloxolone plus SOC is $1,534,503 when compared with SOC alone (health care payer perspective). A price reduction of 97% would be required for omaveloxolone plus SOC to achieve an ICER of $50,000 per QALY compared to SOC alone.	—
Feasibility of adoption		
6. The economic feasibility of adoption of omaveloxolone plus SOC must be addressed.	At the submitted price, the incremental budget impact of omaveloxolone plus SOC is expected to be greater than $40 million in year 1, year 2, and year 3.	—

CDEC = Canadian Drug Expert Committee; FA = Friedreich's ataxia; ICER = incremental cost-effectiveness ratio; mFARS = modified Friedreich's Ataxia Rating Scale; QALY = quality-adjusted life-year; SOC = standard of care.

Discussion Points

- **Reconsideration request:** The sponsor requested a reconsideration of the initial draft recommendation to reimburse (with conditions) omaveloxolone for the treatment of FA in patients aged 16 years and older. CDEC discussed 4 issues outlined by the sponsor in the request for reconsideration. First, the sponsor requested revising the initiation criteria to an mFARS score of 80 or less instead of the current range of mFARS scores of 20 or more and 80 or less. Second, the sponsor requested the removal of the requirement that patients must be ambulatory to initiate treatment with omaveloxolone. Third, the sponsor requested using mFARS as the primary indicator for continuation, with a score of 80 or higher as the cut-off, rather than relying on the loss of ambulation. Finally, the sponsor asked that the renewal criteria allow for the possibility of disease worsening, rather than requiring stabilization (i.e., no deterioration from baseline).
- **Criteria for significant unmet need are met:** CDEC noted that there was uncertainty with the clinical evidence; therefore, the committee deliberated on omaveloxolone considering the criteria for significant unmet need described in the Procedures for Reimbursement Reviews. Considering the rarity and severity of the condition, and the absence of clinically effective alternatives, the committee concluded that the available evidence reasonably suggests that omaveloxolone has the potential to slow disease progression, although the available evidence is associated with uncertainty.
- **GRADE assessment**: CDEC discussed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment of selected outcomes from the MOXIe Part 2 trial which concluded with moderate certainty that treatment with omaveloxolone would likely result in a slower progression of the mFARS score and decrease in the ADL score in patients with FA compared to placebo, while omaveloxolone may result in little to no difference in the change in 9-Hole Peg Test (9-HPT), Timed 25-Foot Walk test, and change in frequency of falls compared to placebo in patients with FA.
- **Clinical meaningfulness of the results**: The clinical experts indicated to CDEC that a change of 2 points in the mFARS score is considered clinically meaningful, but also that stabilization of disease over a long period would be considered beneficial given the progressive nature of FA. The MOXIe Part 2 trial demonstrated a statistically significant improvement in mFARS scores after 48 weeks of treatment compared to placebo (difference of −2.40 points, P = 0.014). However, CDEC noted that there is no defined MID for mFARS, and therefore there is uncertainty regarding how important the difference is between omaveloxolone and placebo, observed in the MOXIe Part 2 trial, and how meaningful this is to patients. CDEC also deliberated on the appropriate method to assess treatment response. While acknowledging the limitations of mFARS, they noted that it is a validated tool for assessing neurologic function across 4 domains: bulbar, upper limb coordination, lower limb coordination, and upright stability. Therefore, CDEC recommended its use for evaluating the response to treatment with omaveloxolone.
- **mFARS scale**: The clinical experts noted to CDEC that while the modified mFARS is a valid research tool, it is time consuming and not routinely employed in standard clinic visits and that requiring its use could limit equitable access, favouring patients who live closer to large centres with more resources.

CDEC recommended that the sponsor be required to cover the cost of the training and/or the resources required for the use of the mFARS scale.

- **Initiation criteria – mFARS score**: During the reconsideration meeting, the clinical experts noted to CDEC while most patients have an mFARS score of 20 or higher following confirmation of diagnosis, a small subset of patients, particularly those diagnosed early through prompt molecular testing may present with lower scores. The clinical experts emphasized that there is no biological rationale to exclude these patients, and that earlier treatment could help preserve function and delay disease progression. CDEC noted that although the sponsor-submitted data from the 3 patients with an mFARS score of less than 20 in the MOXIe Part 1 trial, it offered limited insight into the efficacy of omaveloxolone in this group, and the 1 patient who received a dose of omaveloxolone (160 mg) had a worse mFARS score compared with baseline. Although patients with an mFARS score of less than 20 were enrolled in the MOXIe Part 1 trial, patients with an mFARS score of less than 20 were not enrolled in the MOXIe Part 2 trial. Hence, there is no evidence that omaveloxolone would benefit patients with an mFARS score of less than 20 and as a result, CDEC recommended restricting the initiation criteria to those with mFARS scores between 20 and 80.
- **Initiation criteria – ambulatory**: During the reconsideration meeting the clinical experts noted to CDEC that while the subgroup of patients who were nonambulatory (n = 6) in the MOXIe Part 2 trial did not show statistical significance, the observed point estimate suggested a potential benefit. They also emphasized that nonambulatory status does not necessarily imply a lack of functional independence. CDEC noted that patients enrolled in the MOXIe Part 2 trial were considered ambulatory if they could walk with assistive devices, including canes, and the intermittent use of wheelchairs, and that the use of a wheelchair does not negate a patient from being ambulatory as per the trial baseline characteristics. CDEC noted that the mFARS score more effectively captures multiple dimensions of functional preservation, including upper extremity function, and is a more appropriate tool for identifying patients who are likely to benefit from treatment.
- **Discontinuation criteria**: During the reconsideration meeting, the clinical experts noted to CDEC that treatment discontinuation should be based on an mFARS score of more than 80 or by evidence of failure to slow disease progression, rather than on loss of ambulation. While CDEC acknowledged the considerable uncertainty regarding the efficacy of omaveloxolone in patients who are nonambulatory at baseline or who become nonambulatory during treatment, CDEC recognized that these individuals may still experience meaningful clinical benefits from therapy, such as preservation of upper limb or bulbar function. CDEC further noted that the mFARS score is a more appropriate tool for guiding treatment discontinuation decisions than the criterion of loss of ambulation.
- **Renewal criteria:** During the reconsideration meeting, CDEC acknowledged that although patients in the MOXIe Part 2 trial continued to experience disease progression despite receiving omaveloxolone, the rate of progression was slower compared to those who did not receive treatment. As a result, CDEC recommended that continued treatment with omaveloxolone be contingent upon the patient's mFARS score not increasing by more than 2 points annually and remaining at or below a threshold of 80. CDEC also discussed the option of using FA-ADL as an outcome for renewal. However, despite

being rated as moderate certainty by GRADE, the statistical significance of FA-ADL is uncertain as this analysis fell outside the prespecified hierarchical testing procedure due to the lack of significance in preceding outcomes. As a result, CDEC recommended focusing annual assessments on the mFARS score.

- **Severe liver disease and severe heart failure**: CDEC discussed that the MOXIe Part 2 trial excluded patients with a history of clinically significant left-sided heart disease and/or clinically significant cardiac disease. The trial also excluded patients with clinically significant liver disease and CDEC noted that clinicians should use their clinical judgment when prescribing omaveloxolone for patients with these comorbidities. CDEC also noted that the Health Canda product monograph indicated that management of fluid overload and heart failure may require discontinuation of omaveloxolone.
- **Adverse events:** The clinical experts noted to CDEC that some adverse events due to omaveloxolone can be managed and reversed, therefore, temporary discontinuation and subsequent reintroduction of omaveloxolone can be an option.
- **Long-term efficacy**: CDEC discussed that the open-label extension (OLE) study (a comparison of patients who have not yet received treatment and patients maintaining treatment) supports the clinical trial findings but illustrates that the treatment effects may wain or decrease since patients who were newly treated had better mFARS scores after 48 weeks. The real-world evidence comparison, in which there was an observed improvement in mFARS scores maintained through a period of up to 3 years compared to an external cohort, illustrated that patients who were treated and nontreated progressed at similar rates after the first year. While this provides supportive evidence of effectiveness in clinical practice, there are important limitations including potential selection bias in the Friedreich's Ataxia Clinical Outcome Measures Study (FACOMS) cohort and missing data at later time points that warrant cautious interpretation.
- **Impact on HRQoL**: Key outcomes identified as important by patient groups included maintaining independence in ADL, slowing disease progression, improving quality of life, managing fatigue and energy levels, and maintaining the ability to work and/or attend school. While the mFARS score captures aspects of physical function and disease progression as encapsulated in the mFARS end point, direct measures of quality of life, fatigue, and ADL were either not assessed in the clinical trial or did not show significant treatment effect. This also includes the key secondary outcomes of Patient Global Impression of Change (PGIC) and Clinical Global Impression of Change (CGIC). Beyond the primary outcomes, all outcomes tested in the MOXIe trial either included the null or fell outside of the statistical testing hierarchy, suggesting that the only evidence of efficacy for omaveloxolone was seen in the mFARS end point. This represents a gap in the evidence for outcomes most meaningful to patients. The clinical experts noted that improvements in mFARS would be expected to translate to functional benefits, but this relationship has not been formally established.
- **Evidence gap**: CDEC discussed that there is no evidence on the effectiveness of omaveloxolone in patients with more advanced disease, impact on non-neurologic manifestations, effects on disease progression in very early disease, and comparative long-term efficacy beyond 3 years.

- **Moral distress**: CDEC discussed the potential ethical challenges faced by providers due to the indication for omaveloxolone being limited to patients aged 16 or older. While they discussed the importance of setting clear parameters around reimbursement that relied on available clinical evidence, they also acknowledged that providers may face moral distress in restrictions on access to younger patients with FA, as well as pressure from patients and their caregivers to prescribe earlier (i.e., off label). Given the life-limiting nature of FA, and vulnerability of pediatric patients broadly, the committee understood that providers are confronted with an ethical dilemma of balancing unknown efficacy and safety of omaveloxolone in patients aged younger than 16 years against the risk of waiting to treat in the context of early-onset, progressive disease.
- **Equity of access**: CDEC discussed ethical and equity considerations posed by the need for omaveloxolone to be prescribed, provided, and monitored by multidisciplinary care teams in specialized treatment centres. While they noted the geographic challenges to access arising from this need are neither unique to the implementation of omaveloxolone for FA, nor rare conditions more broadly, they stressed the importance of considering actions that may help to alleviate some of the potential inequities in geographic access (e.g., telemedicine for long-term monitoring).
- **Economic uncertainty:** CDEC discussed the uncertainty in the sponsor's economic analyses. In the absence of robust comparative evidence, the incremental gains in QALYs with omaveloxolone plus SOC predicted by the sponsor's model for both the health care payer and societal perspective analyses may overestimate the incremental benefits relative to SOC. Further price reductions may therefore be required.
- **Societal perspective:** CDEC discussed the sponsor's societal perspective analysis, which included indirect costs and outcomes such as transportation, education support, respite care, caregiver support, and productivity loss, as well as potential negative impacts on caregiver HRQoL. CDEC noted that indirect costs and outcomes were not assessed in the MOXIe trial and that no evidence was submitted by the sponsor to support an impact of omaveloxolone on these costs or outcomes. Thus, the incremental costs and QALYs predicted in the sponsor's societal analysis are highly uncertain due to a lack of evidence of the impact of omaveloxolone and uncertainty associated with the chosen model inputs, and the committee deemed that the results of this analysis were too uncertain to inform decision-making.
- **Budget impact:** CDEC discussed the uncertainty in the number of patients eligible for omaveloxolone. Canada's Drug Agency (CDA-AMC) estimated the budget impact of reimbursing omaveloxolone based on registry data from Muscular Dystrophy Canada (MDC). Although not all people with FA may choose to register with MDC, clinical expert input received by CDA-AMC indicated that these registry data represent the most reliable estimates for Canada. If the number of people with FA in Canada is higher than estimated, the budget impact of reimbursing omaveloxolone will be greater.

Background

FA is a rare autosomal recessive ataxia caused by loss of function mutations from trinucleotide repeat expansions in the *FXN* gene located on chromosome 9q13. FA accounts for up to one-half of all hereditary ataxia cases and affects approximately 1 in 30,000 to 1 in 50,000 individuals. In Canada, estimates suggest between 300 and 1,000 patients are affected. FA typically presents in childhood or adolescence with a complex neurologic phenotype characterized by progressive gait ataxia. Additional cerebellar signs including dysarthria and dysphagia; peripheral motor and sensory neuropathy combined with pyramidal signs; and, in advanced disease, visual and hearing impairment. Most affected individuals develop hypertrophic cardiomyopathy, which in some cases may precede the onset of ataxia. Diabetes mellitus and skeletal abnormalities such as pes cavus and scoliosis are also common. The disease considerably shortens life expectancy because of cardiac complications, with a mean age of death of 37 years. Currently, there are no approved disease-modifying therapies available in Canada for FA. Management focuses on supportive care, rehabilitation, and symptomatic treatment of complications.

FA is associated with inhibition of nuclear factor erythroid 2-related factor 2 (Nrf2), involved in cellular response and oxidative stress. The suppression of Nrf2 in FA results in oxidative damage leading to cell death and tissue degradation. Activation of Nrf2 by omaveloxolone has been shown to restore Nrf2 levels, increase Nrf2 activity, rescue mitochondrial dysfunction, and restore redox balance. The precise mechanism by which omaveloxolone exerts therapeutic effects in patients with FA is unknown.

The recommended dose of omaveloxolone is 150 mg (3 capsules of 50 mg each) taken orally once daily. The Health Canada indication is for the treatment of FA in patients aged 16 years and older.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 pivotal phase II randomized controlled trial in patients aged 16 to 40 years, who have an mFARS score between 20 and 80 and genetically confirmed FA; 1 ongoing OLE study; and 1 propensity score matched analysis included in the Studies Addressing Gaps in the Evidence From the Systematic Review section
- patients' perspectives gathered by 4 patient groups, MDC, National Ataxia Foundation (NAF), Ataxia Canada – Claude St-Jean Foundation, and Friedreich's Ataxia Research Alliance (FARA)
- input from public drug plans that participate in the reimbursement review process
- input from 4 clinical specialists with expertise diagnosing and treating patients with FA
- input from 1 clinician group, Neuromuscular Disease Network for Canada (NMD4C)
- a review of the pharmacoeconomic model and report submitted by the sponsor
- a review of relevant ethical issues related to omaveloxolone
- information submitted as part of the sponsor's request for reconsideration (described subsequently)

- feedback on the draft recommendation.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

Four patient groups, MDC, NAF, Ataxia Canada – Claude-St-Jean Foundation, and FARA provided their input. The MDC identified and contacted adults living with FA and parents of children aged 16 years and older to participate in a health care experience survey and semistructured virtual interview. They gathered insights from 85 individuals (between the ages of 16 and 70 years) with confirmed FA diagnosis on diagnostics delays, gaps in treatment, emotional and social effects, and access to care and support systems. The NAF conducted a survey of their community members with FA living in different provinces across Canada and received 14 responses (9 people with FA and 5 caregivers). Ataxia Canada gathered experiences of patients and caregivers living in Canada through a combination of interviews and a survey and received 85 responses. Feedback from FARA regarding the disease experience was drawn from 2 sources. First, a white paper which included views from parents of children with FA living in the US highlighting the importance of pediatric inclusion in clinical trials. Second, a patient-focused drug development meeting that included 145 patients and caregivers, where participants were polled about current disease state, experience with different symptoms, and perspectives on future treatments.

Ataxia Canada and the MDC highlighted that patients with FA experience significant impact on the following: coordination and/or maintaining balance, mobility and scoliosis, productivity at home and work, independence and social participation, and mental health. Additionally, FARA noted that patients and caregivers indicated neurologic symptoms (balancing, walking, regular falls, and coordination of hands and/or arms) and fatigue having the most impact on daily quality of life. The NAF, Ataxia Canada, and FARA indicated that people with FA and their caregivers spend hours with symptom-based therapies (such as occupational therapy, speech therapy, and physiotherapy), visiting medical specialists, and obtaining mobility devices which can be challenging, expensive, and time consuming.

The patient groups agreed that there is a significant need for a treatment that is a cure or a treatment to reverse the effects of FA. Patients are also seeking a treatment that slows down and/or stops disease progression, promotes better symptom management, helps regain and/or preserve mobility, increases energy levels, improves HRQoL and independence while reducing the physical and emotional burden on families and caregivers, and prevents complications such as scoliosis or diabetes. Currently, individuals require genetic testing to confirm the presence of biallelic mutations of the *FXN* gene. The MDC and NAF highlighted the process to be easy, especially for people with family members who had been diagnosed with FA. However, the process was often emotionally challenging but provided clarity about the diagnosis.

Four respondents (1 each from MDC and NAF, and 2 from Ataxia Canada) shared their experience of accessing omaveloxolone via clinical trials. All respondents highlighted that receiving the drug slowed disease progression, of which 2 were already using wheelchairs. Viewpoints of individuals with FA and parents of individuals who participated in the MOXIe trial gathered by FARA included slowing progression,

longer retention of motor function (improved endurance, speech, ability to walk, stay upright, and eat), better coping with fatigue, and minimal side effects (transient elevation of liver enzymes, cholesterol, headache, nausea, and/or diarrhea).

Clinician Input

Input From Clinical Experts Consulted for This Review

The information in this section is based on input received from a panel of 4 clinical specialists consulted by CDA-AMC for the purpose of this review.

The clinical experts consulted for this review emphasized that there are currently no approved disease-modifying treatments for FA in Canada, representing a critical unmet need. Current management relies on supportive care and symptom management, which do not alter the underlying progressive disease course.

The experts indicated that omaveloxolone would represent the first disease-modifying therapy for FA and would be positioned as a first-line option for eligible patients aged 16 years and older with genetically confirmed disease. They noted it would be used alongside existing supportive care measures rather than replacing them.

Regarding patient selection, the experts suggested that while all patients with confirmed FA could theoretically benefit, those at earlier disease stages may show more discernible stabilization before irreversible neurologic damage occurs. However, they emphasized that patients who were nonambulatory should not be excluded, as preserving upper limb or bulbar function could still provide meaningful benefit.

For assessing treatment response, the experts acknowledged challenges in translating the clinical trial measures to routine practice. While the mFARS was used in trials and in natural history studies, it is not commonly employed in clinical settings. Furthermore, they suggested monitoring for 2 years to establish efficacy but noted that even partial slowing of disease progression may be valuable. According to the experts, treatment discontinuation should be based primarily on safety and tolerability rather than lack of improvement alone, given the progressive nature of FA, the variability of the disease and its rate of progression, and the absence of alternative disease-modifying options.

The experts emphasized that diagnosis and treatment should be guided by specialists experienced in FA management, such as neuromuscular or movement disorder neurologists. They noted that while regular monitoring is important, requiring intensive specialized outcome measures (such as standardized scales designed for clinical trials and that require trained users for reliable administration) could limit equitable access to treatment.

Clinician Group Input

A single clinician group input was received from NMD4C. Input from 4 clinicians familiar with the clinical trials on treatments with FA, and specifically for omaveloxolone, was gathered from 1:1 ratio submissions and group discussions. The group noted that primary therapeutic goals are to slow disease progression, preserve or enhance function, extend survival, and improve patient well-being.

The clinician group indicated that omaveloxolone is poised to be incorporated into the current treatment paradigm. However, they also highlighted that there is not enough evidence to establish those patients who are most likely to respond to omaveloxolone. Regarding the outcomes used to determine a patient's response, the clinician group indicated the use of standardized tests used in neurologic exams (mFARS) and functional assessments (Friedreich's Ataxia Rating Scale Activities of Daily Living [FARS-ADL]). Measurements every 6 months in the first year and then annually were noted as reasonable and practical. In terms of a clinically meaningful response to treatment, the group noted that there should be an improvement in patient function and well-being (for example, this could be reflected by just a 1-point improvement in upright stability score compared to its expected progression, indicating preserved balance in the short term and predicting delayed loss of ambulation).

The clinician group noted that omaveloxolone may be discontinued due to lack of efficacy (to be determined after a year based on clinician's and patient's global impression of change), or due to side effects (evidence of organ dysfunction). Additionally, it was recommended that a statin be prescribed to manage cardiovascular risk factors due to increased LDL (a common side effect of omaveloxolone) rather than discontinuing omaveloxolone. The clinician group highlighted that people with FA must be treated at specialized centres that offer comprehensive interdisciplinary care, regardless of omaveloxolone treatment. For patients without easy access to such centres, care should be managed by a neurologist knowledgeable about the disease and its management.

Drug Program Input

Input was obtained from the drug programs that participate in the reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a recommendation for omaveloxolone:

- relevant comparators
- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- system and economic issues.

The clinical experts consulted for the review provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
Are there other medications that are in the pipeline that show slowing of the progression of FA?	The clinical experts noted to CDEC that there are no currently approved disease-modifying therapies for FA, and no other medications are well-established to slow FA progression. Experts noted that there are some therapeutic drugs currently in the development pipeline (e.g., vatiquinone) that could present future opportunities, but are unaware of any imminent pipeline drugs with clear evidence of disease modification. While research is ongoing globally, omaveloxolone would be the first of its kind in this space if approved.
Considerations for initiation of therapy	
In the lifespan of a person with FA, when is genetic testing usually done, and who pays for this test?	The clinical experts noted to CDEC that genetic testing is typically done at the time of suspected diagnosis, usually in childhood or adolescence. It is covered by provincial health care plans in Canada, although this may vary by jurisdiction. CDEC recommended that diagnosis of FA be confirmed by genetic testing.
Overall, should the initiation criteria for omaveloxolone reflect the inclusion criteria for the MOXIe Part 2 trial?	The clinical experts noted to CDEC that strict adherence to the MOXIe trial criteria may not be fully necessary. While genetic confirmation and age thresholds, as per Health Canada's indication, should be respected, excluding certain subgroups (e.g., those with more severe disease) may not be desirable in clinical practice. The clinical experts noted the lack of clinical evidence of efficacy and safety for patients aged younger than 16 years or 40 years and older. However, they also noted that, theoretically, patients outside this age group could also benefit from omaveloxolone although evidence of such theoretical benefit is lacking. The study only included patients with a baseline mFARS score between 20 and 80 points. The experts noted that the lower bound (20 points) only ensures that patients are symptomatic and may not be a useful criterion for initiation. However, measuring progress in patients with a baseline mFARS score of more than 80 points could be challenging. CDEC recommended that an mFARS score be used for initiation of treatment and assessment of response.
In practice, what is the proportion of patients who are > 40 years? What proportion of these patients are diagnosed with FA > 40 years?	The clinical experts noted to CDEC that late diagnosis in patients aged 40 years and older is rare. Most patients are identified well before this age. The proportion of patients aged 40 years and older living with FA exists but is relatively small, as diagnosis typically occurs in childhood or early adolescence.
In practice, what is the proportion of patients who are < 16 years with a diagnosis of FA?	The clinical experts noted to CDEC that the majority of patients diagnosed with FA are aged younger than 16 years, often around 10 to 15 years of age. Pediatric populations are an important portion of patients under clinical care. CDEC recommended that treatment with omaveloxolone be initiated in patients who are at least aged 16 years.
Should the initiation criteria of omaveloxolone reflect the age thresholds in the MOXIe Part 2 trial?	The clinical experts noted to CDEC that while the trial included patients ≥ 16 years, experts acknowledge pressure to consider use in younger patients. Given limited data, it may be prudent to initially follow the age threshold from the trial (≥ 16 years), but clinical trial evidence over time

Implementation issues	Response
	may support earlier use. CDEC recommended that treatment with omaveloxolone be initiated in patients who are at least aged 16 years.
If a patient with FA discontinues treatment, e.g., due to side effects, are they eligible for re-treatment?	The clinical experts noted to CDEC that there is no known contraindication to rechallenging after side effect resolution. If the reason for stopping (e.g., transaminase elevations) resolves and the patient and/or family wishes to try again, re-initiation at the physician's discretion may be reasonable.
Considerations for continuation or renewal of therapy	
In patients with FA, is there a definition of full vs. partial responder? How would you monitor continuous response?	The clinical experts noted to CDEC that no standardized definition of "full" or "partial" responder exists. Response may be interpreted as stabilization or slower disease progression. Monitoring would be through clinical judgment, patient function (gait, upper limb coordination, or bulbar function), and possibly adapted objective measures every 6 to 12 months rather than strictly using trial scales. CDEC recommended that an mFARS score be used for initiation of treatment and assessment of response.
Considerations for discontinuation of therapy	
The recommendation by the sponsor is to assess patients for progression annually after starting treatment. What parameters would inform discontinuation of omaveloxolone?	The clinical experts noted to CDEC that persistent severe adverse events (e.g., significant liver enzyme elevations), severe allergic reactions, or patient preference might warrant discontinuation. Disease progression alone may not be a reason to stop, as even partial stabilization is considered beneficial. CDEC recommended that an mFARS score be used for assessment of response to treatment.
If a patient is achieving therapeutic response on omaveloxolone at 150 mg/day, is a "drug holiday" a consideration?	The clinical experts noted to CDEC that there is no established rationale for a drug holiday if the patient is stable and tolerating therapy. Experts suggested that discontinuation could risk losing whatever benefit was gained, and reintroducing therapy without data on off-on effects is uncertain. However, the clinical experts noted to CDEC that some adverse events can be managed and reversed. In which cases, temporary discontinuation and subsequent reintroduction of the treatment can be an option.
Considerations for prescribing of therapy	
Omaveloxolone dosing is 150 mg/day. Apart from hepatic impairment where there are lower dosing recommendations according to the product monograph, are there any other instances or circumstances where a lower dose of omaveloxolone may be appropriate?	The clinical experts did not identify other clear scenarios. The 150 mg/day dose resulted from the initial, dose-seeking part of the MOXIe trial when lower and higher doses were tested. Though numbers were low, results clearly pointed to that as an optimal dose. Standard dosing is 150 mg/day unless hepatic impairment necessitates adjustments. Pediatric dosing or off-label modifications are not supported by current evidence.
Given that patients with FA require a multidisciplinary approach, can you comment on where patients will be receiving their care across Canada?	The clinical experts noted to CDEC that patients are typically followed in specialty neuromuscular or movement disorder clinics often affiliated with tertiary care centres. Care is multidisciplinary, involving neurologists, cardiologists, physiotherapists, OTs, and genetic counsellors. This care model ensures comprehensive management and appropriate monitoring if omaveloxolone is introduced. Ideally, establishing additional sites in Canada of the FA-GCC would facilitate proper care and participation in clinical research of patients with FA.

Implementation issues	Response
Generalizability	
With the extensive exclusion criteria of the MOXIe Part 2 trial, what subgroups of patients with FA will this medication not be indicated (e.g., patients with active substance use, concomitant medications that cause significant drug-drug interactions)?	The clinical experts noted to CDEC that while no subgroup is explicitly excluded in practice, those with severe cardiac disease or other major comorbidities were underrepresented in the trial. Clinicians would exercise caution, but no absolute exclusion is anticipated. Substance use or complex drug interactions would need individual assessment.
If a patient is deemed "ambulatory" or "nonambulatory" as per the definitions within the trial, should it affect access to omaveloxolone?	Experts do not support restricting treatment based on ambulatory status. Patients who are nonambulatory may still benefit (e.g., preserved upper limb or bulbar function). CDEC recommended that treatment with omaveloxolone can be initiated in patients who are "ambulatory" or "nonambulatory" as long as they have genetically confirmed FA and an mFARS score between 20 and 80.
System and economic issues	
As it is a rare drug, access will be variable, given jurisdictions may have a specific department managing requests for rare drugs.	This is a comment from the drug programs to inform CDEC deliberations.

CDEC = Canadian Drug Expert Committee; FA = Friedreich's ataxia; FA-GCC = Friedreich's Ataxia Global Clinical Consortium; mFARS = modified Friedreich's Ataxia Rating Scale; OT = occupational therapists; vs. = versus.

Clinical Evidence

Systematic Review

Description of Studies

One pivotal phase II randomized controlled trial (MOXIe Part 2) (N = 103) was included in the review to evaluate whether omaveloxolone 150 mg once daily improved mFARS scores compared to placebo after 48 weeks of treatment in patients aged 16 to 40 years, who have an mFARS score between 20 and 80, and genetically confirmed FA. The trial included secondary end points assessing changes in ADL, upper limb function (9-HPT), mobility (Timed 25-Foot Walk test), and frequency of falls.

Despite randomization, there were imbalances in baseline characteristics between treatment groups. The omaveloxolone group had a higher proportion of females (60% versus 33%) and lower proportion of males (40% versus 67%), more patients with cardiomyopathy (48% versus 29%), higher baseline mFARS scores (40.94 versus 38.77), and more patients with GAA1 repeat lengths of 675 or higher ([redacted]) compared to the placebo group. The mean age was similar between groups (approximately 24 years), and the majority of patients in both groups were ambulatory (93%), [redacted]. Other disease characteristics were generally balanced, including mean age of FA onset (15 years), disease duration (4.8 years), and prevalence of conditions like scoliosis (74%) and sensory neuropathy (49%).

Efficacy Results

Change in mFARS Score at Week 48

The mFARS measures neurologic function across 4 domains: bulbar, upper limb coordination, lower limb coordination, and upright stability. Scores range from 0 to 93 with higher scores indicating greater impairment. Assessments were conducted at baseline and week 48.

In the prespecified primary analysis population (full analysis set), patients receiving omaveloxolone had a mean baseline mFARS score of 40.94 (standard deviation [SD] = 10.39) points and showed a mean improvement (decrease) from baseline of) at week 48. The placebo group had a mean baseline score of 38.77 (SD = 11.03) points and showed a mean worsening (increase) from baseline of). The mixed model for repeated measures (MMRM) estimate of mean difference in change from baseline between omaveloxolone and placebo was −2.40 points (95% CI = −4.31 to −0.50; P = 0.0141).

In the all-randomized population, which included patients with severe pes cavus, omaveloxolone treatment improved mFARS scores by an estimated mean difference of −1.93 points relative to placebo (95% CI, −3.70 to −0.15; P = 0.0342). The mean baseline scores were) for omaveloxolone and) for placebo, with mean changes from baseline of) and 0), respectively.

Change in Performance on 9-HPT

The 9-HPT measures upper extremity function based on the time taken to place and remove 9 pegs in a pegboard. The test was performed at baseline and week 48, with faster times indicating better function. Results are reported as the reciprocal of average time (1 per second) for the dominant hand.

In the full analysis set (FAS) population, patients receiving omaveloxolone had a mean reciprocal of average time (1 per second) baseline value of) and showed little to no change from baseline (mean change) at week 48. The placebo group had a mean reciprocal of average time (1 per second) baseline value of) and showed little to no change (mean change). The MMRM estimated mean difference between groups was).

Change in Performance on a Timed 25-Foot Walk Test

The Timed 25-Foot Walk test measures mobility based on the time taken to walk 25 feet. Assessments were conducted at baseline and week 48, with results reported as the reciprocal of average walk time (1 per second). Higher values indicate better function.

In the FAS population, patients receiving omaveloxolone had a mean baseline score of and showed a decline from baseline of at week 48. The placebo group had a mean baseline score of and showed a decline of . The MMRM estimated mean difference between groups was 0.0058 (95% CI ; P = 0.4635).

Frequency of Falls at Week 48

Falls were recorded daily by patients in a study diary throughout the 48-week treatment period. A fall was defined as “the patient unintentionally coming to rest on the ground or at a lower level.”

In the FAS population, patients receiving omaveloxolone reported a mean of [redacted]) during treatment compared to [redacted]) in the placebo group. The Poisson estimated difference in incidence rate of falls between omaveloxolone and placebo was [redacted]).

ADL at Week 48

The ADL assessment included 9 questions evaluating speech, swallowing, cutting food or handling utensils, dressing, personal hygiene, falling, walking, quality of sitting position, and bladder function. Total scores range from 0 to 36 with higher scores indicating greater impairment. Assessments were conducted at baseline and week 48.

In the FAS population, patients receiving omaveloxolone had a mean baseline ADL score of 10.7 (SD = 4.8) and showed an improvement (decrease) from baseline [redacted]) at week 48. The placebo group had a mean baseline score of 9.9 (SD = 4.8) and showed a worsening (increase) of [redacted]). The MMRM estimated mean difference between groups was –1.30 points (95% CI, [redacted]; P = 0.0420).

Harms Results

All patients in both treatment groups experienced at least 1 adverse event during the 48-week trial. Common adverse events occurring more frequently with omaveloxolone included nausea (33.3% versus 13.5%), abdominal pain (21.6% versus 5.8%), diarrhea (19.6% versus 9.6%), fatigue (21.6% versus 13.5%), and increased liver enzymes (alanine transaminase = 37.3% versus 1.9%; aspartate transaminase = 21.6% versus 1.9%). Serious adverse events occurred in 9.8% of patients receiving omaveloxolone versus 5.8% of patients receiving placebo. Treatment discontinuations due to adverse events were more frequent with omaveloxolone (7.8% versus 3.8%). Notable harms of special interest included liver enzyme elevations, which occurred more often in the omaveloxolone group. No deaths were reported during the study period.

Critical Appraisal

Overall, the MOXIe trial demonstrated acceptable internal validity, benefiting from its randomized, double-blind, placebo-controlled design, proper allocation concealment, validated primary outcome measure, and appropriate statistical methods. Key limitations affecting internal validity included baseline imbalances between treatment groups despite randomization, with the omaveloxolone group having characteristics suggesting more advanced disease (higher mFARS scores, longer GAA1 repeat lengths, and greater proportion with cardiomyopathy). Furthermore, the imbalance in the male to female ratio between omaveloxolone and placebo may also bias the results against omaveloxolone, as observed in subgroup analyses showing better response in males. The impact of some of these imbalances was explored in post hoc analyses which suggested a potential underestimation of treatment effect in the primary end point. Additionally, a higher discontinuation rate in the omaveloxolone group (13.7% versus 3.8%), primarily due

to adverse events, raises concerns about potential bias from missing data. The absence of an established minimal clinically important difference for mFARS also creates uncertainty in interpreting the clinical significance of the observed treatment effect. All outcomes besides the primary outcome either include the null or are outside the statistical testing hierarchy.

Overall, external validity of the MOXIe Part 2 trial was limited by the restriction of eligibility and the exclusion of patients with significant cardiac issues and capping those with severe pes cavus. The sponsor justified the decision to cap patients with severe pes cavus on evidence from the MOXIe Part 1 trial that suggested patients with severe pes cavus may represent a different subtype of FA and likely interferes with the ability to perform assessments that require standing or pedalling. Clinical experts involved in this review suggested that all patients with FA have a certain level of pes cavus and has not been suggested as clinically prognostic of FA prognosis. The trial excluded patients aged younger than 16 years despite most patients being diagnosed around age 11, creating uncertainty about treatment effects in pediatric populations. However, the current Health Canada indication restricts the population to patients aged 16 years or older. As such, this limitation to external validity is of limited impact if the drug is prescribed according to the indication. The restriction to patients with mFARS scores between 20 and 80 and exclusion of those with significant cardiac issues limits generalizability to patients with more severe disease. Furthermore, the outcomes used in the trial, particularly mFARS, are not routinely implemented in clinical practice, creating challenges for translating trial results to real-world assessment of treatment response. While the absence of sites in Canada was noted, clinical experts did not consider this a major limitation given the similarity of the patient population and treatment approaches across countries.

GRADE Summary of Findings and Certainty of the Evidence

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- change in mFARS score
- change in 9-HPT performance
- change in Timed 25-Foot Walk test
- change in frequency of falls
- change in ADL.

Table 3: Summary of Findings for Omaveloxolone vs. Placebo for Patients With FA

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Omaveloxolone	Difference		
Change in mFARS at week 48							
Change in mFARS score (less is better) Follow-up: 48 weeks	82 (1 RCT)	NA	[redacted]	[redacted]	[redacted]	Moderate[a]	Omaveloxolone likely results in a slower progression of the mFARS score in patients with FA compared to placebo.
Change in performance on 9-HPT at week 48							
Change in 9-HPT performance (reciprocal of average walk time [per second] – more is better) Follow-up: 48 weeks	82 (1 RCT)	NA	[redacted]	[redacted]	[redacted]	Low[b]	Omaveloxolone may result in little to no difference in the change in 9-HTP compared to placebo in patients with FA.
Change in performance on a Timed 25-Foot Walk test at week 48							
Change in Timed 25-Foot Walk test (reciprocal of average walk time [per second] – more is better) Follow-up: 48 weeks	82 (1 RCT)	NA	[redacted] 1 per second	[redacted] 1 per second	0.0058 more 1 per second ([redacted])	Low[b]	Omaveloxolone may result in little to no difference in the in Timed 25-Foot Walk test compared to placebo in patients with FA.
Change in frequency of falls at week 48							
Change in frequency of falls (less is better) Follow-up: 48 weeks	82 (1 RCT)	NA	[redacted]	[redacted]	[redacted]	Low[b]	Omaveloxolone may result in little to no difference in the change in frequency of falls compared to placebo in patients with FA.
Change in activities of daily living at week 48							
Changed in ADL (less is better) Follow-up: 48 weeks	82 (1 RCT)	NA	[redacted]	[redacted]	[redacted]	Moderate[c]	Omaveloxolone likely results in a decrease in the

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Omaveloxolone	Difference		
							ADL score in patients with FA.

9-HPT = 9-Hole Peg Test; ADL = activities of daily living; CI = confidence interval; FA = Friedreich's ataxia; mFARS = modified Friedreich's Ataxia Rating Scale; MID = meaningful improvement difference; NA = not applicable; RCT = randomized controlled trial; vs = versus.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a]No published between-group MID was identified. Clinical experts consulted by CDA-AMC identified 2 points as potential clinically meaningful threshold. Rated down 1 level for imprecision as the upper bound of the CI suggests no clinically meaningful difference and the lower bound of the 95% CI suggests benefit.

[b]No published between-group MID was identified, and the clinical experts consulted by CDA-AMC were unable to estimate a threshold for clinically important effects, therefore the null was used. Rated down 2 level for very serious imprecision as the lower CI suggests harm while the upper CI suggests benefit of little to no difference.

[c]No published between-group MID was identified, and the clinical experts consulted by CDA-AMC identified 1 point as potential clinically relevance threshold. Rated down 1 level for imprecision as the upper bound of the CI suggests no clinically meaningful difference and in the lower bound of the CI suggests clinically meaningful difference. Did not rate down for imprecision; a between-group difference of less than the null and a CI that excludes the null.

Source: Details included in the table are from the sponsor's Summary of Clinical Evidence.

Summary of Clinical Evidence. Long-Term Extension Studies

Description of Studies

One ongoing OLE study was included to assess the long-term safety and tolerability of omaveloxolone in patients with FA following the completion of Part 1 or Part 2 of the MOXIe trial. The study enrolled 149 patients from the MOXIe Parts 1 and 2 trials, including 106 patients who had not received treatment with omaveloxolone (placebo-omaveloxolone group) and 43 patients who previously received omaveloxolone (omaveloxolone-omaveloxolone group). All patients received omaveloxolone (150 mg daily), with interim analysis data available up to 144 weeks. Baseline characteristics were generally balanced between groups, though the placebo-omaveloxolone group had a higher proportion of males ([redacted]%) and patients with pes cavus ([redacted]%).

Efficacy Results

At 144 weeks, the mean change from baseline in the mFARS score was [redacted] in the placebo-omaveloxolone group and [redacted]) in the omaveloxolone-omaveloxolone group. ADL scores showed mean increases (indicating worsening) of [redacted] points in the placebo-omaveloxolone group and [redacted] points in the omaveloxolone-omaveloxolone group at week 144. Additional functional measures including the 9-HPT and Timed 25-Foot Walk test showed similar patterns.

Harms Results

The safety profile in the OLE study was consistent with the controlled trial. Common adverse events included coronavirus infection (18.8%), increased aspartate aminotransferase (18.8%), headache (18.1%), upper respiratory tract infection (16.8%), nausea (16.1%), and fatigue (13.4%). Serious adverse events occurred in 8.7% of patients (7.5% placebo-omaveloxolone group, 11.6% omaveloxolone-omaveloxolone group), and [redacted] discontinued due to adverse events ([redacted] placebo-omaveloxolone group, [redacted] omaveloxolone-omaveloxolone group). Liver enzyme elevations remained a notable adverse event of special interest but appeared manageable with monitoring. No deaths were reported.

Critical Appraisal

The main limitations of the long-term extension include the lack of a control group, an open-label design with subjective outcomes, and the potential selection bias from enrolling only patients who completed the original trials. There is a risk of attrition bias as the number of patients contributing to the analyses declined steadily over time and final measures of the outcome are based on less than one-half of patients who enrolled. The COVID-19 pandemic also impacted study visits and treatment continuity, with 14.8% of patients experiencing treatment interruptions. The use of historical controls for contextualizing progression rates, while informative, has inherent limitations due to potential differences in patient populations and assessment methods.

The clinical experts consulted on this review suggested that, with the exception of the exclusion of pediatric patients, the eligibility criteria of the OLE study were comparable to the population in Canada. The trial's strict inclusion and exclusion criteria; however, including constraints around cardiac involvement, may have led to a healthier cohort than what is typically encountered in routine clinical practice in Canada. Furthermore, the

study did not include any sites in Canada, reducing the generalizability and applicability of the results to the practice in Canada.

Indirect Comparisons

No indirect treatment comparisons were submitted for this review.

Studies Addressing Gaps in the Evidence From the Systematic Review

Description of Studies

A propensity score matched analysis compared long-term outcomes between patients in the MOXIe trial extension (N = 136) and matched patients from the FACOMS group natural history database (N = 136). Patients were matched on key characteristics including age, sex, baseline mFARS score, age at FA onset, and baseline gait score, with a mean follow-up of approximately 2.5 years in both cohorts.

Efficacy Results

The estimated 3-year change from baseline in mFARS score was 6.61 points (standard error [SE] = 0.65) in matched patients from the FACOMS group compared to 3.00 points (SE = 0.66) in patients in the MOXIe trial extension, representing a statistically significant difference of −3.61 points (95% CI, −1.79 to −5.43) favouring omaveloxolone. This suggests that patients from the MOXIe OLE study experienced a slower increase in mFARS scores than patients included from the matched FACOMS group (indicative of slowed disease progression).

Harms Results

Safety outcomes were not assessed in this analysis.

Critical Appraisal

The choice of study design was considered appropriate given the constraints of the rare disease. The real-world evidence used comparative evidence to describe treatment efficacy in a population that is treatment-naive, but the choice of baseline in the FACOMS group could introduce indication bias due to unmeasured confounding factors. While the timing of treatment initiation was not an issue, the primary analysis cohort included patients who completed 48 weeks of follow-up, potentially differing systematically from those in the FACOMS group. Limited bias due to exposure or outcome misclassification was noted, though measurement error at year 3 could slightly favour omaveloxolone. Propensity score matching variables were sufficient, and diagnostic results showed comparability between the FACOMS group and the MOXIe trial cohorts. However, the estimation of progression at 3 years relied on a missing-at-random assumption, with missing outcome analyses not provided, raising concerns about dropout due to adverse events.

Ethical Considerations

Patient group, clinician group, and drug plan input, as well as consultation with clinical experts were reviewed to identify ethical considerations specific to the use of omaveloxolone for the treatment of FA in adults and adolescents aged 16 years or older.

Diagnosis, Treatment, and Experiences of People Living With FA

- FA substantially reduces life expectancy, with most patients living an average of 37 years worldwide. Cardiac complications account for the majority of deaths, alongside risks such as pneumonia, stroke, and diabetic coma. Beyond its life-limiting nature, FA imposes significant physical and psychosocial burdens on patients and caregivers. The progressive loss of coordination, balance, and muscle strength typically leads to reliance on mobility aids within 8 to 10 years of symptom onset, with many patients requiring a wheelchair 11 to 15 years after diagnosis. Comorbidities like cardiomyopathy, diabetes, and scoliosis further contribute to fatigue, pain, and reduced mobility. Patient group input noted that as the condition progresses, people slowly lose their ability to function independently and often become unable to participate in social activities or the workplace due to impacts on mobility, coordination, and speech. This not only may result in social isolation and a lost sense of autonomy, but it can also impact people's mental health with patient group input reporting experiences of anxiety and depression among patients with FA. Caregivers similarly face challenges as they strive to balance the demands of care with their own mental health, work responsibilities, and financial stability.
- Patient and clinician group input indicated that while FA is typically diagnosed in childhood or adolescence, disparities in diagnosis and referral pathways can delay access to essential care. Though the requisite genetic testing for confirmation of FA is broadly available across Canada, clinician group input noted that non-neurologic presentations may still delay recognition, and testing only occurs when clinical suspicion arises.
- There are currently no therapies indicated to slow down or halt the progression of FA. Instead, patients and clinicians rely on treatment options oriented toward managing complications associated with FA and rehabilitation (e.g., physiotherapy and occupational therapy). Patient group input and clinical experts suggested that existing care is inadequate, with supportive therapies providing inconsistent benefits and access often limited by factors such as out-of-pocket costs, lack of insurance coverage, and variable geographic availability of specialized services. In advanced stages, logistical and financial barriers to accessing specialized care centres compound these challenges. Taken together, this underscores the high unmet need for an accessible treatment option that can address the progression of FA and improve quality of life for patients and their families.
- Patient group input and clinical experts indicated that people with FA want an intervention that can slow down or stop the progression of FA. Interventions that could improve symptom control (which may come with slowed progression), preserve mobility, improve energy levels, preserve existing quality of life, and prevent long-term complications (e.g., scoliosis, diabetes, heart problems) would also be highly valued.

Clinical Evidence Used in the Evaluation of Omaveloxolone

- The safety and efficacy of omaveloxolone in patients aged 16 to 40 years with genetically confirmed FA were evaluated in the pivotal phase II, randomized, double-blinded, placebo-controlled MOXIe trial (N = 103). The trial's primary objective was to assess whether a daily oral dose of omaveloxolone

(150 mg) improved mFARS scores at week 48 when compared to placebo. mFARS is a composite measure that evaluates neurologic function in patients with FA, including assessments of speech, upper and lower limb coordination, and standing and walking ability. Results demonstrated a statistically significant improvement in mFARS scores for patients receiving omaveloxolone versus placebo. However, the Clinical Review report notes that the clinical significance of this improvement remains uncertain due to the absence of an established minimal clinically important difference for mFARS scores. Additionally, other functional measures included as secondary outcomes (e.g., changes in performance on a 9-HPT and a Timed 25-Foot Walk test) did not demonstrate meaningful improvements with treatment. No end points examined changes in HRQoL or experiences with symptoms such as fatigue, which are important outcomes to patients. Further details on the MOXIe trial are provided in the Clinical Review report.

- Sponsor-submitted real-world evidence suggests that the benefits observed in mFARS scores during the initial 48 weeks of treatment may be maintained over 3 additional years of treatment, with patients who were treated showing slower disease progression compared to natural history. However, long-term data beyond 3 years is limited, making ongoing data collection and monitoring essential for understanding whether omaveloxolone offers sustained clinical value.
- Clinical experts considered the MOXIe results broadly generalizable to the population with FA, and the trial population consisted of patients who were predominately white (98%). This was seen as appropriate given the condition primarily occurs in people who are white. However, the exclusion of patients with clinically significant cardiac disease, a common FA comorbidity, represents a notable gap in the evidence. While this absence would not deter clinical experts from prescribing omaveloxolone to patients with comorbid cardiac disease, they emphasized the importance of careful monitoring and the collection of real-world data to inform future clinical decision-making in this population. Similarly, individuals aged younger than 16 years were excluded from the MOXIe trial, leaving a significant data gap in understanding the safety and efficacy of omaveloxolone for this population.

Clinical Use of Omaveloxolone

- Omaveloxolone represents the first potential disease-modifying treatment for FA, addressing a critical unmet need in this population. Clinical experts indicated they would prescribe it as a first-line treatment for patients aged 16 years and older, given the lack of alternatives. They expressed confidence in its safety profile and considered the observed slowing of disease progression, as measured by changes in mFARS scores over the first 48 weeks of treatment, to be promising. Real-world evidence suggests the initial benefit in delayed progression may be sustained for up to 3 years. Both clinical experts and patient group input underscored the significance of this potential benefit, with patients emphasizing their hope for treatments that could slow disease progression.
- While omaveloxolone appears well-tolerated overall, clinical experts highlighted uncertainties in managing specific adverse events and pre-existing comorbidities. Elevated liver enzymes were noted as a particular challenge, with the lack of clear guidance from the sponsor making decisions about discontinuing treatment difficult in cases of prolonged elevation. Similarly, the exclusion of individuals with significant cardiac disease limits understanding of the safety of omaveloxolone in this group, leaving providers to navigate potential risks without robust evidence. These gaps underscore the importance of thorough informed consent processes and close monitoring to address patient-specific complexities.
- If recommended for public reimbursement, clinical experts anticipate caregivers will be interested in prescribing omaveloxolone off label to patients aged younger than 16 years, despite the current absence of data in this population. This scenario poses an ethical dilemma for providers, who may experience moral distress when trying to balance an uncertain risk-benefit profile in this population against the potential harm of waiting to treat in the context of this early-onset, progressive disease. Clinical experts noted that this could lead to disparate prescribing practices, with some providers offering off-label treatment and others adhering strictly to the indicated population, potentially creating inequities in access and care. This variability in prescribing practices could also risk eroding trust in health care providers, as families navigating these decisions may encounter conflicting recommendations. If providers choose to prescribe to this population, clinical experts noted they will need to engage in transparent conversations with families, clearly addressing the known risks, lack of evidence, and uncertainties surrounding potential outcomes.
- Clinical experts noted that patients with FA are typically managed by multidisciplinary care teams with specialization in FA and in specialized settings. With the introduction of omaveloxolone, clinical experts indicated that continued reliance on these specialized clinics will be essential to ensure appropriate monitoring and treatment. However, this requirement could create barriers for patients in rural or underserved regions who may already face challenges accessing care. Additionally, implementing intensive or standardized outcome measures, such as mFARS, could strain clinical capacity and limit accessibility. Ensuring equitable access to omaveloxolone will require careful consideration of how monitoring protocols can be adapted to balance feasibility and fairness across diverse care settings.

Health Systems Impact

Introducing omaveloxolone raises ethical considerations about resource allocation and health system sustainability, given the therapy's high cost and limited long-term safety and efficacy evidence. Patient group input suggested potential downstream savings, such as reduced emergency department visits and prolonged workforce participation, but there is currently no evidence to support this. Clinical experts emphasized the importance of collecting real-world data through registries to better understand the impact on function, symptoms, quality of life, mortality, and health care costs of omaveloxolone. However, they cautioned that data-collection efforts could place great financial and administrative burdens on clinicians and health systems, particularly in under-resourced settings.

The potential use of mFARS as a standardized tool to guide treatment initiation, monitoring, and renewal raises significant practical and resource challenges, as it risks overburdening the health system with unknown benefit. While mFARS was the primary end point in the MOXIe trial, it is not routinely used in clinical practice and would require specialized training, extended appointment times, and greater administrative coordination to implement effectively. These requirements could strain under-resourced clinics, particularly those in underserved areas, and bias prescribing toward larger, well-equipped centres. Further, as a measure reliant on clinician interpretation and subject to variability, the use of mFARS in clinical practice may create inconsistencies in treatment decisions. As such, clinical experts questioned whether such intensive monitoring efforts justify the significant resources required, particularly given the subjective nature of the measures and their perception that providers would be reluctant to discontinue therapy in the absence of serious harms. Instead, clinical experts suggested that long-term monitoring should rely on clinical judgment, assessing patient function (e.g., gait, upper limb coordination, and bulbar function), and possibly using adapted objective measures every 6 to 12 months, instead of solely depending on trial scales.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Regression-based model
Target population	Adults and adolescents aged 16 years and older with FA
Treatment	Omaveloxolone plus SOC (SOC assumed by the sponsor to comprise treatments for symptom and comorbidity management)
Dose regimen	Omaveloxolone: 150 mg once daily
Submitted price	Omaveloxolone: $364.30 per capsule
Submitted treatment cost	Omaveloxolone: $346,933 per year[a]
Comparator	SOC

Component	Description
Perspective	Canadian publicly funded health care payer Societal perspective[b]
Outcomes	QALYs, LYs
Time horizon	Lifetime (84 years)
Key data sources	• Efficacy of omaveloxolone was informed by observations from the MOXIe trials (omaveloxolone vs. placebo); efficacy of SOC was based on data from the FACOMS natural history study. • The sponsor submitted a propensity-matched analysis comparing disease progression (via mFARs score) in patients in the FACOMS natural history study to those in the MOXIe trial. Rate ratios from this analysis were applied to the mFARS trajectory for patients with SOC to derive the mFARS trajectory for patients who received omaveloxolone.
Key limitations	• Evidence from the MOXIe trial suggests that omaveloxolone likely results in slower neurologic decline (based on mFARS score) compared to placebo over 48 weeks. However, the clinical importance of this finding is uncertain due to the lack of an established minimum clinically important difference. Other functional outcomes (e.g., upper limb function, mobility, or frequency of falls) did not show significant improvements with use of omaveloxolone. • The long-term relative effectiveness of omaveloxolone compared to SOC alone is highly uncertain owing to a lack of direct comparative data beyond 48-weeks (MOXIe trial duration). To inform the comparative effectiveness of omaveloxolone in the economic model, the sponsor undertook a propensity-matched analysis using data from the FACOMS natural history study for SOC and the ongoing MOXIe long-term extension study for omaveloxolone (up to 3 years of observation); however, the interpretation of finding from this analysis are limited by the open-label design and potential selection bias (refer to CDA-AMC Clinical Review). In the economic model, the sponsor assumed that the estimated effectiveness of omaveloxolone plus SOC from the propensity-matched analysis would be maintained indefinitely, without consideration of effectiveness waning. Approximately 96% of the incremental QALYs predicted to be gained with omaveloxolone were accrued after the 48-week MOXIe trial period. • The impact of omaveloxolone on HRQoL: In the MOXIe trial, the mean change in SF-36 scores from baseline to week 48 were small and similar between omaveloxolone and placebo. The health state utility values used in the sponsor's model are highly uncertain owing to the use of mapping in their derivation. The results of a sponsor-submitted scenario analysis using alternative utility values indicate that the estimated cost-effectiveness of omaveloxolone is highly sensitive to the chosen utility values, with ICERs from both perspectives increasing approximately 2-fold. • The sponsor submitted an analysis from a societal perspective, which included indirect costs and the impact of treatment on costs and the HRQoL of caregivers. This analysis required assumptions about the impact of FA on the caregiver's HRQoL, hours worked by patients and caregivers, the proportion of patients and caregivers employed, and costs paid by patients and caregivers vs. the health care system. Indirect costs and caregiver HRQoL were not outcomes of the MOXIe trial, and the impact of omaveloxolone on these costs and outcomes is highly uncertain.
CDA-AMC reanalysis results	• No reanalyses were performed owing to uncertainty in the clinical evidence that could not be resolved through reanalysis. • Based on the sponsor's submission, omaveloxolone-SOC is not cost-effective at a WTP of $50,000 per QALY gained when either the public health care payer or a societal perspective is adopted. Price reductions of 95% to 97% would be required for

Component	Description
	omaveloxolone-SOC to be cost-effective compared to SOC from the societal and public payer perspectives, respectively, at this threshold.

CDA-AMC = Canada's Drug Agency; FA = Friedreich's ataxia; FACOMS = Friedreich's Ataxia Clinical Outcome Measures; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; LY = life-year; mFARS = modified Friedreich's Ataxia Rating Scale; QALY = quality-adjusted life-year; SF-36 = Short Form (36) Health Survey; SOC = standard of care; vs. = versus; WTP = willingness-to-pay.

[a]Assuming 87% relative dose intensity. Annual cost without adjustment: $399,180.

[b]Omaveloxolone is being reviewed by CDA-AMC through the complex review pathway; as such, CDA-AMC has appraised 2 cost-effectiveness analyses submitted by the sponsor; 1 adopting a publicly funded health care payer perspective and 1 adopting a societal perspective.

Budget Impact

CDA-AMC identified the following key limitations with the sponsor's analysis: the number of people aged 16 years and older with FA is likely underestimated and the uptake of omaveloxolone is uncertain and may be higher than anticipated by the sponsor. In the CDA-AMC reanalysis, the number of patients eligible for omaveloxolone was derived using registry data from MDC. In the CDA-AMC base case, the 3-year budget impact of reimbursing omaveloxolone for the treatment of FA in people aged 16 years and older is expected to be $224,535,025 (year 1 = $53,122,535; year 2 = $78,574,132; and year 3 = $92,838,358). The estimated budget impact is highly sensitive to the number of patients eligible for omaveloxolone and assumptions about its uptake among eligible patients.

Request for Reconsideration

The sponsor filed a request for reconsideration of the draft recommendation for omaveloxolone for the treatment of FA in patients aged 16 years and older. In their request, the sponsor identified the following issues:

- The sponsor requested that the initiation criteria be changed to an "mFARS score ≤80" rather than an mFARS score of 20 or more and 80 or less.
- The sponsor requested that the condition indicating patients must be ambulatory to receive omaveloxolone be removed from the initiation criteria.
- The sponsor requested that mFARS be considered as the primary indicator for continuation, with a score of 80 or more as the cut-off, rather than loss of ambulation.
- The sponsor requested that the renewal criteria also consider the possibility of worsening rather than just stabilization (i.e., no deterioration from baseline).

In the meeting to discuss the sponsor's request for reconsideration, CDEC considered the following information:

- information from the initial submission related to the issues identified by the sponsor
- feedback from 3 clinical specialists with expertise in diagnosing and treating patients with FA
- feedback on the draft recommendation from 3 patient groups, NAF, MDC, and FARA

- feedback on the draft recommendation from 2 clinician groups, the Canadian Movement Disorders Society and the NMD4C Neuromuscular Clinician Group
- feedback on the draft recommendation from the public drug plans that participate in the reimbursement review process.

All feedback received in response to the draft recommendation is available on the CDA-AMC website.

CDEC Information

Initial Meeting Date: February 26, 2025

Members of the Committee

Dr. Peter Jamieson (Chair), Dr. Kerry Mansell (Vice Chair), Dr. Sally Bean, Daryl Bell, Dan Dunsky, Dr. Trudy Huyghebaert, Morris Joseph, Dr. Dennis Ko, Dr. Christine Leong, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Nicholas Myers, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Dr. Edward Xie, and Dr. Peter Zed.

Regrets: One expert committee member did not attend.

Conflicts of interest: None

Reconsideration Meeting Date: June 26, 2025

Members of the Committee

Dr. Peter Jamieson (Chair), Dr. Kerry Mansell (Vice Chair), Dr. Sally Bean, Daryl Bell, Dan Dunsky, Dr. Ran Goldman, Dr. Trudy Huyghebaert, Morris Joseph, Dr. Dennis Ko, Dr. Christine Leong, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Nicholas Myers, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Dr. Edward Xie, and Dr. Peter Zed.

Regrets: Three expert committee members did not attend.

Conflicts of interest: None

Canada's Drug Agency
L'Agence des médicaments du Canada
Drugs. Health Technologies and Systems. Médicaments, technologies de la santé et systèmes.

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Canada's Drug Agency (CDA-AMC) is a pan-Canadian health organization. Created and funded by Canada's federal, provincial, and territorial governments, we're responsible for driving better coordination, alignment, and public value within Canada's drug and health technology landscape. We provide Canada's health system leaders with independent evidence and advice so they can make informed drug, health technology, and health system decisions, and we collaborate with national and international partners to enhance our collective impact.

Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.