# Disease-Specific Treatments for Friedreich's Ataxia

**Draft Background and Scope**

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## Background

Friedreich's ataxia (FA) is a rare, hereditary, neurodegenerative illness caused by a deficiency in the mitochondrial protein frataxin.[1,2] FA is characterized by worsening ataxia, where patients experience progressive loss of balance, gait, and coordination of the arms and legs, often followed by broader neurologic deficits affecting swallowing and speech. Due to the ubiquity of frataxin, patients with FA can experience non-neurologic complications, including cardiomyopathy, musculoskeletal deformities (i.e., scoliosis), and metabolic dysfunction (i.e., diabetes). The average life expectancy is 35-40 years.[3] FA affects about 5,000 persons in the United States and is most common among populations of European and Indian ancestry. Mean total annual healthcare costs are estimated to be $18,150, driven most by paid homecare, with substantial indirect costs.[4,5]

The diagnosis of FA is confirmed by genetic testing. Nearly all patients with FA inherit two copies of a mutated gene that includes repeated short DNA sequences that preclude the body from making sufficient frataxin, a protein that is essential for energy metabolism and preventing cellular damage from oxidative stress. The number of these repeat DNA expansions strongly correlates with an earlier age of onset. While on average symptoms begin between eight and 14 years with gradual loss of the ability to walk over 10-15 years, the rate of progression and severity of disease are highly variable and most strongly correlate with the age of onset.[6,7] Early-onset FA (<eight years) is the most severe, declining 50% faster than typical onset (eight-14 years) and twice as fast as intermediate onset (15-24 years), with patients often dying young from cardiomyopathy or aspiration pneumonia from trouble swallowing, the two leading causes of death. Late-onset FA (≥25 years) presents with milder and more slowly progressive impairments with fewer non-neurologic complications.

There are no available cures for FA. Until recently, there were also no disease-modifying therapies. Clinical practice guidelines published in 2022 recommended multidisciplinary anticipatory care, including rehabilitation, clinical specialist evaluations, and regular screening and management for FA complications.[8] In 2023, the FDA approved omaveloxolone (SKYCLARYS, Biogen Inc.) as the first disease-specific therapy for FA.[9] Omaveloxolone is a small-molecule and is taken orally once daily.[10] The drug is approved for adolescents and adults 16 years of age or older, in accordance with the

pivotal clinical trial eligibility criteria. Clinical trials enrolling younger patients with FA are currently underway.[11]

One potential therapeutic approach to FA is to replace the deficient frataxin protein. Nomlabofusp (Larimar Therapeutics, Inc.) is a recombinant fusion protein with a cell penetrating peptide bound to frataxin. It is administered daily as a subcutaneous injection.[12] Submission of a Biologics License Application (BLA) to the FDA is anticipated in June 2026.[13]

## Stakeholder Input

This draft scoping document was developed with input from diverse stakeholders, including patients, clinicians, researchers, and manufacturers of the agents of focus in this review. This document incorporates feedback gathered during preliminary calls with stakeholders and open input submissions from the public. A revised scoping document will be posted following a three-week public comment period. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments.

Because FA is a heterogenous, multisystem, progressive illness, people living with the disease have many different symptoms and varied experiences.[14] Difficulties with physical functioning occur in nearly all patients. Many people with FA have increasing difficulty swallowing, speaking, hearing, and seeing. Patients' greatest worries are loss of independence and development of life-limiting heart disease. The progressive worsening of symptoms requires constant adaptations, which is challenging both physically and emotionally, and necessitates adequate home care support.

There are also considerable emotional, physical, and financial impacts on caregivers. As a person's disease progresses, there is often an increased dependence on caregivers. Caregivers may need to reduce work hours to provide care, assist with transportation (including to medical appointments), and/or contribute financially to the cost of treatment.

All stakeholders we spoke to echoed the unmet need for this population, especially given the lack of FA-specific therapies until 2023. Even if a cure is not available, patients and clinicians alike expressed that new therapies that either slowed disease progression or managed or prevented symptoms or complications of FA would be considered highly valuable.

## Report Aim

This project will evaluate the health and economic outcomes of omaveloxolone and nomlabofusp for Friedreich's ataxia. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

## Applicable Framework Adaptations

We propose to assess omaveloxolone and nomlabofusp under an adaptation of the ICER Value Framework for treatments of serious, ultra-rare conditions because we believe they meet the following criteria:

- The eligible patient populations for the treatment indication(s) included in the scope of the ICER review is estimated at fewer than approximately 10,000 individuals.
- There are no ongoing or planned clinical trials of the treatment for a patient population greater than approximately 10,000 individuals.

## Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see ICER's grey literature policy).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the revised scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

## Populations

The population of interest for this review is adolescents and adults with Friedreich's ataxia.

Data permitting, we will evaluate the evidence for treatment effect modification by subpopulations defined by:

- Age of onset (early, typical, intermediate, late-onset, etc.)
- Ambulation Status
- Number of guanine-adenine-adenine (GAA) repeat expansions
- People with complications of FA (e.g., pes cavus or high arch)
- Sociodemographic factors (e.g., sex, age, race, ethnicity)

## Interventions

The intervention(s) of interest of this review are:

- Omaveloxolone (SKYCLARYS, Biogen Inc.)
- Nomlabofusp (Larimar Therapeutics, Inc.)
- Nomlabofusp added to omaveloxolone

## Comparators

- No disease modifying therapy
- The interventions to each other

## Outcomes

The outcomes of interest are described in the list below.

- Patient-important Outcomes
    - Function (i.e., bulbar, upper limb, lower limb, upright stability)
    - Mobility/need for assistive devices
    - Activities of daily living
    - Fatigue
    - Spasticity
    - Cardiomyopathy
    - Diabetes requiring treatment
    - Musculoskeletal deformities (e.g., scoliosis)
    - Vision
    - Hearing

    - Employment
    - Quality of Life
    - Need for a personal caregiver
- Other Outcomes
    - Changes in FA biomarkers
    - A1c
- Adverse events (AEs) including but not limited to:
    - Serious AEs
    - Discontinuation due to AEs
    - AEs of interest
        - Anaphylaxis
        - Injection-site reactions
        - Liver injury
        - Cardiomyopathy

### Timing

Evidence on intervention effectiveness and harms will be derived from studies of any duration.

### Settings

All relevant settings will be considered, with a focus on outpatient settings in the United States.

## Benefits Beyond Health and Special Ethical Priorities

Our reviews seek to provide information on benefits beyond health and special ethical priorities offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements (i.e., not specific to a given disease) are listed in the table below.

**Table 1.1. Benefits Beyond Health and Special Ethical Priorities**

| Benefits Beyond Health and Special Ethical Priorities* |
|---|
| There is substantial unmet need despite currently available treatments. |
| This condition is of substantial relevance for people from a racial/ethnic group that have not been equitably served by the healthcare system. |
| The treatment is likely to produce substantial improvement in caregivers' quality of life and/or ability to pursue their own education, work, and family life. |
| The treatment offers a substantial opportunity to improve access to effective treatment by means of its mechanism of action or method of delivery. |

*Benefits beyond health and special ethical priorities shape to some extent how the value of any effective treatments for a particular condition will be judged and are meant to reflect the broader effects of a specific

treatment on patients, caregivers, and society. For additional information, please see the ICER Value Assessment Framework.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

## Scope of Comparative Value Analyses

A detailed economic model analysis plan with proposed methodology, model structure, model parameters, model inputs, and model assumptions will be published on August 21, 2026. This scoping document provides early thoughts about the overall model structure.

As a complement to the evidence review, we will develop an economic model to assess the lifetime cost-effectiveness of omaveloxolone and nomlabofusp as treatments for Friedreich's ataxia compared with no disease modifying therapy. The model structure will be based in part on a literature review of prior published models in Friedreich's ataxia. Analyses will be conducted from the health care system perspective and the modified societal perspective. The base case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Societal impacts (e.g., patient and caregiver productivity) and other indirect costs will be considered in a separate modified societal perspective analysis. This analysis will be considered as a co-base case when (a) direct data on indirect costs are available, (b) the societal costs of care are large relative to direct health care costs, and (c) the impact of treatment on these costs is substantial. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than $200,000 per QALY, and/or when the result crosses the threshold of $100,000-$150,000 per QALY gained. If direct data are lacking on patient and/or caregiver productivity, we will implement a method to capture the potential impacts of omaveloxolone and nomlabofusp on productivity (patient and caregiver) as well as certain other impacts (e.g., patient time in treatment).

The target population will consist of adolescents and adults living with Friedreich's ataxia. As a scenario, we may explore treatment in younger patients. If data allow, subgroups within the target population will be explored based on age at disease onset (e.g., early vs. late onset). The model will consist of health states representing different levels of neurological impairment, based on the modified Friedreich's Ataxia Rating Scale (mFARS) scores or disability levels. Subject to data availability, additional non-neurological manifestations, such as cardiomyopathy, may also be incorporated into the model. A cohort of patients will transition between states during predetermined cycles of one year over a lifetime time horizon, modeling patients from treatment initiation until death.

Key model inputs will include clinical probabilities, quality of life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between interventions. Treatment effectiveness will be estimated using relevant clinical trials.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events (AEs), and direct medical costs. The health outcome of each intervention will be evaluated in terms of ambulatory years gained (pending data), life-years gained, quality-adjusted life years (QALYs) gained, and equal value of life years gained (evLY). Quality of life weights will be applied to each health state, including quality of life decrements for serious adverse events and non-neurological manifestations not captured via health states. The model will include direct medical costs, including but not limited to costs related to drug administration, drug monitoring, condition-related care, and serious adverse events. In addition, patient and caregiver productivity changes and other indirect costs will be included in a separate analysis, as available data allow. Relevant pairwise comparisons will be made between treatment and no disease modifying therapy, and results will be expressed in terms of the marginal cost per QALY gained, cost per evLY gained, cost per life-year gained, and cost per year in a non-ambulatory state avoided (pending data).

In separate analyses, we will explore the potential health care system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the economic model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact, and will allow assessment of any need for managing the cost of such interventions. More information on ICER's methods for estimating potential budget impact can be found here.

## Identification of Low-Value Services

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see ICER's Value Assessment Framework). These services are ones that would not be directly affected by omaveloxolone and nomlabofusp (e.g., use of assistive devices), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of Friedreich's ataxia beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

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