Disease-Specific Treatments for Friedreich's Ataxia: Effectiveness and Value

Draft Evidence Report

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AUTHORS:

Anil N. Makam, MD, MAS
Associate Professor of Medicine
University of California, San Francisco

Woojung Lee, PharmD, PhD
Associate Director of Health Economics and Decision Modeling
Institute for Clinical and Economic Review

Avery McKenna, BS
Research Lead
Institute for Clinical and Economic Review

Marie Phillips, BA
Health Economics Research Assistant
Institute for Clinical and Economic Review

Sophia Cassim, BA
Research Assistant
Institute for Clinical and Economic Review

Daniel A. Ollendorf, PhD, MPH
Chief Scientific Officer and Director of HTA Methods and Engagement
Institute for Clinical and Economic Review

David M. Rind, MD, MSc
Chief Medical Officer
Institute for Clinical and Economic Review

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Anil N. Makam served as the lead author for the report. Avery McKenna led the systematic review and authorship of the comparative effectiveness section of this report with assistance from Sophia Cassim. Woojung Lee developed the cost-effectiveness model and authored corresponding sections of the report with support from Daniel Ollendorf. Marie Phillips conducted the analysis for the budget impact model. David M. Rind provided methodologic guidance on the clinical and economic evaluations. We would also like to thank Becca Piltch, Chloe Fandetti, and Tea Gianoulis for their contributions to this report.

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In the development of this report, ICER's researchers consulted with clinical experts, patients, manufacturers, and other stakeholders. The following individuals served as external reviewers of the initial draft evidence report:

Expert Reviewers
Manuela Corti, PhD, PT
Associate Professor
University of Florida

Kellyn Madden, MS, CGC
Director of Patient Engagement
Friedreich's Ataxia Research Alliance

Ronan Mahon, PhD, BSc, MSc
Lecturer, Economics
University of Galway, Ireland

Susan Perlman, MD
Clinical Professor of Neurology
UCLA Medical Center

None of the external reviewers or other experts we spoke to are responsible for the final contents of this report, nor should it be assumed that they support any part of it. Furthermore, it is possible that external reviewers may not have had the opportunity to review all portions or iterations of the report. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.

To protect patient confidentiality, ICER does not routinely name individual patients or care partners who provided us with input and feedback.

For a list of stakeholders from whom we requested input, or who have submitted public comments so far, please visit our website.

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Table 1. ICER Authors and External Collaborators Conflict of Interest Disclosures

ICER Authors and External Collaborators	Conflict of Interest
Sophia Cassim, BA, Research Assistant, Institute for Clinical and Economic Review	No conflicts to disclose.
Woojung Lee, PharmD, PhD, Associate Director of Health Economics and Decision Modeling, Institute for Clinical and Economic Review	No conflicts to disclose.
Anil N. Makam, MD, MAS, Associate Professor of Medicine, University of California, San Francisco	No conflicts to disclose.
Avery McKenna, BS, Research Lead, Institute for Clinical and Economic Review	No conflicts to disclose.
Daniel A. Ollendorf, PhD, MPH, Chief Scientific Officer and Director of HTA Methods and Engagement, Institute for Clinical and Economic Review	No conflicts to disclose.
Marie Phillips, BA, Health Economics Research Assistant, Institute for Clinical and Economic Review	No conflicts to disclose.
David M. Rind, MD, MSc, Chief Medical Officer, Institute for Clinical and Economic Review	No conflicts to disclose.

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Expert Reviewer	Conflict of Interest
Manuela Corti, PhD, PT, Associate Professor, University of Florida	Dr. Corti has disclosed receiving financial support for serving as Chair of the Advisory Board for Reata Pharmaceuticals, Inc.
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List of Acronyms and Abbreviations Used in this Report

AE	Adverse event
ALT	Alanine aminotransferase
ARP	All randomized participants
AST	Aspartate aminotransferase
BLA	Biologics License Application
BLS	Bureau of Labor Statistics
BMI	Body mass index
CDA-AMC	Canada's Drug Agency
CDR	Clinical Trial Diversity Rating Tool
CE	Cost-effectiveness
CFB	Change from baseline
CGIC	Clinical Global Impression of Change
CI	Confidence interval
CNS	Central nervous system
DNA	Deoxyribonucleic acid
ED	Emergency department
eGFR	Estimated glomerular filtration rate
EQ-5D-3L	EuroQol 5-Dimension 3-Level
evLY	Equal value life year
FA	Friedreich's ataxia
FA-ADL	Friedreich's Ataxia – Activities of Daily Living Scale
FA-COMS	Friedreich's Ataxia Clinical Outcome Measure Study
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
FXN	Frataxin
GAA	Guanine-adenine-adenine
HbA1c	Hemoglobin A1c
HF	Heart failure
HIDI	Health Improvement Distribution Index
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
IQR	Interquartile range
ITT	Intention-to-treat
JNHB	Joint Nordic HTA-Bodies
Kg	Kilogram
LS	Least squares
LVEF	Left ventricular ejection fraction
MAD	Multiple ascending dose
MCID	Minimal clinically important difference
mFARS	modified Friedreich's Ataxia Rating Scale
MFIS	Modified Fatigue Impact Scale
mg	milligram
mL	Milliliter
mmHg	Millimeters of mercury
MMRM	Mixed model for repeated measures
NA	Not applicable
NR	Not reported
OL	Open label
OLE	Open label extension

Omav	Omaveloxolone
OS	Overall survival
PAS	Primary analyzed subset
PBAC	Pharmaceutical Benefits Advisory Committee
PBM	Pharmacy benefit manager
PD	Pharmacodynamics
Pg	Picogram
PGIC	Patient Global Impression of Change
PK	Pharmacokinetics
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
QALY	Quality-adjusted life year
QoL	Quality of Life
RCT	Randomized control trial
ROR	Reporting odds ratio
RR	Risk ratio
SAD	Single ascending dose
SAE	Serious adverse event
SARA	Scale for the Assessment and Rating of Ataxia
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean
SF-36	36-Item Short Form Health Survey
SMD	Standardized mortality difference
SoC	Standard of care
T25-FW	Timed 25-Foot Walk
TBD	To be determined
TEAE	Treatment-emergent adverse event
TTO	Time trade-off
US	United States
USD	United States dollars
USS	Upright Stability Score
WAC	Wholesale acquisition cost
Yr	Year
µg	Microgram
9-HPT	Nine-hole peg test

Executive Summary

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 fatigue and progressive loss of balance, gait, and coordination of the arms and legs, often followed by broader neurologic deficits affecting swallowing, speech, vision, and hearing. 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 rate of progression and severity of disease are highly variable and most strongly correlate with the age of onset.[3,4] The average life expectancy is 35-40 years, with cardiomyopathy as the leading cause of death.[5] 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 mostly by paid homecare, with substantial indirect costs.[6,7]

There are no available cures for FA. In 2023, the Food and Drug Administration (FDA) approved omaveloxolone (SKYCLARYS, Biogen Inc.) as the first disease-specific therapy for FA.[8] Omaveloxolone is a small-molecule drug and is taken orally once daily.[9] The drug is approved for adolescents and adults 16 years of age or older. Nomlabofusp (Larimar Therapeutics, Inc.) is a recombinant fusion protein that delivers frataxin to mitochondria. It is administered daily as a subcutaneous injection.[10] A rolling Biologics License Application (BLA) was initiated on June 29, 2026 with completion of the application to the FDA expected in the second half of 2026.[11]

In a 48-week randomized trial in 103 patients with FA between 16 and 40 years of age, omaveloxolone slowed disease progression by 1.93 points compared to the placebo group (95% confidence interval [CI]: -3.70 to -0.15; p=0.03) on the modified Friedreich's Ataxia Rating Scale (mFARS), a composite measure of function across four domains. However, the clinical meaningfulness of this modest improvement is uncertain because patients and clinicians did not clearly perceive a benefit, and analyses of the broad randomized population showed a smaller, non-significant improvement in the secondary functional outcome, Friedreich's Ataxia Rating Scale – Activities of Daily Living (FA-ADL). Additionally, there were fewer participants in the omaveloxolone group completing the 48-week mFARS assessment than the placebo group. In a propensity-matched analysis of patients in an open-label extension (OLE), treatment with omaveloxolone was associated with slower progression at year three (-3.61 points; p=0.0001), which persisted in a 5-year follow-up analysis. The trial and the OLE found few serious harms.

The evidence base for the efficacy of nomlabofusp is derived from the ongoing JIVE study, an open-label, single arm trial of patients 12 years of age or older with FA. At the time of this report, efficacy data are based on a March 2026 data cut obtained from manufacturer press releases and corporate presentations. Among 13 patients who had outcomes data at 12 months, the mean reduction was 1.0 mFARS points compared to baseline (range of -6.5 to 3.0 points). This was better than an

unmatched natural history reference group. Among seven patients with 18-month follow-up data, the mean reduction was 2.3 points (range of -10.0 to +4.5 points). Skin frataxin level, the key biomarker outcome, increased by the first month of treatment in the subset of 26 participants with available data.

Nearly half of patients treated with nomlabofusp discontinued therapy (21 of 43), most commonly because of anaphylaxis (n=10). Anaphylaxis observed to date most often appears to occur early on during retreatment among patients with a prolonged treatment interruption (n=9).

For omaveloxolone, given the modest benefits found in the randomized control trial (RCT) and open-label extension and its favorable safety profile, which are consistent with the experiences described by clinical experts and patients, but with uncertainty about the magnitude and clinical meaningfulness of benefit, we have high certainty that it does not cause net harm and it may provide a small or substantial net health benefit ("**C++**").

The evidence for nomlabofusp is limited and immature. The early data show a potential signal of improvement in mFARS in the absence of a concurrent control group. There is substantial reason to believe that the drug may not reach the central nervous system, and there is a serious safety signal of anaphylaxis. Given the limited evidence of clinical benefit and remaining uncertainty about serious harms, we cannot exclude the possibility of net harm, and therefore rate the evidence for nomlabofusp compared to no disease-specific therapy in adolescents and adults with FA as insufficient ("**I**").

There are no data comparing omaveloxolone with nomlabofusp or evaluating nomlabofusp as an add-on therapy to omaveloxolone. We therefore rate the evidence for both of these treatment strategies as insufficient ("**I**").

Table ES1. Evidence Ratings

Treatment	Comparator	Evidence Rating
Adolescents and Adults with Friedreich's Ataxia		
Omaveloxolone	No disease-specific therapy	C++
Nomlabofusp	No disease-specific therapy	I
Nomlabofusp added to omaveloxolone	Omaveloxolone	I
Nomlabofusp	Omaveloxolone	I

Cost-Effectiveness Results

At the current net price of $319,000 per year, omaveloxolone was associated with higher incremental costs ($2.8 million) and health gains of approximately 1.2 QALYs (quality-adjusted life years) and 1.6 evLYs (equal value life years) compared with standard of care from a healthcare sector perspective. This resulted in incremental cost-effectiveness ratios of $2.3 million per QALY gained and $1.8 million per evLY gained. The incremental cost-effectiveness ratios remained above commonly accepted cost-effectiveness thresholds across all sensitivity and scenario analyses.

Given the limited available data, the cost-effectiveness of nomlabofusp was evaluated in exploratory analyses using a range of assumptions regarding its long-term treatment effects. Even in extremely favorable scenarios, at a placeholder annual price of $625,000, incremental cost-effectiveness ratios would exceed commonly accepted thresholds. The actual cost-effectiveness of nomlabofusp will depend on its net health benefit and its price.

1. 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 fatigue and progressive loss of balance, gait, and coordination of the arms and legs, often followed by broader neurologic deficits affecting swallowing, speech, vision, and hearing. 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). Additionally, mental health disorders are common secondary complications associated with the physical, social, and emotional burden of living with the disease and its resulting disability, and they can substantially affect quality of life.[12] The average life expectancy is 35-40 years, with premature mortality driven by cardiomyopathy and aspiration pneumonia due to trouble swallowing.[5] FA affects about 5,000 persons in the United States (US) and is most common among populations of European and Indian ancestry. Mean total annual healthcare costs are estimated to be $18,150, driven mostly by paid homecare, with substantial indirect costs.[6,7]

The diagnosis of FA is confirmed by genetic testing. Nearly all patients with FA inherit two copies of a mutated gene that includes an excessive number of repeated short deoxyribonucleic acid (DNA) sequences (guanine-adenine-adenine [GAA] repeat expansions) that preclude the body from making sufficient frataxin, a protein that is essential for mitochondrial energy metabolism and preventing cellular damage from oxidative stress. A greater number of these GAA repeats strongly correlate with an earlier age of onset. While, on average, symptoms begin between eight and 14 years of age 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.[3,4] Among ambulatory individuals with FA, early-onset FA (before age eight) is associated with the fastest neurologic progression, with annual modified Friedreich's Ataxia Rating Scale (mFARS) declining nearly 50% faster than typical onset (8-14 years of age) and approximately twice as fast as intermediate onset (15-24 years of age). Late-onset FA (after age 24) generally presents with milder, slowly progressive disease and fewer non-neurologic manifestations, particularly skeletal abnormalities, cardiomyopathy, and hearing loss.

About one in five patients with FA are at high risk for developing cardiac complications with progressively worsening cardiac function. The risk of cardiac complications is associated with longer GAA repeat length and the degree of baseline cardiac involvement, whereas the baseline neurological functional disability was not predictive of cardiac change over time.[13]

There are no available cures for FA. Until recently, there were also no disease-specific therapies. Clinical practice guidelines published in 2022 recommended multidisciplinary anticipatory care, including rehabilitation, clinical specialist evaluations, and regular screening and management for FA complications.[14] In 2023, the FDA approved omaveloxolone (SKYCLARYS, Biogen Inc.) as the first

disease-specific therapy for FA. Omaveloxolone is thought to improve mitochondrial functioning despite frataxin deficiency.[8] Omaveloxolone is a small-molecule drug and is taken orally once daily.[9] 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.[15]

One potential therapeutic approach to FA is to replace the deficient frataxin protein. Nomlabofusp (Larimar Therapeutics, Inc.) is a recombinant fusion protein with a peptide bound to frataxin designed to facilitate cellular uptake and mitochondrial delivery of frataxin. It is administered daily as a subcutaneous injection.[10] A rolling Biologics License Application (BLA) was initiated on June 29, 2026 with completion of the application to the FDA expected in the second half of 2026.[11]

Table 1.1. Interventions of Interest

Intervention	Mechanism of Action	Delivery Route	Prescribing Information
SKYCLARYS (omaveloxolone)	Nrf2 pathway activator	Oral	150 mg once daily
Nomlabofusp	Recombinant fusion protein that delivers frataxin to mitochondria	Subcutaneous	Daily, details TBD

Mg: milligram, TBD: to be determined

2. Patient and Other Stakeholder Perspectives

2.1. Patient Community Input

ICER spoke with four patients, two caregivers, two patient advocacy organizations, and four clinical experts to understand the perspectives of those living with FA and their caregivers, their specific challenges and unmet needs, contextual considerations, and outcomes most relevant to patients and the FA community (See Supplement Section B for details). ICER also conducted focused sessions with patients and caregivers from the FA community to discuss ICER's early thinking on the approach to the cost-effectiveness analysis. Details of these discussions and the impact on our model development are reported in Supplement Section B.

Because FA is a heterogeneous, multisystem, progressive illness, people living with the disease have many different symptoms and experiences. Many patients described that their symptoms initially began with difficulties with walking or balance, with worsening mobility and loss of independence as the disease progressed. However, patients emphasized that FA affects much more than mobility. Severe fatigue is common, and many people with FA have increasing difficulty swallowing, speaking, hearing, and seeing. Patients described substantial day-to-day variability, with some days when they feel stronger and others when routine activities are much more difficult.[16]

Patients emphasized that what matters most to them changes over the course of their disease. Maintaining the ability to walk may be a priority earlier in the disease, while speech, hearing, vision, upper extremity function (e.g., writing, feeding oneself), or the ability to transfer independently may become more important after a person loses the ability to walk. Loss of hearing and vision can be particularly isolating as other physical limitations accumulate. Patients emphasized wanting to remain engaged with family, friends, work, hobbies, and other activities that bring them joy, and described social isolation as an important concern. Patients also expressed considerable concern about developing symptoms of cardiomyopathy and the life-threatening nature of this complication.

The progressive nature of FA creates additional burden. Patients described constantly adapting to losses in function, only to have the disease progress further and require additional adaptations. Thus, maintaining function and independence and slowing disease progression were consistently described as important treatment goals. Patients expressed hope that treatments could preserve mobility, reduce fatigue, and allow them to continue doing activities that are important to them. Patients consider maintaining their current function or slowing the rate at which function is lost to be a meaningful benefit.

FA also has substantial effects on caregivers and families. As disease progresses, caregivers increasingly assist with daily activities such as transfers from a wheelchair, feeding, and

transportation. Caregivers described the experience as isolating for them as well as for the person with FA.

Prior to the approval of omaveloxolone, patients described having few options to alter the progression of FA despite substantial investments of time and money in exercise, supplements, supportive therapies, and treatment of complications.

Patients were also interested in treatments that address the underlying cause of FA. When considering newer treatments, they wanted to understand their safety risks but generally expressed substantial willingness to accept uncertainty in exchange for the possibility of slowing disease progression. As one patient summarized, patients may be willing to try a treatment despite its known risks because they "know the certainty of the disease." Patients and caregivers have similarly demonstrated substantial willingness to participate in clinical trials, although patients and caregivers expressed a desire for greater opportunities for younger children to participate in research.

Finally, patients described important differences in access to treatment and supportive care depending on where they live and their insurance coverage. Some experienced delays obtaining omaveloxolone or difficulty obtaining coverage for physical therapy and other supportive services. Patients described paying out of pocket for needed durable medical equipment, including wheelchairs, when insurers determined that they retained too much ability to walk to qualify for coverage. Access to clinicians with expertise in FA can also be difficult, particularly for patients living in rural areas. Patients emphasized that people with FA should have access to new treatments if they wish to receive them, and expressed concern that insurance coverage requirements may create additional barriers to care.

2.2. Clinical Input

Clinical experts echoed the high unmet clinical need for effective therapies and were enthusiastic about novel drugs that target frataxin deficiency, the underlying mechanism of FA. Experts we spoke with were hopeful that increasing frataxin levels could halt disease progression and reduce deaths from cardiomyopathy. However, they also expressed uncertainty about the ability to deliver sufficient frataxin to the affected regions of the central nervous system and raised concerns about frataxin replacement treatments potentially causing cellular toxicity if frataxin levels become too high.

3. Comparative Clinical Effectiveness

3.1. Methods Overview

Scope of Review

We evaluated the clinical effectiveness of omaveloxolone versus no disease-specific therapy, nomlabofusp versus no-disease-specific therapy, nomlabofusp as an add-on therapy to omaveloxolone versus omaveloxolone alone, and omaveloxolone and nomlabofusp versus each other. We sought and reviewed evidence on patient important outcomes, including function, mobility, activities of daily living, quality of life, and harms, such as cardiotoxicity and liver injury. The full protocol for the review is available in Supplement Section D1.

Evidence Base

Omaveloxolone

The evidence informing our review of omaveloxolone was primarily derived from the MOXIe Phase II trial, an open-label extension study, and a propensity-matched analysis comparing participants in the extension study with a natural history cohort from the Friedreich's ataxia Clinical Outcome Measures (FA-COMS) observational study.[9,17-19] This was supported by three observational studies.[20-22] Data sources for omaveloxolone include peer-reviewed publications, conference abstracts and presentations, and FDA clinical review documents.

Study Design

The Phase II MOXIe trial was conducted in two parts: a 12-week dose-ranging placebo-controlled randomized controlled trial (RCT) and then a 48-week placebo-controlled RCT to evaluate the efficacy and safety of omaveloxolone. The enrolled participants for each part were distinct. In part 2, 103 participants were randomized 1:1 to receive either 150 mg oral omaveloxolone or placebo. Eligible participants were between 16 and 40 years old, had genetically confirmed FA, a baseline mFARS score between 20 and 80, and were able to use a recumbent stationary bicycle for exercise tests. Key exclusion criteria included uncontrolled diabetes and clinically significant cardiac disease.[9,23,24]

In part 1, participants with pes cavus (high arch feet) did not have significant improvements in functional outcomes.[23] Based on these findings, the protocol for part 2 was amended prior to the finalization of the statistical analysis plan to have the primary analysis focus on the participants without pes cavus, which was 82 of the 103 participants.[25] This is referred to in this report as the "primary analyzed subset" (PAS) and efficacy results were reported for this population. Safety data

were reported for all randomized participants (ARP), which was the original intention-to-treat population prior to the protocol amendment.[9] Additionally, data for all randomized participants on key primary and secondary outcomes were submitted separately to the German HTA agency and are described in Supplement Table D2.25.[26]

To understand the long-term effects of omaveloxolone, an open-label extension study enrolled 149 participants from either Part 1 or 2 who received either placebo or omaveloxolone regardless of pes cavus status to receive omaveloxolone. A 2023 propensity-matched analysis compared three-year outcomes among 136 extension-study participants with those of a natural history cohort from the FA-COMS database with updated five-year results presented in 2025.[18,19] In addition, there is a 2023 publication reporting on three-year data from the extension study for only MOXIe Part 2 participants, and conference abstracts presenting efficacy and safety data for select outcomes on populations within the extension study with six-years of follow-up.[17,27-29]

A Phase III double-blind, placebo-controlled, randomized trial is currently recruiting participants to evaluate the efficacy and safety of omaveloxolone in children and adolescents ages two to 15.[30]

Nomlabofusp

The nomlabofusp clinical development program includes three phase I studies, one Phase II dose exploration study, and an ongoing open-label single arm study (JIVE).[10,31-33] The results presented will primarily focus on the open-label JIVE study, of which the primary data sources are clinicaltrials.gov, press releases, and manufacturer corporate presentations.

Study Design

JIVE is an ongoing open-label study that initially enrolled adult participants from a prior phase I or II trial. In June 2025, it was announced that the study criteria was expanded to include adolescents aged 12 to 17 from a pharmacokinetic run-in study and adolescent and adults who did not participate in prior studies.[34] In June 2026, the study criteria were further expanded to enroll children ages two to 11 years old.[11] Participants received a daily dose of subcutaneous nomlabofusp 50 mg. [31]

Baseline characteristics, efficacy data, and biomarker data from the open label JIVE study were reported from a March 2026 cut-off date and safety data were reported from June 2026. For key clinical outcomes, JIVE data for participants who completed study activities were compared to unadjusted historical benchmark data from the FA-COMS natural history database.[31,35]

A Phase III double-blind, placebo-controlled randomized confirmatory trial is currently recruiting patients and plans to enroll ambulatory FA patients aged two to 40 years old.[31]

Key Outcomes

A key outcome for clinical trials of both drugs is the mFARS. The mFARS is a clinician-administered tool that evaluates disease progression on four domains: bulbar function, upper limb coordination, lower limb coordination, and upright stability. The current standard mFARS scale uses a range from 0 to 93 with a higher score reflecting more advanced disease and functional impairment.[36-38] However, the MOXIe trials used a version of the scale ranging from 0-99 points that included two additional bulbar items that were subsequently removed from the scale.[25] The change from baseline in mFARS score was a primary outcome of the MOXIe Part 2 and JIVE trials. There is no established minimal clinically important difference (MCID) for mFARS.

A secondary functional outcome measure to complement the mFARS is the Friedreich Ataxia Rating Scale – Activities of Daily Living (FA-ADL) which is a 36-point clinician-rated scale with higher scores reflecting increased functional disability. The FA-ADL measures daily activities such as speech, swallowing, personal hygiene, dressing, etc. A 1.1-point change has been suggested as a preliminary estimate of minimal important change for FA-ADL across genetic ataxias, but an FA-specific MCID has not been established.[39]

Detailed definitions for both outcomes are in Supplement Section A. Both trials evaluated other functional outcome measures, such as the 9-hole peg test and patient global impression of change, which are described in Supplement Section D.

Evaluation of Clinical Trial Diversity

We did not rate the demographic diversity (race/ethnicity, sex, age) of the participants in the trials for omaveloxolone and nomlabofusp using the ICER-developed Clinical trial Diversity Rating (CDR) Tool due to a lack of prevalence estimates stratified by demographic categories for FA.[40] Instead, the demographic diversity of the main trials are described qualitatively in Supplement Section D1.

3.2. Results

Clinical Benefits

Omaveloxolone versus Usual Care

Baseline Characteristics

In MOXIe Part 2, participants had a mean age of FA onset of 15 years, a mean age of 24 years at study screening, were predominantly White (97%), and had a mean mFARS score of 39.4. The majority of participants were ambulatory (92%). Compared to the placebo group, the omaveloxolone group had more women (61% vs. 33%), a higher percentage of people with

cardiomyopathy (49% vs. 29%), and longer mean GAA1 repeat length (737 vs. 676).[9] See Supplement Tables D2.4 for complete baseline characteristics.

Modified Friedreich's Ataxia Rating Scale (mFARS)

In the pre-specified primary analyzed subset, which excluded patients with pes cavus (n=82), there was a -2.4-point difference in mFARS at week 48 between the omaveloxolone and placebo groups (95% confidence interval [CI]: -4.31 to -0.50; p=0.01).

Among the 103 randomized participants, 50 (96.2%) for the placebo group and 42 (82.4%) for the omaveloxolone group completed a 48-week mFARS assessment. When evaluating all randomized participants with available data, including those with pes cavus, there was a -1.93-point difference between groups (95% CI: -3.70 to -0.15; p=0.03). In an analysis using the 93-point mFARS scale, the difference between groups for all randomized participants was -1.82 (95% CI: -3.59 to -0.06; p=0.04) (see Supplement Table D2.25).[26]

Among the 20 participants with pes cavus, there was a numerical but not statistically significant difference in mFARS between groups (-1.25 points; p=0.51).[9,25]

In a post hoc analysis of participants with evaluable week 48 data, 47% of participants had improvements in their mFARS scores while 21% had worsening scores. Among placebo participants, 27% had improvements in scores and 44% had worsened scores.[9]

Within the four mFARS subdomains, the greatest improvements were observed in upper limb coordination, followed by upright stability (see Supplement Table D2.13).[9,25]

A propensity-matched analysis of the extension study compared participants treated with omaveloxolone in the MOXIe open-label extension with untreated participants from the FA-COMS natural history cohort. At year three, participants who received omaveloxolone had smaller changes in mFARS scores from baseline compared to the matched FA-COMS cohort (3.00 vs. 6.61 points; difference: -3.61; p =0.0001).[18] A 2025 abstract presented a post-hoc propensity-matched analysis of the OLE up to five years that showed sustained slowing of disease progression for people treated with omaveloxolone with an average of one-point mFARS progression per year compared to two points per year in the matched natural history cohort (see Table 3.1 below).[19]

Table 3.1. Changes in mFARS for MOXIe Part 2 and OLE for All Randomized Participants[9,18,19]

Study	MOXIe Part 2: ARP*		MOXIe OLE: Propensity-Matched Analysis*			
Timepoint	48 Weeks		3 Years		5 Years	
Arm	Omav	Placebo	Pooled Omav	FA-COMS Subset	Pooled Omav	FA-COMS Subset
N at Study Start	51	52	136	136	138	138
Change from Baseline in mFARS, LS mean (SE)	-1.41 (NR)†	0.82 (NR)†	3.00 (0.66)	6.61 (0.65)	5.11 (*0.7*)	9.04 (*0.8*)
Difference, Mean (95%CI); P-Value	-1.93 (-3.7, -0.15); p=0.03		-3.61 (SE: 0.93); p=0.0001		-3.93 (NR); p=0.0001	

*Includes all participants, including those with pes cavus

† Calculated from observed mean mFARS at baseline and week 48, not directly comparable to LS mean difference

ARP: all randomized participants, FA-COMS: Friedreich's Ataxia Clinical Outcome Measures, LS: least squares, mFARS: modified Friedreich's Ataxia Rating Scale, N: number, NR: not reported, OLE: open label extension, Omav: omaveloxolone, SE: standard error

Notes: A reduction in mFARS indicates an improvement, increases indicate worsening. Italicized data were extracted from figures using digitization software. For OLE 5-year data, sample size increased by two in each arm due to data cut-off dates in the two analyses. 97 omav-treated participants and 63 non-treated participants from FA-COMS contributed mFARS data at five years.

Friedreich's Ataxia – Activities of Daily Living Scale (FA-ADL)

In MOXIe Part 2, participants in the primary analyzed subset (n=82) who received omaveloxolone had a mean reduction (improvement) in FA-ADL of 0.17 points compared to an increase (worsening) of 1.14 points in the placebo group at week 48 (difference: -1.30 ± 0.6; p=0.04). Among all randomized participants, participants who received omaveloxolone had a mean increase of 0.28 points compared to an increase of 1.05 points in the placebo group (difference: -0.78; p=0.19).[26]

In a post hoc analysis of participants with evaluable week 48 data, 36% of omaveloxolone-treated participants had improvements in their FA-ADL scores while 47% had worsening scores. Among placebo participants, 20% had improvements in scores and 66% had worsened scores.[9]

A 2025 conference presentation reported that over four years in the extension study, total FA-ADL scores increased by 2.79 points, with an average of 0.67 points per year while natural history data of FA patients reported an average of 0.93 points increase per year.[29]

Other Outcomes

The MOXIe Part 2 trial measured other outcomes such as the patient global impression of change (PGIC), clinician global impression of change (CGIC), 36-Item Short Form Health Survey (SF-36), 9-hole peg test, time 25-foot walk test, frequency of falls, and peak work. There were small changes between groups for these outcomes, with a majority that were not statistically significant.[9] Data can be found in Supplement Table D2.9 and D2.25.

Nomlabofusp versus Usual Care

As of June 2026, there are 43 participants who were dosed in the ongoing open-label study (two dosed after March 2026 cut-off), with 32 having past exposure to nomlabofusp in a prior trial (average time-off treatment: 2.5 years) and 11 who had no prior exposure. Of the 43 participants, 22 are still actively receiving treatment. Of the 22 active participants, 13 have completed one year on nomlabofusp, seven of whom completed 18 months and three completed two years. Participants who discontinued therapy were not included in functional outcome reporting.[31]

Baseline Characteristics

As of the March 2026 data cut (n=41), 59% of participants were female, 49% had prior exposure to omaveloxolone, and 51% were ambulatory. The mean age at trial entry was 29 years old (standard deviation [SD: 11.3]) with a mean age of symptom onset of 12.4 years old (SD: 5.98). Participants had a baseline mean mFARS total score of 55.0 (SD: 16.96) and mean FA-ADL overall score of 17.1 (SD: 7.1).[31]

The data presented on functional outcomes for nomlabofusp were benchmarked to an unadjusted historical reference group consisting of a subset of the FA-COMS database. Among the 955 FA participants in the FA-COMS natural history study, 362 were selected based on having a similar range of baseline characteristics as the JIVE participants (see Supplement Table D2.2). At the time of this review, these data were not adjusted for differences in attributes.[31]

Modified Friedreich's Ataxia Rating Scale (mFARS)

Among participants receiving nomlabofusp, there was a one-point decrease in mFARS score at one year and a 2.3-point decrease at 18 months. Benchmarked to a historical FA-COMS reference group, this reflects a 2.6-point difference at year 1 and an estimated 4.6 difference at 18 months as mFARS is collected annually in the database (see Table 3.2).[31]

Friedreich's Ataxia – Activities of Daily Living Scale (FA-ADL)

Participants who received nomlabofusp had a reduction of 1.1 points in FA-ADL score at one year and a reduction of 0.3 points at 18 months. In the FA-COMS reference group, there was a 1.5 point increase at one year and data were unavailable at 18 months (see Table 3.2).[31]

Table 3.2. Changes in Clinical Outcomes in JIVE OL[31]

Outcome	Baseline Score, Mean (Range)	Mean Change from Baseline (Range)	
		12 Months	18 Months
N	41	13	7
mFARS (Scores 0-93)	55.0 (16.8, 85.5)	-1.0 (-6.5, 3.0)	-2.3 (-10.0, 4.5)
FA-ADL (Score 0-36)	17.1 (0, 27.0)	-1.1 (-9.0, 2.5)	-0.3 (-1.5, 1.0)

FA-ADL: Friedreich Ataxia- Activities of Daily Living, mFARS: Modified Friedreich's Ataxia Rating Scale, N: number, OL: open label

Other Outcomes

Participants who received nomlabofusp had reductions in scores for the 9-hole peg test and modified Fatigue Impact Scale (MFIS) at one year. At 18 months, reductions continued for the 9-hole peg test and there was a slight increase in MFIS score (see Supplement Table D2.8).[31]

Biomarkers

A key biomarker in the JIVE trial was skin tissue frataxin levels. Data for this outcome were from a March 2026 data cut-off. Data were presented as absolute skin frataxin levels over time and the percent of participants with skin frataxin levels in the range of asymptomatic heterozygous carriers. This was considered to be greater than 8.2 pg/μg, or 50% of the mean healthy volunteer frataxin level.[31]

The mean baseline skin frataxin level was 3.7 pg/μg, which increased by the first month of treatment for 26 participants with available data (see Table 3.3). At one year, 100% (9/9) of the participants with follow-up data had skin frataxin levels in the range of asymptomatic heterozygous carriers, which was sustained among the three participants with 18 month data.[31]

At the time of this review, there is no data presented on target tissue engagement, such as cardiac involvement or cardiac function. Exploratory analyses suggest normalization of triglycerides after one month on treatment.[32]

Table 3.3. Skin Frataxin Changes in JIVE OL Study[31]

Timepoint	N	Absolute Skin Frataxin Levels		Percent of Participants with Skin Frataxin Levels in Range of Asymptomatic Heterozygous Carriers
		Mean	Min, Max	
Baseline	27	3.7	1.5, 8.8	4%
Month 1	26	8.9	2.9, 22.9	38%
Month 3	20	12.5	5.6, 37.1	50%
Month 6	11	12.3	5.6, 26.7	82%
Month 12	9	12.1	8.1, 16.1	100%
Month 18	3	10.7	9.9, 11.8	100%

N: number, OL: open label

Nomlabofusp as an Add on to Omaveloxolone

There is no direct evidence evaluating the comparative effectiveness of nomlabofusp as an add-on therapy to omaveloxolone versus omaveloxolone alone.

Omaveloxolone versus Nomlabofusp

There is no direct evidence evaluating the comparative effectiveness of omaveloxolone versus nomlabofusp. Due to limited data availability at the time of the review and differences in study designs, we did not attempt an indirect comparison.

Harms

Omaveloxolone

In MOXIe Part 2, all participants experienced at least one adverse event. Serious adverse events were slightly more frequent in the treatment group (omav: 10% vs. placebo: 6%), most of which were mild to moderate and occurred within the first 12 weeks of receiving treatment. Compared to the placebo group, the omaveloxolone group experienced higher overall treatment discontinuation (omav: 14%, placebo: 4%) and discontinuation due to adverse events (omav: 8%, placebo: 4%). The most commonly reported adverse events among omaveloxolone-treated participants were headache, contusion, nausea, fatigue, and increased alanine aminotransferase (ALT) and alanine aspartate aminotransferase (AST) (See Table 3.4).[24,25,41] The ALT and AST increases were transient, reversible, and did not result in liver injury. In addition, treatment with omaveloxolone was not associated with measures of cardiotoxicity, such as increased wall thickness or reduced ejection fraction. A post-hoc analysis focusing on cardiac safety reported a lower incidence of cardiac-related adverse events among patients in the omaveloxolone group (omav: 9.8% vs. placebo: 13.5%).[42]

Table 3.4. Key Harms from MOXIe Part 2 Trial[9]

Harms, n (%)	Omav	Placebo
N	**51**	**52**
Adverse Event	51 (100)	52 (100)
Serious Adverse Events	5 (10)	3 (6)
Discontinuation due to Adverse Events	4 (8)	2 (4)
Headache	19 (37)	13 (25)
Alanine Aminotransferase Increased	19 (37)	1 (2)
Nausea	17 (33)	7 (14)
Fatigue	11 (22)	7 (14)
Aspartate Aminotransferase Increased	11 (22)	1 (2)
Excoriation	13 (26)	12 (23)
Diarrhea	10 (20)	5 (10)
Abdominal Pain	11 (22)	3 (6)

Note: Adverse events greater than 20% in intervention arm and greater than the placebo group were presented
N: number

Six-year follow-up data from the extension study and real-world sources did not identify new safety signals. Similar to the randomized trial, ALT and AST elevation occurred primarily early, were transient, and did not lead to liver injury.[17,20-22,27-29]

No deaths were reported across any of the MOXIe trials. Additional safety data for omaveloxolone can be found in Supplement Section D2 and Supplement Tables D2.22-24.

Nomlabofusp

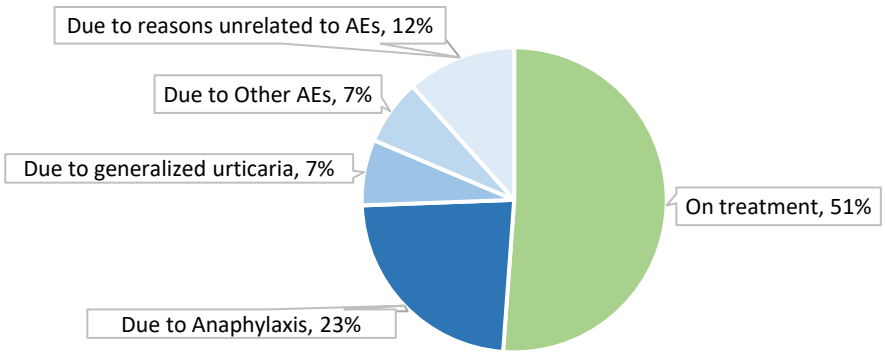
The most common adverse events in the open-label study were local injection site reactions which were reported to be mild to moderate.[31]

Of the 43 participants in the study, 21 participants discontinued treatment, ten of whom because of anaphylaxis. Most participants (9/10) who experienced anaphylaxis had previously been exposed to nomlabofusp.[31] It was reported that anaphylaxis primarily occurred in the first few weeks.[43]

There were three discontinuations due to generalized urticaria, none of which occurred after the initiation of the amended antihistamine therapy mitigation protocol. Eight other participants withdrew from the trial, three of whom discontinued because of other adverse events that were not specified and five for reasons unrelated to an adverse event. (see Figure 3.1 below).[31]

As of June 2026, long-term daily dosing was reported to be generally well tolerated among those remaining on therapy.[31]

Figure 3.1. Nomlabofusp Discontinuation Rates as of June 2026



Subgroup Analyses and Heterogeneity

We sought evidence on effect modification for subgroups of interest including: age of onset, ambulation status, number of GAA repeat expansions, people with complications of FA, and sociodemographic factors (e.g., sex, age, race, ethnicity).

Omaveloxolone

In the MOXIe trial, changes in mFARS from baseline to week 48 were consistent across subgroups stratified by age, gender, GAA1 repeat length, and ambulatory status. The difference versus placebo was numerically greater in participants under 18 years old, male participants, participants with GAA1 repeat length ≥ 675, and non-ambulatory participants. However, the trial was small and not powered to detect statistically significant differences among subgroups.[9]

Nomlabofusp

At the time of the review, data on improvement or worsening of the four functional outcome measures (mFARS, FA-ADL, Nine-hole peg test [9-HPT], MFIS) and data on changes over time for frataxin (FXN) levels, mFARS, FA-ADL, and 9-HPT stratified by duration of disease were available. Groups were categorized as less than 12.5 years duration, 12 to 25 years duration, and greater than or equal to 25 years duration. Due to the few participants in each group, a clear pattern cannot be inferred.[31]

Uncertainty and Controversies

There are a number of uncertainties and controversies for omaveloxolone and nomlabofusp, particularly since this is an emerging evidence base for a rare disease with small trials of short duration.

General Considerations for Both Treatments

- There are challenges to measuring disease severity and treatment effects in FA. mFARs is the primary outcome in clinical trials but is considered a research tool and is not used routinely in clinical practice since it does not directly capture several key manifestations, such as fatigue, hearing impairment, vision loss, and cardiomyopathy. There is also the issue of measurement variability. Although mFARS has excellent test-retest reliability, scores can vary by about 5 points between repeated assessments.[44] While this does not undermine observed treatment effects, smaller differences may be more difficult to appreciate as a meaningful change for an individual patient. Additionally, an improvement in mFARS score may not necessarily translate into a clinically meaningful improvement in functioning or quality of life. It also suffers from ceiling effects as the disease progresses and patients lose the ability to complete some assessments, particularly after loss of ambulation. Repeated testing may also lead to practice effects in trials as patients become familiar with the assessments, potentially complicating interpretation of changes over time. Lastly, there is no established minimal clinically important difference for the mFARS. However, patients and clinical experts alike valued any slowing of disease progression.
- There is uncertainty about the optimal age to begin therapy. At the time of our review, there was no clinical evidence for initiating either therapy in younger children, which might theoretically prevent or delay irreversible disease progression to a greater extent, but the magnitude of benefit and safety of starting treatment at younger ages is unknown.
- There is substantial uncertainty about heterogeneity of treatment effects for either drug. FA varies considerably in its severity, manifestations, and rate of progression. Clinical trials are too small to reliably determine whether treatment effects differ according to important patient characteristics, such as age of onset or GAA repeat length.
- The effects of treatment on cardiomyopathy is uncertain. Cardiomyopathy is the leading cause of death in FA, but neither clinical development program was designed to determine whether treatment improves cardiac function and outcomes.
- There is limited evidence on quality of life and no outcome data for caregiver burden or economic outcomes with either therapy.

Omaveloxolone

- In addition to the general uncertainties about mFARs described above, interpretation of the improvement in mFARs in the MOXIe Phase II trial is challenging for several reasons. First, the benefit may not have been perceptible to patients and clinicians, as reflected by the non-significant patient and clinician global impression change-from-baseline scores and health-related quality of life scores. Second, fatigue, a prominent FA symptom, was numerically worse in the omaveloxolone group than the placebo group. Third, in the original intention-to-treat population (ITT) before the planned protocol amendment to exclude patients with pes cavus

prior to analysis, fewer participants in the omaveloxolone group completed the 48-week mFARS assessment than the placebo group, raising concern for bias if loss-to-follow was because of lack of treatment efficacy or adverse events (e.g., informative censoring). Fourth, in the original ITT population, there was a smaller improvement in the secondary functional outcome, FA-ADL score, than in the primary analyzed subset exclusive of pes cavus (0.78 vs 1.30 improvement), and was not statistically significant.

- The significance of the larger treatment effect observed among patients without pes cavus is uncertain. Although this subgroup was prespecified in Part 2 of the pivotal trial because of the Part 1 findings, it is unclear if pes cavus represents a mechanistically defined subpopulation or a chance finding. Clinical experts we spoke with questioned the clinical relevance of pes cavus.
- The magnitude and durability of the long-term benefits of omaveloxolone are unknown. Longer-term evidence beyond one year comes from an open-label extension study and comparisons with matched patients from a natural history cohort study rather than an RCT, increasing the potential for bias. However, FA is a known progressive illness, with an average decline of approximately 2 mFARS points per year, so the slowing of disease progression in the open label extension period suggests benefit. Also, both clinical experts and patients we spoke with described similarly modest but sustained benefits over time. It is also unclear what happens after treatment is discontinued, including whether some of the accumulated delay in progression persists or is lost after treatment is discontinued. Thus, we are unsure whether the treatment is truly disease-modifying.
- There were significant imbalances for several meaningful patient characteristics between the two groups in the MOXIe trial, which adds uncertainty to the interpretation of the trial findings. While these imbalances could be due to chance given the small size of the trial, they raise questions about whether there were issues with randomization or allocation concealment. However, the larger-than-expected differences in cardiomyopathy and GAA1 repeat length, two of the strongest prognostic factors for FA, favored the placebo group and would therefore be expected to bias findings towards the null hypothesis of no difference. This is supported by post-hoc analyses adjusting for these baseline covariates, which suggested even larger treatment effects for omaveloxolone (see Supplemental Table D2.20).
- It remains uncertain which aspects of FA are most affected by omaveloxolone. Although the overall mFARS benefit was driven most by improvements in upper limb coordination and upright stability, it is unclear whether this reflects greater treatment effects on these aspects of FA or because of difficulty measuring treatment effect across other subdomains as FA progresses.

Nomlabofusp

- There is substantial uncertainty about the clinical benefits of nomlabofusp given the novel mechanism of action and limited and immature evidence from the ongoing, single-arm JIVE study. Available clinical outcomes are limited to a small subset of participants who have

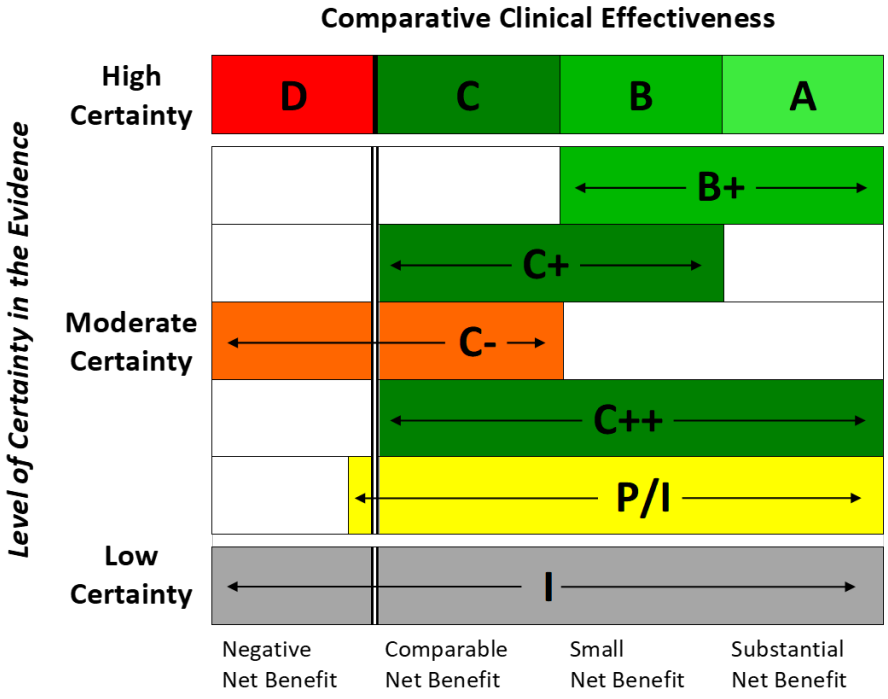
tolerated therapy and completed 12 to 18 months of treatment. Although these data suggest a potential signal of slower disease progression, interpretation is limited by a small sample size, absence of a concurrent control group, and lack of outcome ascertainment among individuals who discontinued treatment.

- Although eight adolescents were reported to have received at least one dose in the JIVE study at the time of this report, it is unclear whether any of these individuals contributed outcomes data at 12 to 18 months. This is due to uncertainty of the timing of the protocol amendment that expanded age eligibility criteria and the lack of information about which participants tolerated therapy and completed mFARS assessments.
- There is uncertainty about how increases in skin frataxin should be interpreted. Frataxin levels could only be analyzed in a subset of participants, and the relationship between changes in skin frataxin level and clinical outcomes has not been established.
- It is uncertain whether nomlabofusp reaches the central nervous system (CNS). Given the progressive neurodegenerative nature of FA, sustained neurologic benefit is thought to depend on adequate delivery of frataxin to the CNS. Experts expressed skepticism that nomlabofusp crosses the blood-brain barrier, and there are currently no compelling evidence of increased frataxin levels in affected regions in the brain. Thus, even if we assumed short-term treatment benefit on mFARS, uncertainty remains about the durability of neurologic benefit if it only increases frataxin levels in peripheral skeletal muscles but not in the CNS.
- Clinical experts were enthusiastic about the possibility that nomlabofusp increases frataxin levels in cardiac muscle, which is supported in part by preclinical animal studies. Even if frataxin levels are not able to be delivered to the CNS, restoration of cardiac frataxin levels would be important since cardiomyopathy is the leading cause of death in FA. However, there are no data demonstrating target-tissue engagement in the heart. The JIVE study has not yet reported cardiac function or measures of cardiac involvement through imaging or biomarkers.
- There remains uncertainty about the risk of anaphylaxis and whether it can be adequately mitigated. Anaphylaxis observed to date mostly appears to occur early on during treatment among patients with prior nomlabofusp exposure followed by a prolonged treatment interruption and subsequent re-exposure. However, the number of treated individuals is small, and it remains uncertain whether anaphylaxis is specifically related to re-exposure after treatment interruption or if it could also occur idiosyncratically during uninterrupted long-term treatment.
- Related to anaphylaxis, the long-term tolerability is unclear as only about half of treated participants remained on therapy after 18 months. Beyond the ten participants who discontinued for anaphylaxis, another 11 participants discontinued therapy for urticaria, other adverse effects, and for reasons unrelated to treatment harms.

3.3. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.2) is provided here.

Figure 3.2. ICER Evidence Rating Matrix



A = "Superior" - *High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" - *High certainty of a small net health benefit*
C = "Comparable"- *High certainty of a comparable net health benefit*
D= "Negative"- *High certainty of an inferior net health benefit*
B+= "Incremental or Better" – *Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Incremental" - *Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
C- = "Comparable or Inferior" – *Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
C++ = "Comparable or Better" - *Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit*
I = "Insufficient" – *Any situation in which the level of certainty in the evidence is low*

Omaveloxolone modestly slowed disease progression by approximately 2 points on the mFARS in the pivotal 48-week MOXIe randomized controlled trial. Slowing of disease progression persisted for up to 5 years in open-label extension compared with a matched untreated control group from a natural history database. Although these longer-term data lack a concurrent control group, FA is a predictably progressive illness, with an average decline of approximately 2 mFARS points per year,

providing additional support for a sustained treatment benefit. The long-term findings are also consistent with the experiences described by clinical experts and patients.

However, there remains uncertainty about the magnitude and clinical meaning of benefit. During the randomized phase, the modest improvement in mFARs was not clearly perceptible to patients and clinicians. In addition, in the original intention-to-treat population, fewer participants in the omaveloxolone group completed the 48-week mFARS assessment, raising the potential for bias from differential loss to follow-up, and the improvement in the secondary functional outcome, FA-ADL, was smaller and not statistically significant compared with the prespecified primary analysis. Given these uncertainties, and that omaveloxolone is generally well tolerated, with few serious harms, we have high certainty that treatment of adolescents and adults with omaveloxolone versus no disease-specific therapy does not cause net harm and it may provide a small or substantial net health benefit ("**C++**").

The evidence for nomlabofusp is limited and immature. JIVE is an ongoing, open-label, single-arm trial with clinical outcomes available at 12 to 18 months for only a minority of participants who have tolerated therapy. These data show a potential signal of improvement in mFARS, but interpretation is limited by the small number of patients and lack of a control group. There is also substantial uncertainty about the mechanism and durability of any clinical benefit. Clinical experts questioned whether nomlabofusp crosses the blood brain barrier and reaches the CNS, raising uncertainty about whether potential benefits from restoration of frataxin in peripheral tissues would be sustained as this progressive neurodegenerative disease advances. There is also uncertainty about how to interpret increases in skin frataxin in the absence of evidence of target tissue engagement, particularly in the heart. Finally, anaphylaxis and treatment discontinuation are important safety concerns. It remains uncertain whether the risk of anaphylaxis is confined to patients with prior exposure followed by an extended treatment interruption. Given the limited evidence of clinical benefit and remaining uncertainty about serious harms, we cannot exclude the possibility of net harm, and therefore rate the evidence for nomlabofusp compared to no disease-specific therapy in adolescents and adults with FA as insufficient ("I").

There are no data comparing omaveloxolone with nomlabofusp or evaluating nomlabofusp as an add-on therapy to omaveloxolone. We therefore rate the evidence for both of these treatment strategies as insufficient ("I").

Table 3.5. Evidence Ratings

Treatment	Comparator	Evidence Rating
Adolescents and Adults with Friedreich's Ataxia		
Omaveloxolone	No disease-specific therapy	C++
Nomlabofusp	No disease-specific therapy	I
Nomlabofusp added to omaveloxolone	Omaveloxolone	I
Nomlabofusp	Omaveloxolone	I

4. Long-Term Cost Effectiveness

4.1. Methods Overview

This analysis compared omaveloxolone (SKYCLARYS®, Biogen) and nomlabofusp versus standard of care (SoC, no disease-specific treatment for FA). For nomlabofusp, the available clinical data were deemed insufficient to adequately inform the model. Therefore, the analysis was considered exploratory, and exploratory results are presented below rather than a formal base-case analysis.

We developed a de novo decision analytic model for this evaluation, informed by key clinical trials and prior relevant economic models.[18,41,45-49] Costs and outcomes were discounted at 3% per year.

The model involved a hypothetical cohort of adolescent and adult patients living with FA being treated with one of the disease-specific treatments for FA (omaveloxolone and nomlabofusp) or SoC. Model cycle length was one year, based on what was observed in prior published economic models and clinical data. A half-cycle correction was used to reflect the continuous nature of patient characteristics and disease progression.

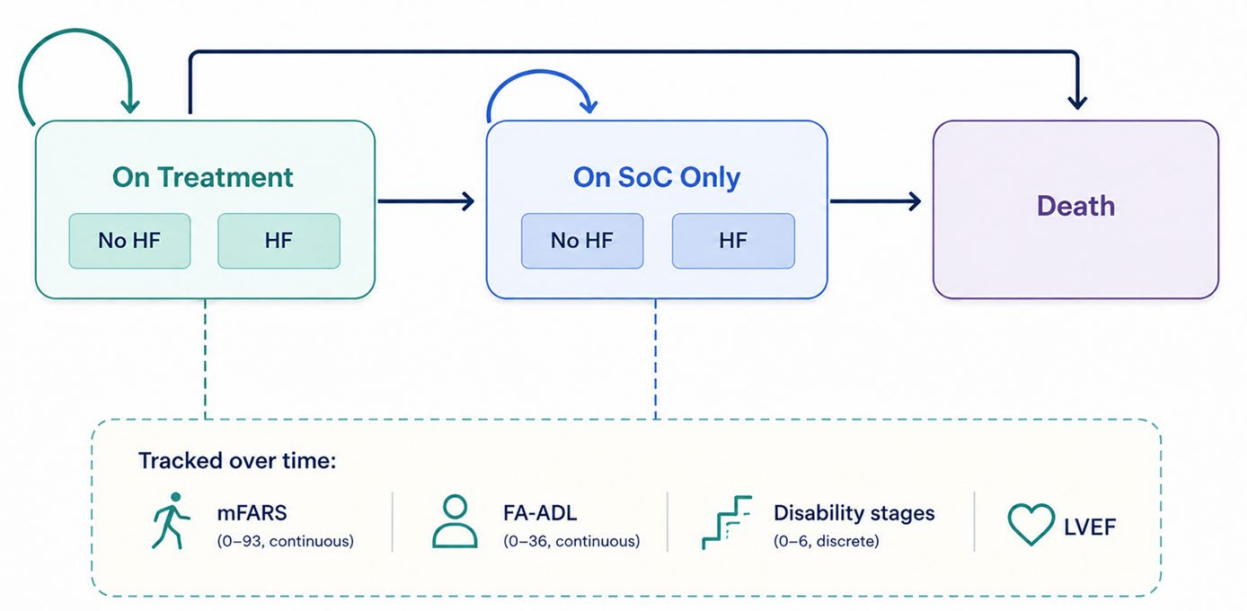
The model primarily focused on simulating the treatment's impact on function, reflecting the clinical evidence generated from the pivotal trials and their open-label extension studies, which primarily evaluated mFARS and FA-ADL outcomes.[18,41,45] Additionally, the model included the ability to capture potential direct effects of treatment on cardiac complications. Although there are currently no clinical data demonstrating a direct treatment effect on cardiac outcomes, clinical experts and data on the mechanism of action of nomlabofusp suggest the potential for improvement in cardiac manifestations. Other non-neurological complications (e.g., diabetes, scoliosis, and dysphagia) for which there is no evidence supporting a direct treatment effect were not modeled explicitly. However, any indirect effects on these manifestations mediated through improvements in function were captured implicitly.

Populations with different ages of disease onset were modeled separately to capture heterogeneity in disease progression: early onset (<8 years), typical onset (8-14 years), intermediate onset (15-24 years), and late onset (>24 years). Results from each age-of-onset subgroup were estimated separately; however, to inform a population-based estimate, the results were weighted according to the distribution of each subgroup in the overall FA population.

The model included health states representing treatment status (i.e., receiving disease-specific treatment versus not receiving treatment) (Figure 4.1). In the model, patients in the intervention arm enter the model in the "on treatment" state and may discontinue treatment, transitioning to the "on SoC only" state. Patients in the control arm enter the model directly in the "on SoC only" state. Patients can die from any health state. Within each treatment arm, progression in function

was tracked over time using measures commonly reported in pivotal clinical trials and the published literature, including mFARS, FA-ADL, and disability levels. These measures informed estimates of mortality, quality of life, and costs over time. Additionally, left ventricular ejection fraction (LVEF) was tracked to characterize changes in cardiac function and determine heart failure (HF) status, which also informed estimates of mortality, quality of life, and costs over time. Treatment benefits were applied while patients remained on treatment.

Figure 4.1. Model Structure



FA-ADL: Friedreich's Ataxia Activities of Daily Living Scale, HF: Heart failure, LVEF: Left ventricular ejection fraction, mFARS: Modified Friedreich's ataxia rating scale, SoC: Standard of care
Note: Patients with an LVEF of less than 50% were classified as having heart failure based on clinical guidelines.[50]

Key model inputs included functional outcome and cardiac function progression rates, treatment effects on disease progression, mortality, quality of life, and health care costs associated with disease progression. Mortality was estimated using age- and sex-specific all-cause mortality from United States (US) life tables as the baseline, with additional adjustments to account for FA-related excess mortality and variations in functional status and cardiac function over time. Quality of life was modeled based on disease progression, primarily represented by mFARS, with scenario analyses exploring alternative measures of impairment (i.e., FA-ADL and disability stages). Cardiac function and treatment-related adverse events were also incorporated as modifiers of quality of life. Similarly, health care costs were estimated based on functional status and cardiac function. In addition to health care costs, non-health care costs associated with FA, including productivity losses and other costs incurred outside the health care system, were included under a modified societal perspective. Results were reported as incremental cost per equal-value life years (evLY) gained, cost per quality-adjusted life years (QALY) gained, and cost per life-year gained. We additionally included

FA-specific outcomes including life-years with ambulation (i.e., life-years before loss of ambulation), life-years before HF onset, cost per year of maintaining ambulation, and cost per year without heart failure.

We also conducted a pilot project to explore patient engagement in development of the cost-effectiveness analysis to inform the model methods. Details of the discussion and the impact of the project on decisions regarding model structure and assumptions are provided in Section B1 of the Supplement.

4.2. Key Model Assumptions and Inputs

Key Model Assumptions

Our model included several key assumptions stated in Table 4.1. Additional assumptions are described in the Supplement Section E2.

Table 4.1. Key Model Assumptions

Assumption	Rationale
Patients living with FA become eligible for omaveloxolone and nomlabofusp upon reaching 16 years and 12 years of age, respectively.	Omaveloxolone is currently indicated for adults and adolescents aged 16 years and older.[41,51] Nomlabofusp has been studied in patients aged 12 years or older in its open-label extension study.[45] As manufacturers may evaluate these treatments among younger populations and earlier treatment initiation may be possible in the clinical practice, the impact of initiating treatment at a younger age was explored in a scenario analysis.
No direct treatment effects on cardiac function were modeled, except for one of the scenarios for nomlabofusp.	There are currently no data supporting a direct treatment effect of either omaveloxolone or nomlabofusp on cardiac outcomes. However, clinical experts noted the potential for nomlabofusp to improve cardiac manifestations based on its mechanism of action. Therefore, the model included functionality to track cardiac function, represented by LVEF, and its impact on mortality, quality of life, and costs. In all primary analyses of omaveloxolone and nomlabofusp, we assumed no direct treatment effect on cardiac function, with the exception of Scenario C for nomlabofusp, in which we assumed that left ventricular ejection fraction (LVEF) stops declining while patients are on treatment. If any data suggesting treatment effects on cardiac function become available, these effects may be further explored.
In the base-case analysis for omaveloxolone, long-term treatment efficacy for those who remain on treatment was extrapolated based on results from the open-label extension study.	The Phase II RCT of omaveloxolone assessed treatment efficacy through week 48.[41] Longer-term treatment effects were examined in the open-label extension study, which followed patients for up to five

	years and compared outcomes with a standard-of-care cohort using propensity score matching.[18,19] Treatment effects after approximately one year were therefore estimated based on the open-label extension data, with extrapolation applied to extend treatment effects over the lifetime model horizon. Based on mFARS outcomes reported at years one and five, treatment with omaveloxolone was assumed to reduce the rate of mFARS progression by 27% relative to SoC, among those who remain on treatment. For FA-ADL, which was used in a scenario analysis to map utilities, we assumed no difference in FA-ADL progression rates between treatment groups after year 1 because of the absence of FA-ADL data from the propensity score-matched analysis. This assumption appeared to be consistent with the progression rate observed in the four-year FA-ADL trajectory data after year 1 among those on omaveloxolone.[29]
In the analysis for nomlabofusp, the treatment discontinuation rate was informed by short-term data available from the open-label study as of the June 2026 cutoff date.	The treatment discontinuation data for nomlabofusp indicates that 51% (21/41) of patients discontinued treatment in the open-label study as of the June 2026 cutoff date. Based on manufacturer input that most discontinuations occur early during the treatment course, we assumed that this 51% discontinuation rate occurs during the first model cycle. Please note, however, that this short-term discontinuation rate should be interpreted with additional context, which is provided in the Section 4.3 'Uncertainty and Controversies.' Given the limited available data, the long-term discontinuation rate after year 1 was informed by data for omaveloxolone.
mFARS scores were the primary measure for mapping to quality of life, with other measures explored in scenario analyses.	Although mFARS is a key outcome of interest in the clinical studies of omaveloxolone and nomlabofusp, clinical experts and patients noted that mFARS is primarily a research measure, may not fully capture patients lived experiences, and may be subject to ceiling effects. We also heard from patients that FA-ADL may better capture patients' daily functioning across multiple domains. Despite concerns about mFARS, we chose it as the primary measure for mapping to quality of life for the following reasons: (a) long-term treatment efficacy data for other measures, including FA-ADL, are limited compared with those for mFARS; (b) quality-of-life values reflecting general population preferences are available only for mFARS; and (c) manufacturers noted that FA-ADL exhibits substantial variability among patients, making it difficult to achieve sufficient statistical power to demonstrate treatment efficacy. Alternative approaches to mapping quality of life using FA-ADL

	and disability stages were explored in scenario analyses.

FA: Friedreich's ataxia, FA-ADL: Friedreich's Ataxia – Activities of Daily Living Scale, LVEF: Left ventricular ejection fraction, mFARS: Modified Friedreich's ataxia rating scale, RCT: Randomized controlled trial, SoC: Standard of care

Key Model Inputs

Key model inputs are shown in Table 4.2.

Clinical Inputs

Natural disease progression in the comparator arm was tracked using multiple measures. Functional impairment was characterized using mFARS, FA-ADL, and disability stages, which are commonly used in clinical trials and published literature.[18,38,41,45] To account for heterogeneity by age of onset, each subgroup followed a distinct disease trajectory, with earlier-onset groups experiencing more rapid disease progression. Annual changes in mFARS and FA-ADL were derived from Rummey et al. (2022), which analyzed the FA-COMS dataset, a longitudinal natural history dataset that includes measures of disease progression such as mFARS, FA-ADL, and disability stages among individuals with FA.[52,53] mFARS disability stages were tracked over time by estimating the proportion of patients in each of seven disability stages. Friedreich's ataxia rating scale (FARS) disability stages categorize patients into seven groups based on functional ability and independence: normal (stage 0), no disability (stage 1), minimal disability (stage 2), mild disability (stage 3), moderate disability (stage 4), severe disability (stage 5), and total disability (stage 6).[38,54] The relationship between disability stages and 10-point mFARS bands (e.g., 0-9, 10-19, 20-29) was estimated using the FA-COMS dataset and applied to project disability stage distributions over time.[53,55] Cardiac function was tracked using LVEF. Annual changes in LVEF for each age-of-onset subgroup were estimated based on Pousset et al. (2015), a long-term cardiac outcomes study among individuals with FA.[56]

The treatment efficacy data for omaveloxolone versus SoC were obtained from the MOXIe study, a Phase II RCT comparing omaveloxolone with placebo, and the open-label MOXIe extension study.[18,41,19,26,29] Specifically, the mean differences in mFARS and FA-ADL scores comparing omaveloxolone and SoC at year 1 were derived from the MOXIe study among the ITT population. Because the results reported in the original publication of the MOXIe study were based on the 99-point mFARS, whereas the other studies used in the model are based on the 93-point mFARS (the newer, modified version), we used the mean difference in mFARS between the two arms that the manufacturer re-analyzed using the 93-point mFARS.[26] After the first year of treatment, the relative difference in the annual rate of change in mFARS for omaveloxolone versus SoC was informed by the five-year data from the open-label MOXIe extension study, in which patients receiving omaveloxolone in the extension phase were matched with FA-COMS patients using propensity score methods.[19] In terms of the relative difference in the annual rate of change in FA-ADL, no propensity-matched results were available from the same study. Therefore, we assumed no

treatment effect on FA-ADL post year 1, which appeared to be consistent with the manufacturer-reported four-year follow-up data among patients who remained on omaveloxolone without a matched comparison with the SoC arm.[29]

There was substantial uncertainty around the treatment efficacy of nomlabofusp. The open-label study compared patients who remained on nomlabofusp with a sub cohort of FA-COMS patients selected based on having the same range of baseline characteristics of participants in the open-label study.[11] These unadjusted results were used to inform the mean differences in mFARS during the first two years of treatment and in FA-ADL scores during the first year. After that, there was even greater uncertainty regarding the long-term treatment effect of nomlabofusp, given the lack of available data. We, therefore, explored the following assumptions regarding the long-term treatment effect of nomlabofusp beyond the short-term period, ranging from conservative to optimistic as exploratory analyses: (Scenario A) no treatment benefit after the short-term period, with disease progression occurring at the same rate as SoC, (Scenario B) disease progression slowing by 27% for mFARS among those who remained on the treatment, informed by long-term data of omaveloxolone, (Scenario C) a disease-stabilizing effect, with no progression in mFARS, FA-ADL, or LVEF after the short-term period. Scenario C also assumed no treatment discontinuation and treatment initiation at disease onset. Scenario C was designed to illustrate the potential value of nomlabofusp under the most favorable assumptions, rather than to represent expectations regarding its treatment effects or use in clinical practice based on the limited data currently available.

No treatment effect of nomlabofusp on cardiac outcomes was assumed in Scenarios A and B due to the absence of supporting data, whereas Scenario C explored an optimistic assumption that treatment halts LVEF progression while patients remain on treatment.

All-cause treatment discontinuation rates for omaveloxolone were based on the MOXIe study and the long-term open-label study for omaveloxolone during the first three years of treatment, and an assumption was made after year three.[18,41,46] For nomlabofusp, the first year discontinuation rate was informed by the rate observed in the open-label study, and an assumption made for the long-term rate based on data for omaveloxolone.[45] Once patients discontinued treatment, the rate of disease progression was assumed to mirror that of the SoC arm. An alternative assumption about disease progression after discontinuation was explored in a scenario analysis.

Mortality rates were determined based on four factors: age, sex, mFARS score, and LVEF. Age- and sex-specific mortality for the overall FA population was estimated by applying the standardized mortality ratio (SMR) for FA to mortality rates from the US general population.[57] The SMR was derived from Perlman et al. (2025), which compared survival among individuals with FA with that of matched controls without FA.[58] Hazard ratios (HR) for overall survival by 10-point mFARS score bands, relative to the overall FA population, were obtained from an HTA submission (Joint Nordic) by the manufacturer of omaveloxolone, which used FA-COMS data.[46] Due to a lack of data in the FA

population, HRs associated with LVEF levels were obtained from Angaran et al (2020), which evaluated the association between LVEF and mortality in the general population.[59] The potential risk of double-counting mortality effects when mortality was modeled based on both mFARS and LVEF was addressed through scenario analysis and external validation against mortality studies in FA.[56,58,60,61]

Key model input values and sources are shown in Table 4.2, with additional details provided in Supplement Section E2.

Health State Utility Inputs

Health-related quality of life depended on three factors in the model: function, cardiac function, and adverse events.

In the base case, function, as measured as mFARS scores, was used to model quality of life over time. Among the available clinical measures of function, mFARS was selected as the primary measure because (a) long-term treatment efficacy data are available primarily for mFARS; (b) quality-of-life values reflecting general population preferences are available only for mFARS; and (c) manufacturers noted that it is challenging to identify treatment effects on FA-ADL scores.

The utility values based on mFARS scores were derived from Deger et al. (2026) that estimated health state utilities for 20-point mFARS bands (i.e., 0-19, 20-39, 40-59, 60-79, and 80-93) using time trade-off (TTO) interviews with a sample of the general population in the UK.[62] Because this study had not yet been published and was not specific to the US population, we explored the associated uncertainty in a scenario analysis using health utility values estimated from FA-COMS data. Specifically, the association between mFARS scores and health utility values was estimated using FA-COMS data.[53] To estimate the utility values using the FA-COMS data, 36-Item Short Form Health Survey (SF-36) scores were converted to EuroQol 5-Dimension 3-Level (EQ-5D-3L) using a published mapping algorithm.[63] The relationship between EQ-5D-3L utility values and mFARS scores was then estimated using a linear mixed-effects model to account for repeated observations and within-individual correlations over time. The utility decrement associated with a one-point increase in mFARS was applied to the age-specific utility values of the general US population, which served as the baseline utility for individuals with an mFARS score of 0 (e.g. no impairment).[64]

Although we chose mFARS as the primary measure to map patient quality-of-life, we heard concerns from clinical experts that mFARS is a research-oriented assessment that may not directly reflect patients' day-to-day functioning, may not comprehensively capture the aspects of health that are most important to patients, and may be subject to ceiling effects. Patients also noted that FA-ADL may capture more domains that are important to them than mFARS (Supplement B1). Therefore, we explored alternative approaches using FA-ADL scores and disability stages in scenario analyses. To estimate the association between FA-ADL and health-related quality of life, we used

FA-COMS data and applied the same mixed-effects modeling approach used to estimate the relationship between mFARS and EQ-5D-3L utility values described above. For the disability stage-based approach, we used FA-COMS data to estimate the mean EQ-5D-3L utility value associated with each disability stage.

Key model input values and sources are shown in Table 4.2, with additional details including the disutilities associated with cardiac function and adverse events provided in Supplementary Section E2.

Economic Inputs

All costs used in the model were updated to 2025 dollars using the consumer price index published by the US Bureau of Labor Statistics (BLS).[65]

For omaveloxolone drug costs, we obtained the mean discount from wholesale acquisition cost (WAC) using data from SSR Health, LLC, which combines unit sales with publicly disclosed US sales figures—net of discounts, rebates, patient assistance programs, and concessions to wholesalers and distributors—to derive a discount rate.[66] We applied this average discount to the most recent available WAC to arrive at an estimated net price per unit.[67] For nomlabofusp, an annual placeholder price was used based on IPD Analytics estimates. If the manufacturer provides a more appropriate net price, the price in the model may be updated.

Non-drug health care costs included both related and unrelated components. Health care costs associated with the management of FA were sourced from Polek et al. (2013), a retrospective cross-sectional survey study that aimed to estimate health care resource utilization and costs among individuals with FA in the US and Canada.[68] US-specific cost estimates from the study were used in the model. The study stratified health care cost estimates based on disease severity, defined as severely affected (i.e., mostly wheelchair-bound) or less affected (i.e., not wheelchair-bound). Estimates for severely affected individuals were applied to patients with disability stages ≥5, as stage 5 represents being wheelchair-bound. Estimates for less affected individuals were applied to patients in the remaining disability stages. To account for the potential financial impact of cardiac function, ongoing costs associated with HF were applied to those with LVEF of less than 50%, based on Kazi et al.(2024).[69] For those taking nomlabofusp and experiencing anaphylaxis, a one-time cost of managing anaphylaxis was applied for the incident cases.

Sex- and age-specific unrelated health care costs were additive to the related health care costs associated with FA and were obtained from Jiao et al. (2021).[70]

We included non-health care costs associated with FA management (e.g., vehicle adaptations, assistive devices, and home modifications) and formal and informal productivity for patients and caregivers in the modified societal perspective. Details on these inputs are provided in Supplementary Section E2.

Table 4.2. Key Model Inputs

Parameter	Input	Source
Baseline Characteristics		
Mean Age*	Early onset: 16 years for omaveloxolone and 12 years for nomlabofusp Typical onset: 19 years Intermediate onset: 30 years Late onset: 49 years	Rummey 2022[52]
Percent Female	Early onset: 47% Typical onset: 51% Intermediate onset: 52% Late onset: 60%	Rummey 2022[52]
mFARS [0-93]†	Early onset: 60.0 for omaveloxolone and 51.2 for nomlabofusp Typical onset: 49.1 Intermediate onset: 44.9 Late onset: 43.2	Rummey 2022[52]
Distribution of Disease-Onset Groups	Early onset: 29% Typical onset: 39% Intermediate onset: 21% Late onset: 11%	Rummey 2022[52]
Natural Disease Progression Rate		
Annual Change of mFARS, Ambulatory‡	Early onset: 2.62 Typical onset: 1.83 Intermediate onset: 1.24 Late onset: 1.18	Rummey 2022[52]
Annual Change of mFARS, Non-Ambulatory‡	Early onset: 1.21 Typical onset: 0.9 Intermediate onset: 0.75 Late onset: 0.53	Rummey 2022[52]
Treatment Efficacy		
Absolute Difference in mFARS in Year 1, Omaveloxolone vs. SoC§	-1.82 points	Biogen GmbH 2025 [26]
Reduction in the mFARS Slope After Year 1, Omaveloxolone vs. SoC#	27% reduction	Nachbauer 2025[19]
Absolute Difference in mFARS in Year 1 and Year 2, Nomlabofusp vs. SoC#	Year 1: -2.6 points Year 2: -4.6 points	Larimar's Press Release[45]
Reduction in the mFARS Slope After Year 2, Nomlabofusp vs. SoC#	Several assumptions as described in the text	Assumption
All-Cause Treatment Discontinuation		
Annual Discontinuation Rate, Omaveloxolone	Year 0-1: 13% Year 1-3: 5.6% Year 3+: 5.6%	JNHB 2024,[46] Lynch 2021[41], Lynch 2024[18], Assumption
Annual Discontinuation Rate, Nomlabofusp	Year 0-1: 51.2%¤ Year 1+: 5.6%	Larimar's Press Release[45], Assumption
Adverse Events		
Percent Experiencing Anaphylaxis, Nomlabofusp	24.4%	Larimar's Press Release[45]

Utility Values		
Utility Values Based on the 20-score mFARS Bands	mFARS 0-19: 0.85 mFARS 20-39: 0.76 mFARS 40-59: 0.60 mFARS 60-79: 0.25 mFARS 80-93: -0.18	Deger 2026[62]
Drug Costs		
Annual Net Price, Omaveloxolone	$318,706	Redbook[67], SSR Health[66]
Annual Placeholder Price, Nomlabofusp	$625,000	IPD Analytics

FA-ADL: Friedreich's Ataxia – Activities of Daily Living Scale, JNHB: Joint Nordic HTA-Bodies, mFARS: Modified Friedreich's ataxia rating scale, SoC: Standard of Care

*Treatment initiation at age 16 years for omaveloxolone, consistent with its indication for patients aged ≥16 years, and at age 12 years for nomlabofusp, consistent with the age range studied in clinical trials; In Scenario C for nomlabofusp, treatment was instead assumed to begin at the age of disease onset, rather than the age at study participation. The corresponding treatment initiation ages were 11, 18 and 32 years for the typical-, intermediate-, and late-onset groups, respectively. The treatment initiation age for the early-onset group remained unchanged because of the minimum age criterion for nomlabofusp described above.

†Higher scores indicate greater disease severity; The baseline mFARS scores were adjusted upward for omaveloxolone using the average annual rates of increase in mFARS to account for potential differences in disease severity by age at treatment initiation; In Scenario C for nomlabofusp, treatment was assumed to begin at the age of disease onset. Accordingly, baseline mFARS scores were adjusted based on the annual rate of mFARS progression for each onset group, resulting in baseline scores of 37.1, 31.5, and 25.5 for the typical-, intermediate-, and late-onset groups, respectively.

‡The proportion of ambulatory patients at each time point was informed by the distribution of disability stages based on mFARS scores, estimated using FA-COMS data.

§The MOXIe Part 2 study estimated treatment efficacy using the 99-point mFARS rather than the 93-point version.[41] Because the other studies used in this model are based on the 93-point mFARS, we used the treatment efficacy estimated by the manufacturer using the 93-point mFARS in the intention-to-treat (ITT) population.

#Applied only among patients who remain on treatment; not applied to those who discontinued treatment.

¤Additional context regarding the first-year discontinuation rate of nomlabofusp is provided in Section 4.3, "Uncertainty and Controversies."

4.3. Results

Base-Case Results

Table 4.3 presents the discounted intervention costs, non-intervention costs, total costs, quality-adjusted life years (QALYs), equal-value life years (evLYs), and life years, as well as FA-specific clinical outcomes, including life-years with ambulation and life-years before HF onset, for omaveloxolone compared with SoC. Tables 4.4 and 4.5 present the incremental results estimated based on the clinical and cost outcomes shown in Table 4.3.

Table 4.3. Base-Case Results for Omaveloxolone Compared to SoC

Treatment	Intervention Acquisition Costs	Non-Intervention Costs	Total Costs	Life-years with Ambulation	Life-Years Before HF Onset	QALYs	evLYs	Life Years
Omaveloxolone	$2,816,000	$779,000	$3,596,000	5.65	13.75	6.62	6.98	17.07
SoC	$0	$803,000	$803,000	4.22	13.51	5.43	5.43	16.49

evLYs: equal value life years, HF: heart failure, QALY: quality-adjusted life year

Table 4.4. Incremental Results for the Base-Case Analysis of Omaveloxolone Compared to SoC

Treatment	Intervention Acquisition Costs	Non-Intervention Costs	Total Costs	Life-years with ambulation	Life-years Before HF Onset	QALYs	evLYs	Life Years
Omaveloxolone vs. SoC	$2,816,000	-$24,000	$2,792,000	1.43	0.24	1.19	1.56	0.58

evLYs: equal value life years, HF: heart failure, QALY: quality-adjusted life year

Table 4.5. Incremental Cost-Effectiveness Ratios for the Base-Case Analysis of Omaveloxolone Compared to SoC

Treatment	Cost per additional Year of Ambulation	Cost per Additional Year Without HF	Cost per QALY Gained	Cost per evLY Gained	Cost per Life Year Gained
Omaveloxolone vs. SoC	$2,000,000	$11,800,000	$2,300,000	$1,800,000	$4,800,000

evLYs: equal value life years, HF: heart failure, QALY: quality-adjusted life year

Table 4.6 presents the discounted intervention costs, non-intervention costs, total costs, QALYs, evLYs, and life years, as well as FA-specific clinical outcomes, including life-years with ambulation and life-years before HF onset, for the exploratory analysis of nomlabofusp compared with SoC.

As described in the Methods section, these analyses explored three alternative assumptions regarding the long-term treatment effect of nomlabofusp beyond the short-term period (i.e., the first 1-2 years for which comparative effectiveness data are available): (Scenario A) no treatment benefit after the short-term period, with disease progression occurring at the same rate as with SoC; (Scenario B) a 27% reduction in the rate of mFARS progression among patients who remain on treatment, informed by long-term data for omaveloxolone; and (Scenario C) a disease-stabilizing effect, with no progression in mFARS, FA-ADL, or LVEF after the short-term period. Scenario C also assumed no treatment discontinuation and treatment initiation at disease onset. Note that SoC results differ between Scenarios A&B and Scenario C because treatment initiation was assumed to

occur at different ages. Tables 4.7 and 4.8 present the incremental results estimated based on the clinical and cost outcomes shown in Table 4.6.

Table 4.6. Exploratory Results for Nomlabofusp Compared to SoC

Treatment	Intervention Acquisition Costs*	Non-Intervention Costs	Total Costs*	Life-years with ambulation	Life-Years Before HF Onset	QALYs	evLYs	Life Years
Nomlabofusp: Scenario A	$3,275,000	$767,000	$4,043,000	6.57	13.89	7.26	7.60	17.52
Nomlabofusp: Scenario B	$3,289,000	$765,000	$4,055,000	6.90	13.94	7.57	8.01	17.70
Nomlabofusp: Scenario C	$15,826,000	$449,000	$16,275,000	21.78	25.32	18.18	18.90	25.32
SoC: Scenarios A&B†	$0	$809,000	$809,000	4.78	13.64	6.06	6.06	16.97
SoC: Scenario C†	$0	$788,000	$788,000	8.97	15.19	8.69	8.69	19.80

evLYs: equal value life years, HF: heart failure, QALY: quality-adjusted life year

*Based on placeholder price

†The SoC results differ between Scenarios A&B and Scenario C because different baseline patient characteristics were assumed to reflect differences in the timing of treatment initiation. Scenarios A and B use the age and mFARS scores of prevalent patients living with FA, whereas Scenario C uses the age and mFARS scores at disease onset. Details are provided in the Methods section.

Table 4.7. Incremental Results for the Exploratory Analysis of Nomlabofusp Compared to SoC

Treatment	Intervention Acquisition Costs*	Non-Intervention Costs	Total Costs*	Life-Years with Ambulation	Life-Years Before HF Onset	QALYs	evLYs	Life Years
Nomlabofusp vs. SoC: Scenario A	$3,275,000	-$42,100	$3,233,000	1.79	0.25	1.19	1.53	0.54
Nomlabofusp vs. SoC: Scenario B	$3,289,000	-$44,100	$3,245,000	2.12	0.30	1.50	1.95	0.72
Nomlabofusp vs. SoC: Scenario C	$15,826,000	-$340,000	$15,486,000	12.81	10.13	9.49	10.21	5.52

evLYs: equal value life years, HF: heart failure, QALY: quality-adjusted life year

*Based on placeholder price

Table 4.8. Incremental Cost-Effectiveness Ratios for the Exploratory Analysis of Nomlabofusp Compared to SoC

Treatment	Cost per Additional Year of Ambulation*	Cost per Additional Year Without HF*	Cost per QALY Gained*	Cost per evLY Gained*	Cost per Life Year Gained*
Nomlabofusp vs. SoC: Scenario A	$1,800,000	$12,900,000	$2,700,000	$2,100,000	$6,000,000
Nomlabofusp vs. SoC: Scenario B	$1,500,000	$10,700,000	$2,200,000	$1,700,000	$4,500,000
Nomlabofusp vs. SoC: Scenario C	$1,200,000	$1,500,000	$1,600,000	$1,500,000	$2,800,000

evLYs: equal value life years, HF: heart failure, QALY: quality-adjusted life year

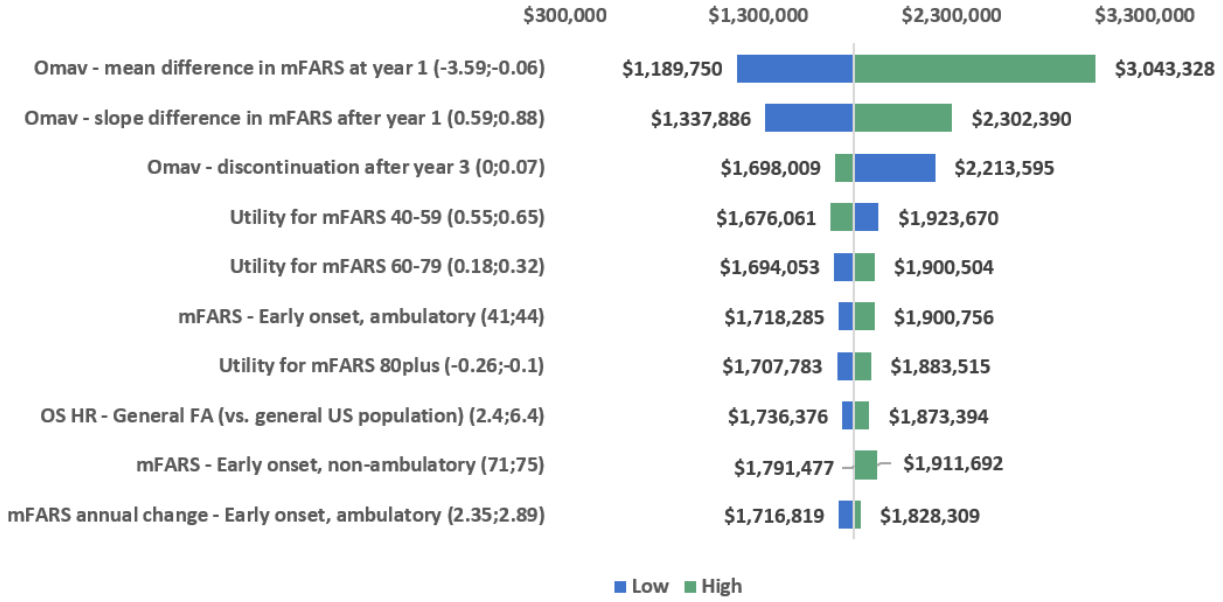
*Based on placeholder price

Sensitivity Analyses

To demonstrate the impact of parameter uncertainty on the incremental cost-effectiveness ratios, we varied input parameters using available estimates of uncertainty (e.g., standard errors or plausible parameter ranges). Given that we conducted exploratory analyses for nomlabofusp, we did not conduct additional sensitivity analyses. Figure 4.2 presents the tornado diagram from the one-way sensitivity analysis for omaveloxolone versus SoC, using cost per evLY gained as the outcome.

The parameters with the greatest influence on the cost-effectiveness results for omaveloxolone were the short- and long-term treatment effects, specifically, mean differences in mFARS between treatment and SoC during the first year after treatment initiation and the long-term treatment effect on the rate of mFARS progression after the short-term period. The findings were consistent when cost per QALY gained was used as an outcome (See Supplement Section E4).

Figure 4.2. Tornado Diagram for the Base-Case Analysis of Omaveloxolone (Cost per evLY Gained)



Omav: Omaveloxolone, mFARS: modified Friedreich's Ataxia Rating Scale, OS: Overall Survival, HR: Hazard Ratio, FA: Friedreich's Ataxia, US: United States

Table 4.9 presents the probabilities of omaveloxolone being cost-effective at thresholds of $50,000, $100,000, $150,000, and $200,000 per evLY gained. The probabilistic sensitivity analysis (PSA) results showed that the probability of being cost-effective was 0% for omaveloxolone across all evaluated thresholds. Please refer to Supplement Section E4 for the mean and 95% credible intervals for model outcomes.

Table 4.9. Probabilistic Sensitivity Analysis for the Base-Case Analysis of Omaveloxolone versus SoC (Cost Per evLY Gained)

	Cost Effective at $50,000 per evLY Gained	Cost Effective at $100,000 per evLY Gained	Cost Effective at $150,000 per evLY Gained	Cost Effective at $200,000 per evLY Gained
Omaveloxolone	0%	0%	0%	0%

evLYs: equal value life years

Scenario Analyses

We conducted several scenario analyses to examine the uncertainty and potential variations in the findings. Additionally, the cost-effectiveness of the interventions was estimated separately by age-of-onset subgroup. The scenario analyses are outlined below, with details on each scenario provided in Supplement Section E5. We presented the key scenario results for omaveloxolone in

Table 4.10, while the full results for omaveloxolone and nomlabofusp are available in Tables E5.2–E5.7 in Supplement Section E5.

Scenario analyses conducted:

1. Modified Societal Perspective
2. Exclusion of Unrelated Health Care Costs
3. Removal of Minimum Treatment Age
4. Assuming No Long-term Treatment Effect on mFARS (for omaveloxolone only)
5. Alternative Approaches to Estimating Utilities: mFARS-Based Utilities Derived from FA-COMS Data, FA-ADL-Based Utilities Derived from FA-COMS Data, and Disutility Stage-Based Utilities Derived from FA-COMS Data
6. Cost-offset Using the Price of Omaveloxolone (for nomlabofusp only): Cost-offset Using the Omaveloxolone Actual Net Price and Cost-offset Using the Omaveloxolone Threshold Price at $150,000 per QALY Gained
7. Removal of Mortality Associated with LVEF
8. No Disease Modifying Effects
9. Pre-clinical Treatment (for nomlabofusp under Scenario C only)
10. Subgroup Analysis Based on the Age of Onset
    a. Early onset (0-7 years)
    b. Typical onset (8-14 years)
    c. Intermediate onset (15-24 years)
    d. Late onset (>24 years)

The costs per QALY or evLY gained for both omaveloxolone and nomlabofusp exceeded the commonly used cost-effectiveness thresholds across all scenarios. However, there were some scenarios where the incremental cost-effectiveness ratios substantially changed. For both interventions, the source of utility values (i.e., Deger et al. (2026) versus FA-COMS) had a substantial impact on the cost-effectiveness results. For omaveloxolone, removing the minimum treatment age (i.e., assuming that patients could initiate treatment at the average age of diagnosis rather than waiting until age 16) moderately improved the cost per QALY and evLY gained. The scenario in which no long-term treatment effect of omaveloxolone on mFARS scores was assumed resulted in costs per QALY or evLY gained that were substantially higher than the base case. The cost-offset scenario using the actual net price of omaveloxolone, combined with Scenario C (where it is assumed that disease progression is halted with nomlabofusp and no patients discontinue treatment), represented the most optimistic scenario among all scenarios for nomlabofusp and resulted in costs per QALY and evLY gained that were substantially lower than in other scenarios, although they were still higher than the commonly used cost-effectiveness thresholds. The assumption of no disease modification (i.e., after treatment discontinuation, the mFARS score itself, rather than only the rate of mFARS change, reverts to that of SoC) considerably increased the cost

per QALY or evLY gained. More explanation on the impactful scenarios as well as the full results are provided in Supplement Section E5.

Table 4.10. Key Scenario Analysis Results for Omaveloxolone

Scenarios	Cost per QALY Gained	Cost per evLY Gained
Base-Case	$2,300,000	$1,800,000
Modified Societal Perspective	$2,300,000	$1,800,000
Removal of Minimum Treatment Age	$2,100,000	$1,600,000
Assuming No Long-term Treatment Effect on mFARS	$4,800,000	$3,700,000
mFARS-Based Utilities Derived from FA-COMS Data	$4,800,000	$3,900,000
FA-ADL-Based Utilities Derived from FA-COMS Data	$5,300,000	$4,100,000
Disutility Stage-Based Utilities Derived from FA-COMS Data	$6,400,000	$4,500,000
No Disease Modifying Effects	$3,600,000	$2,800,000

FA-ADL: Friedreich's Ataxia – Activities of Daily Living Scale, FA-COMS: Friedreich Ataxia Clinical Outcome Measures Study, mFARS: Modified Friedreich's ataxia rating scale

Threshold Analyses

Tables 4.11 and 4.12 report the threshold prices at $50,000, $100,000, $150,000, and $200,000 per QALY and evLY gained, respectively.

Table 4.11. QALY-Based Threshold Analysis Results

	Annual Net or Placeholder Price*	Annual Price to Achieve $50,000 per QALY Gained	Annual Price to Achieve $100,000 per QALY Gained	Annual Price to Achieve $150,000 per QALY Gained	Annual Price to Achieve $200,000 per QALY Gained
Omaveloxolone	$318,706	$9,452	$16,193	$22,934	$29,675
Nomlabofusp: Scenario A	$625,000	$19,416	$30,803	$42,190	$53,578
Nomlabofusp: Scenario B	$625,000	$22,645	$36,917	$51,188	$65,460
Nomlabofusp: Scenario C	$625,000	$32,157	$50,898	$69,639	$88,380

QALY: quality-adjusted life year

*Placeholder price was used for Nomlabofusp

Table 4.12. evLY-Based Threshold Analysis Results

	Annual Net or Placeholder Price*	Annual Price to Achieve $50,000 per evLY Gained	Annual Price to Achieve $100,000 per evLY Gained	Annual Price to Achieve $150,000 per evLY Gained	Annual Price to Achieve $200,000 per evLY Gained
Omaveloxolone	$318,706	$11,532	$20,352	$29,172	$37,992
Nomlabofusp: Scenario A	$625,000	$22,639	$37,251	$51,862	$66,473
Nomlabofusp: Scenario B	$625,000	$26,857	$45,340	$63,824	$82,307
Nomlabofusp: Scenario C	$625,000	$33,571	$53,726	$73,881	$94,037

evLYs: equal value life years

*Placeholder price was used for Nomlabofusp

Model Validation

See Supplement Section E6 for details on model validation.

Prior Economic Models

See Supplement Section E7 for a description of prior economic models.

Uncertainty and Controversies

There are several areas of uncertainty in this model. First, there is uncertainty surrounding the treatment effects of both interventions due to limited clinical data. For omaveloxolone, the follow-up period of the Phase II RCT was 48 weeks. Longer-term treatment effects were subsequently assessed using several years of data from the OLE study through a propensity score-matched comparison with external controls. Both the RCT and propensity score-matched OLE analyses have been published and peer reviewed. However, even when matched groups have similar observed baseline characteristics, nonrandomized analyses such as propensity score matching remain subject to residual confounding due to unmeasured or inadequately measured factors, including those that may influence enrollment in or continuation of the OLE study. In addition, as mentioned in the Uncertainty and Controversies subsection of Section 3.2, there is a concern for informative censoring if participants in the MOXIe trial dropped out due to lack of perceived efficacy or adverse events, which may have affected the short-term treatment effects.

In terms of the treatment effects of nomlabofusp, there is substantial uncertainty in both the short- and long-term efficacy data because evidence is still being generated and no peer-reviewed data have yet been published. To date, the treatment efficacy of nomlabofusp has been evaluated in the open-label study over approximately the first 1-2 years for patients who remained on therapy after

treatment initiation. Because the study is ongoing, the currently available results are based on a limited sample size, and statistical uncertainty ranges have not been reported. In addition, the short-term treatment effects were estimated using a group-level matching approach, in which patients from the external control cohort were selected based on the ranges of baseline characteristics observed among participants in the open-label study. This approach may be more susceptible to confounding than individual-level matching methods that achieve balance across measured baseline characteristics. Longer-term efficacy data after the first two years for nomlabofusp are not yet available. Due to all these uncertainties surrounding short-term and long-term treatment effects, we explored several alternative assumptions regarding the long-term treatment effect trajectory in exploratory analyses.

There is also uncertainty surrounding the short-term and long-term treatment discontinuation rates, especially for nomlabofusp. The open-label extension study of nomlabofusp reported that 21 out of 41 study participants discontinued nomlabofusp, mostly early in treatment. However, it is unclear whether this short-term discontinuation rate observed in the study will reflect the rate in clinical practice, once the reasons for the discontinuations are taken into account. Specifically, the manufacturer reported that ten patients discontinued treatment due to anaphylaxis, and nine of them had previously received nomlabofusp and were later re-exposed after a prolonged treatment interruption. Three additional participants discontinued treatment due to generalized urticaria, because of concern that it could represent a prodrome to anaphylaxis. The remaining eight discontinuations were unrelated to anaphylaxis, including five due to protocol deviations or other non-safety reasons, and three due to other mild or moderate safety events. Given that the observed anaphylaxis pattern was particularly associated with treatment interruption followed by re-initiation after a prolonged gap, the discontinuation rate may not translate directly into the rate seen in clinical practice if prolonged stop-and-restart patterns are avoided in future use. Moreover, there are no data on long-term discontinuation of nomlabofusp, which adds further uncertainty to its overall discontinuation pattern.

Moreover, it is also worth noting that the functional measures used in this model (i.e., mFARS, FA-ADL, and disability stages) may not fully capture patients' lived experiences. We relied on these measures because they were used in the pivotal clinical studies to estimate the treatment effects of omaveloxolone and nomlabofusp. However, we heard from patients that several symptoms important to them, including vision loss, hearing loss, and fatigue, are not directly captured by these measures, although some symptoms, such as fatigue, may be indirectly reflected in other domains. Additionally, several clinical experts and patients noted that mFARS, despite being used as a primary endpoint in clinical studies, is a research-oriented measure that is not commonly used in clinical practice and may be subject to ceiling effects. We heard that FA-ADL better reflects patients' lived experiences, although it may still not comprehensively capture all aspects of the disease that are important to patients. To the extent that these clinical measures do not fully capture treatment effects across relevant aspects of FA, our model may consequently underestimate the overall

impact of treatment on disease progression and patient outcomes. This gap between patients' lived experiences and the outcomes captured by commonly used clinical measures highlights the importance of developing and using clinical measures that more comprehensively reflect patient perspectives.

We found that the model results are significantly affected by the source of utility values. Specifically, the source that we used for the primary analysis (i.e., Deger et al. (2026)) resulted in substantially greater incremental QALYs compared to when we used FA-COMS data, resulting in an incremental cost-effectiveness ratio that is substantially lower. Although the incremental cost-effectiveness ratios for omaveloxolone and nomlabofusp did not cross the cost-effectiveness thresholds in any of the scenarios using an alternative utility source, the potential parameter uncertainty in the utility values and its potential impact on the model results are worth noting. We used Deger et al. (2026) as the primary source for utility values because we prioritize health state utilities that reflect those of the general population (as opposed to patients living with the condition), since ICER models primarily inform decisions at the population level. However, this study was conducted in the United Kingdom, full details on how it was conducted are not yet available, and it has not been peer-reviewed or published. Therefore, there could be potential parameter uncertainty around the health state utility values reported in the study, with both the magnitude and the potential direction of that uncertainty unclear.

Another uncertainty regarding the utility values is that no difference in Health-related quality of life (HRQoL) was detected between omaveloxolone and placebo in MOXIe.[26,46] This may be because HRQoL was assessed using the generic SF-36 instrument at week 48 in a relatively small trial, which may have limited the sensitivity to detect a treatment-related difference. One expert also noted that gastrointestinal adverse events, although mostly mild to moderate, were more frequent with omaveloxolone and may have contributed to the lack of a difference in HRQoL. However, the reason for the absence of a difference is unknown. Lastly, although both the healthcare and non-healthcare costs associated with FA management were stratified based on whether a patient is wheelchair-bound and whether a patient has heart failure, this stratification may not be granular enough to capture the potential differences in costs across the different disease states. Given that FA is characterized by a continuous spectrum of disease progression, there could still be variation in how much needs to be spent on FA management among those in the same category. Furthermore, FA is characterized by many different types of symptoms, either neurologic or non-neurologic, and our cost estimates may not be granular enough to reflect a patient's exact symptoms. Additionally, the study that we used to inform the healthcare and non-healthcare costs (Polek et al. (2013)) was dated, and thus the costs may not fully reflect current clinical practice. More research on healthcare spending or costs associated with disease progression is needed to better inform the value of new treatments for FA.

4.4 Summary and Comment

Our cost-effectiveness analyses indicate that omaveloxolone may provide modest health gains and savings in non-drug healthcare costs. However, omaveloxolone is expected to exceed standard cost-effectiveness thresholds at its current net price ($319,000 per year), because of the high drug costs associated with lifelong treatment. Probabilistic sensitivity analyses showed that the probability of omaveloxolone being cost-effective was zero across all cost-effectiveness thresholds. For nomlabofusp, the exploratory analysis results varied substantially depending on the assumed treatment effect, although the results did not approach commonly used cost-effectiveness thresholds in any scenario. Given the limited data on treatment efficacy at this point, additional treatment effect data are needed to better estimate the cost-effectiveness of nomlabofusp.

5. 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 was not available in the evidence base nor could be adequately estimated within the cost-effectiveness model. These elements are listed in the table below, with related information gathered from patients and other stakeholders. Following the public deliberation on this report the appraisal committee will vote on the degree to which each of these factors should affect overall judgments of long-term value for money of the intervention(s) in this review.

Table 5.1. Benefits Beyond Health and Special Ethical Priorities

Benefits Beyond Health and Special Ethical Priorities	Relevant Information
There are particular obligations to people with this condition because of disease severity and/or unmet need with currently available therapies.	To inform unmet need as a benefit beyond health, the results for the evLY and QALY absolute and proportional shortfalls have been reported for the modeled populations below. Individuals treated with SoC in the omaveloxolone vs. SoC comparison were used as a reference group. evLY shortfalls Absolute shortfall: 41.0 Proportional shortfall: 85.6% QALY shortfalls Absolute shortfall: 40.4 Proportional shortfall: 85.5% The absolute and proportional shortfalls represent the total and proportional health units of remaining quality adjusted life expectancy, respectively; that would be lost due to un- or under-treated illness. Please refer to the ICER Reference Case – Section 2. Quantifying Unmet Need (QALY and evLY Shortfalls) for the shortfalls of other conditions assessed in prior ICER reviews. These shortfalls suggest that there is significant unmet need in this patient population.
There are particular obligations to people with this condition because it disproportionately affects those from a racial/ethnic group that have not been equitably served by the health care system.	The prevalence of FA varies by ancestry and is highest among people with European ancestry. We did not identify evidence that FA disproportionately affects racial or ethnic groups that have been historically underserved by the health care system.
Apart from issues around disease severity/unmet need and race/ethnicity, there are other particular obligations to people with this condition.	Since these treatments have only reported results for adolescents and adults thus far, we do not yet know if there are benefits for children with FA. This is important because FA often begins before young adulthood when FA

	causes substantial disability during formative years of education, employment, and relationships. Given that FA is inherited, multiple members can be affected within the same family, causing additional strain and hardships.
The treatments are likely to improve caregivers' quality of life and/or ability to pursue their own education, work, and family life.	FA is a progressive illness with increasing caregiver burden. Treatments that can slow or halt the disease earlier in the disease course would have the greatest benefit for caregivers.
If payment/cost were not an issue, the treatments are likely to improve access to treatment because of its method of delivery and/or treatment setting.	Omaveloxolone is a well tolerated oral daily therapy. Nomlabofusp can also be delivered at home, however the subcutaneous daily injection combined with anaphylaxis risk can create a meaningful treatment burden.

ICER did not calculate the Health Improvement Distribution Index (HIDI) due to a lack of sufficient data on FA prevalence in subgroups defined by race and/or ethnicity.

6. Health Benefit Price Benchmark

ICER does not provide a Health Benefit Price Benchmark as part of draft reports because results may change with revision following receipt of public comments. We therefore caution readers against assuming that the values provided in the Threshold Analyses section of this draft report will match the Health Benefit Price Benchmark that will be presented in the next version of this Report.

7. Potential Budget Impact

7.1. Overview of Key Assumptions

We used results from the exploratory cost-effectiveness analysis to estimate the total potential budgetary impact of nomlabofusp for the Friedreich's ataxia population. Potential budget impact is defined as the total differential cost of using an intervention rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in averted health care events. All costs were undiscounted and estimated over a five-year time horizon. We used the placeholder price and the exploratory threshold prices (at $50,000, $100,000, $150,000, and $200,000 per evLY gained) for nomlabofusp in these estimates, and we calculated separate budget impact analyses for Scenario A, Scenario B, and Scenario C (as described in the cost-effectiveness section). We did not include omaveloxolone in this analysis because it has already been on the market for several years, and this budget impact analysis is intended to evaluate the potential short-term budget impact of a new drug immediately following market entry. For 2025-2026, the five-year annualized potential budget impact threshold that should trigger actions to manage access and affordability is approximately $821 million per year for new drugs.

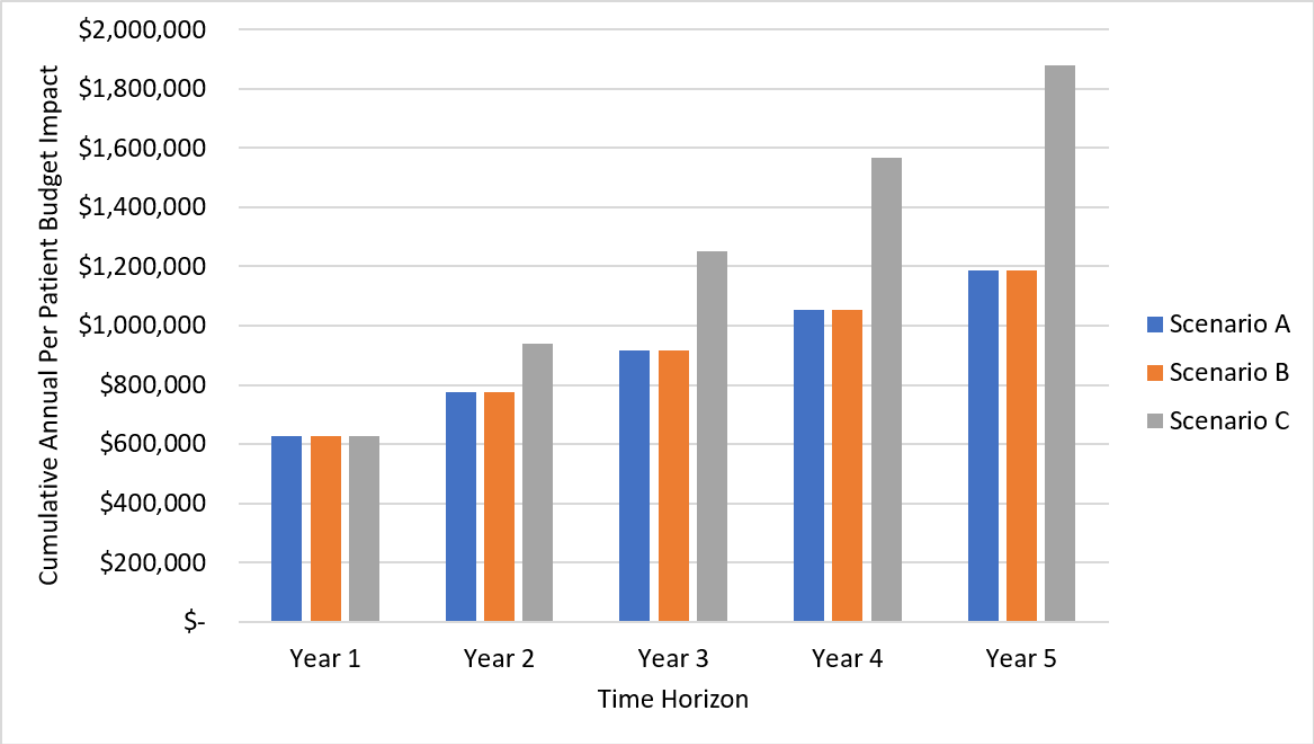
To estimate the size of the potential candidate population for treatment, we used inputs for the total US population aged 12 and older averaged over the next five years (approximately 297.3 million),[71] and the prevalence of FA in the United States (approximately 1 in 40,000).[72] We then subtracted the estimated number of FA patients in the US who are already taking omaveloxolone based on available net sales data, which is approximately 1,000 patients.[66,73] Applying these sources results in estimates of 6,432 eligible patients in the US. For the purposes of this analysis, we assumed that 20% of these patients would initiate treatment in each of the five years, or 1,286 patients per year.

7.2. Results

Figure 7.1 illustrates the cumulative annual per patient budget impact for nomlabofusp compared to standard of care. The cumulative annual budget impact represents the incremental costs of nomlabofusp compared to standard of care across all patients treated within a time horizon (including those who initiated the treatment in previous years), assuming nomlabofusp is used with a 20% uptake each year over five years. At the placeholder price of $625,000 and using Scenario A or Scenario B assumptions, the average annual budget impact per patient treated was approximately $627,900 in year 1 and increased to $1,185,100 by year five. At the placeholder price of $625,000 and using Scenario C assumption, the average annual budget impact per patient treated was approximately $627,900 in year 1 and increased to $1,877,500 by year five. The results of this analysis did not differ between Scenario A and B, because the differences in disease severity

assumptions between these scenarios did not have a significant impact on outcomes in years one through five. The difference in budget impact results in Scenario C is largely due to the assumptions around discontinuation. Whereas it is assumed that many patients discontinue nomlabofusp in Scenarios A and B, in Scenario C it is assumed that no patients discontinue treatment with nomlabofusp due to the optimistic treatment efficacy and safety assumptions. Therefore, the cumulative annual per patient budget impact results are significantly higher by year 5 in Scenario C compared to Scenarios A and B. Although Scenario C resulted in some savings in non-drug medical costs due to the more favorable treatment efficacy assumptions, the increase in drug costs exceeded these savings, resulting in a higher cumulative budget impact.

Figure 7.1. Cumulative Annual Budget Impact Per Patient Treated with Nomlabofusp



Assuming a 20% uptake of nomlabofusp per year, 54%, 54% and 34% of the eligible population could be treated at the annual placeholder price of $625,000 before reaching the ICER potential budget impact threshold in scenarios A, B, and C, respectively. At the $200,000, $150,000, $100,000, and $50,000 per evLY gained threshold prices for nomlabofusp in all scenarios, 100% of eligible patients could be treated before reaching the ICER potential budget impact threshold.

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Supplemental Material

A. Background: Supplemental Information

A1. Definitions

Friedreich's Ataxia (FA): An autosomal-recessive, neurodegenerative disease that is caused by mutation of the frataxin gene responsible for encoding the mitochondrial protein frataxin. FA is characterized by a reduction in functional abilities (i.e., loss of balance and muscular weakness) and neurologic deficits including swallowing, speech, and vision. Age of onset is a strong indicator of the rate of progression and disease severity, with symptoms most often manifesting in late childhood or adolescence. It is the most common inherited ataxia in that age range.[2]

Frataxin (FXN): A mitochondrial protein encoded by the FXN gene and a key component for the disease mechanism of FA. Mutations of the FXN gene lead to reductions in frataxin expression and triggers mitochondrial dysfunction.[5]

Modified Friedreich's Ataxia Rating Scale (mFARS): A neurological functional rating scale out of 93 points to measure a patient's disease progression. Based on four functional domains, the tool evaluates bulbar function, upper limb coordination, lower limb coordination, and upright stability. A higher mFARS score indicates greater impairment. An earlier scoring system ranging from 0 – 99 was used in the MOXIe trials.[36,37]

Friedreich's Ataxia Rating Scale- Activities of Daily Living (FARS-ADL / FA-ADL): A tool capturing daily life activities among patients living with Friedreich's ataxia to assess disease severity and functional disability. The scale includes nine items (e.g., speech, swallowing, walking) and scores range from 0 to 36 points, with a higher score reflecting greater impairment. A meaningful important change of the tool is 1.1 points.[39]

9-Hole Peg Test (9-HPT): A standardized performance-based test of manual dexterity and hand function that measures the time required to place nine pegs into nine holes and then remove them.[74]

Modified Fatigue Impact Scale (MFIS): A self-reported measure evaluating the effects of fatigue across physical, cognitive, and psychosocial domains. Scores can range from 0 to 84, and higher scores reflect a greater impact on quality of life.[75]

Cardiomyopathy: Disease of the heart muscle that can cause it to thicken, become fibrotic, or weaken, potentially impairing the heart's ability to fill with and pump blood effectively. Cardiomyopathy is a common cardiac manifestation of FA and a leading cause of premature death in affected individuals.[76]

Other Relevant Definitions

Absolute and Proportional Shortfalls: Absolute and proportional shortfalls are empirical measurements that capture different aspects of society's instincts for prioritization related to the severity or burden of an illness. The absolute shortfall is defined as the total absolute amount of future health patients with a condition are expected to lose without the treatment that is being assessed.[77] The ethical consequences of using absolute shortfall to prioritize treatments is that conditions that cause early death or that have very serious lifelong effects on quality of life receive the greatest prioritization. Thus, certain kinds of treatments, such as treatments for rapidly fatal conditions of children, or for lifelong disabling conditions, score highest on the scale of absolute shortfall. The proportional shortfall is measured by calculating the proportion of the total health units of remaining life expectancy that would be lost due to untreated illness.[78,79] The proportional shortfall reflects the ethical instinct to prioritize treatments for patients whose illness would rob them of a large percentage of their expected remaining lifetime. As with absolute shortfall, rapidly fatal conditions of childhood have high proportional shortfalls, but high numbers can also often arise from severe conditions among older adults who may have only a few years left of average life expectancy but would lose much of that to the illness without treatment. Details on how to calculate the absolute and proportional QALY and evLY shortfalls can be found in ICER's reference case. Shortfalls will be highlighted when asking the independent appraisal committees to vote on unmet need despite current treatment options as part of characterizing a treatment's benefits beyond health and special ethical priorities (Section 5).

Health Improvement Distribution Index (HIDI): The HIDI identifies a subpopulation that has a higher prevalence of the disease of interest and therefore, creates an opportunity for proportionately more health gains within the subpopulation. This opportunity may be realized by achieving equal access both within and outside the identified subpopulation to an intervention that is known to improve health. The HIDI is defined as the disease prevalence in the subpopulation divided by the disease prevalence in the overall population. For example, if a disease has a prevalence of 10% among Black Americans whereas the disease prevalence among all Americans is 4%, then the Health Improvement Distribution Index is 10%/4% = 2.5. In this example, a HIDI of 2.5 means that Black Americans as a subpopulation would benefit more on a relative basis (2.5 times more) from a new effective intervention compared with the overall population. HIDIs above 1 suggest that more health may be gained on the relative scale in the subpopulation of interest when compared to the population as a whole. The HIDI may be helpful in characterizing a treatment's benefits beyond health and special ethical priorities (Section 5). We did not calculate the HIDI for this review given a lack of data on prevalence in different subpopulations. However, FA is primarily diagnosed in populations of Caucasian or Indian ancestry.[2]

A2. Potential Cost-Saving Measures in Friedreich's Ataxia

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 headroom in health care budgets for higher-value innovative services (for more information, please reference ICER's Value Assessment Framework). These services are ones that would not be directly affected by therapies for Friedreich's ataxia (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. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with Friedreich's ataxia that could be reduced, eliminated, or made more efficient. No suggestions were received.

A3. Research, Development, and Manufacturing Costs

Manufacturers of treatments for Friedreich's ataxia, an ultra-rare disease, were invited to submit information on research, development, and manufacturing costs relevant to the value assessment and fair pricing of their treatment.

ICER did not receive any feedback on this inquiry.

A4. Patient Input on Clinical Trial Design

Manufacturers were asked to submit a written explanation of how they engaged patients in the design of their clinical trials, including the methods used to gather patient experience data and how they determined the outcomes that matter most to patients.

The manufacturer of nomlabofusp shared the following:

"Patient perspectives have been integrated throughout the clinical development program through ongoing engagement with the Friedreich's ataxia (FA) community. The company interacts with patients and caregivers on a weekly basis to better understand the lived experience of the disease and ensure that the clinical development program reflects patient priorities. Patient advocacy groups have provided input on clinical trial protocols and study design, helping to inform aspects of the clinical program and the selection of outcomes that are meaningful to patients.

In addition, the company's Board of Directors includes the parent of an individual living with FA who also serves on the Board of the Friedreich's Ataxia Research Alliance (FARA) and is an active member of the broader FA patient community. Through this dual perspective, they provide ongoing input into the clinical development program, including strategic discussions regarding program development, patient needs, and the overall conduct and progression of the clinical program.

Insights from prior patient-focused discussions, including Voice of the Patient meetings, have also been considered to further inform the understanding of outcomes and disease impacts that matter most to individuals living with Friedreich's ataxia."

B. Patient and Other Stakeholder Perspectives: Supplemental Information

B1. Patient Community Input: Methods

We spoke with four individuals living with Friedreich's ataxia who had various stages of disease onset and progression. We also spoke with two caregivers for individuals living with FA and two patient advocacy groups.

In addition, we reviewed the 2017 Voice of a Patient report that discussed impacts on quality of life, concerns about disease progression, and desire for new treatment options.[16] We did not receive any Share Your Story forms for this review.

Quality of Life Estimates

- Patient comments: Patients noted that mobility and functional abilities are important determinants of their quality of life, but that other factors, including vision, hearing, and social interactions, also contribute to quality of life and are not captured by mFARS, FA-ADL, or disability stages. Patients also identified HF as a potential contributor to quality of life. One patient living with heart problems reported that they do not experience a noticeable impact on their quality of life on a daily basis with progression, while others noted that cardiac dysfunction can begin to negatively affect quality of life once it reaches a certain level of severity.

- Impact on the model: The limitations of existing measures (e.g., mFARS, FA-ADL, and disability stages) in capturing all domains that are important to patients' quality of life were highlighted in the evidence report. Hearing from patients that cardiac function could be an important contributor of quality of life supported our decision to include a quality-of-life decrement associated with LVEF. However, given the mixed patient feedback and the view that cardiac dysfunction may not substantially affect quality of life until it reaches a certain level of severity, the use of broader LVEF categories to estimate heart function-related quality of life was considered appropriate. No other quality of life decrements were modeled (other than anaphylaxis associated with nomlabofusp) given that there were no other major quality of life domains identified.

Pilot Project to Explore Patient Engagement in Cost Effectiveness Analysis

We discussed the preliminary model structure and assumptions with four members of the patient community as part of a pilot project to explore enhanced patient engagement in the cost-

effectiveness analysis. The pilot consisted of three one-hour discussions held virtually over the Zoom meeting platform. Two sessions (Sessions 1 and 2) were completed prior to the posting of this Draft Evidence Report. The third session (Session 3) is an optional discussion for participants that is scheduled to take place after the posting of the Draft Evidence Report for ICER to share the findings from the cost-effectiveness analysis and the impact of patient engagement in the modeling effort. Specific aims of the pilot project were to:

1. Engage in education and information-sharing with participants regarding the goals of cost-effectiveness analysis as part of a broader health technology assessment process.

2. Work with participants on a proposed draft analysis plan to ensure that the patient's experience and goals for treatment are reflected in ICER's cost-effectiveness analysis structure, data, and key assumptions.

3. Obtain feedback from participants to understand the value of patient engagement, opportunities for improvement, challenges or barriers to engagement, and the impact of the discussions on the final results of the cost-effectiveness analysis and ICER report more broadly.

The first session provided background information on the role of cost-effectiveness analysis in health technology assessment and provided a summary of ICER's draft analysis plan. The second session consisted of a semi-structured group discussion with open-ended questions to ensure that the draft analysis plan reflected the perspectives and experiences of patients living with FA. The feedback received informed the following aspects of our model development:

Model Structure: Measures Used to Characterize Disease Progression

- Patient comments: Patients noted that although mFARS largely reflects their functional challenges and generally tracks their experience of disease progression, several domains that are important to patients are not captured, including vision, hearing, sleep quality, mental health, fine dexterity (e.g., handwriting), social interactions, and fatigue. Patients also noted a potential ceiling effect, whereby mFARS may not adequately capture changes in disease severity once impairment reaches a certain level. For FA-ADL, patients noted that although it is also not a comprehensive measurement system, it captures more domains that are important to patients than mFARS, such as bladder function, and is more closely tied to the challenges they experience in their daily lives. For disability stages, patients noted that although certain milestones (e.g., loss of mobility) have a more substantial impact on their lives than others, disease progression is generally experienced as a continuous process rather than as a series of discrete stages.

- Impact on the model: Although patient comments supported our original decision to use FA-ADL as the primary measure to map patients' quality of life, with mFARS and disability stages explored in scenario analyses, the team ultimately selected mFARS as the primary measure because of other critical limitations associated with FA-ADL (see Section 4.2 for details). However, given that none of these measures fully captures all aspects of patients' quality of life, we continued to explore alternative measures in scenario analyses. Also, the limitations of these measures and their potential implications for the model results were highlighted in the limitations section of the evidence report.

Model Structure: Non-Neurologic Complications

- Patient comments: Patients noted that among non-neurological complications, loss of cardiac function leading to HF is the complication that has the greatest impact on their lives and is of greatest concern. No other non-neurological complications were identified as significant concerns by patients.

- Impact on the model: Patient comments supported our decision to model cardiac function, specifically the development of HF, as the primary non-neurological complication. Currently, there are no data demonstrating treatment effects on cardiac function. However, we included functionality in the model to explore potential treatment effects on cardiac function if such data become available. Other non-neurological complications, although not highlighted during the discussions with patients, were captured implicitly through their effects on measures of neurological function.

Outcomes of Interest

- Patient comments: We heard that the following treatment outcomes are (or will be) most meaningful to the patients: (a) avoiding loss of cardiac function or heart failure, (b) preserving independence, (c) preserving vision and/or hearing, (d) walking without assistance (e.g., no need of wheelchair).

- Impact on the model: As additional model outcomes, we reported the cost per year of maintaining ambulation and the cost per year without heart failure. We were not able to include preservation of independence as an outcome because independence is difficult to quantify objectively, as the level of independence is subjective and may vary across patients. In addition, patient input suggested that there is no clear threshold for defining patients as independent versus not independent, as independence generally changes along a continuum. We were also not able to incorporate vision or hearing as separate outcomes because none of the measures included in the trials (and therefore the model) capture these domains. The lack of measures capturing vision and hearing was highlighted as a limitation of the model.

Treatment of Interest

- Patient comments: Patients who had experience with omaveloxolone reported that they had not experienced any major side effects associated with treatment. Patients also indicated that daily subcutaneous administration of nomlabofusp would not be a concern. No other major concerns regarding either treatment were identified.

- Impact on the model: Patient comments supported the data that suggested no major side effects for omaveloxolone. Also, consistent with discussions with patients, no disutilities or time costs associated with daily subcutaneous administration of nomlabofusp were modeled.

Health Care Costs

- Patient comments: Patients noted that health care costs associated with FA tend to increase gradually as the disease becomes more severe, largely due to increasing frequency of medical visits and monitoring. However, loss of mobility was identified as an important milestone that can substantially increase health care costs. Patients also noted that health care costs are expected to increase as cardiac function deteriorates because of the need for more frequent cardiology visits and monitoring.

- Impact on the model: Polek et al. (2013), which was used to inform health care costs, stratified costs based on whether a patient is predominantly wheelchair-dependent. Patient input supported the use of mobility status as an important determinant of health care costs. Discussions with patients also supported the inclusion of costs associated with HF. Because no available cost data stratify health care costs across more granular levels of disease severity, Polek et al. (2013) continued to be used to estimate health care costs. However, the potential residual effects of disease severity on health care costs that are not captured by this approach were highlighted as a limitation of the model.

Non-Health Care Costs

- Patient comments: We heard that in addition to the domains that we planned to include as non-health care costs (i.e., home and car modifications and devices), patients spend out-of-pocket money on non-traditional treatments such as supplements, massages, acupuncture, and chiropractic care as well as additional costs associated with purchasing a vehicle or living in more expensive housing to accommodate their needs.

- Impact on the model: Polek et al. (2013) captures non-health care costs associated with home and vehicle modifications and assistive devices but may not capture all expenses incurred by individuals with FA. Therefore, a higher upper bound for non-health care costs

was explored in a sensitivity analysis to account for the possibility that some patients incur higher costs than those reported by Polek et al. (2013).

Productivity Costs and Other Societal Costs

- Patient comment: Patients noted that they have generally been able to find employment, but their ability to work is expected to decline as the disease progresses. Patients also noted that committing to volunteer work can be difficult because of the unpredictable nature of their disease and functional status. In addition, patients highlighted that their choices regarding major aspects of their lives, such as where to live and which jobs to pursue, have become increasingly limited as the disease progresses. Finally, patients also highlighted the family burden and the impact of the disease on caregiver's work and non-work activities.

- Impact on the model: Patient comments supported our decision to stratify productivity costs by disease severity. We also incorporated productivity losses associated with reduced workforce participation, consistent with patient feedback that the range of jobs they can pursue becomes increasingly limited as the disease progresses. Patient comments regarding caregiver burden also supported our decision to include both caregiver productivity losses at work and productivity losses associated with non-work activities, including volunteering activities, due to caregiving for individuals with FA.

B2. Clinical Input: Methods

We spoke with clinical experts who are specialists in neurology and scientists with expertise in genetics.

C. Clinical Guidelines

Clinical Management Guidelines for Friedreich Ataxia: 2022

In the 2022 Clinical Management Guidelines for Friedreich's ataxia, 130 clinical recommendations and 95 best practice statements were developed across 17 FA-related topics using the GRADE framework for rare diseases. The guidelines recommend multidisciplinary, longitudinal care focused on surveillance and management of the multisystem manifestations of FA, including neurologic and functional impairment, cardiomyopathy, diabetes, scoliosis and orthopedic complications, dysphagia and speech impairment, vision and hearing loss, respiratory complications, and mental health, among other topics. Management emphasizes regular assessment, rehabilitation and exercise, symptom-directed therapies, assistive technologies, and coordinated specialty care Detailed recommendations can be found here: https://pmc.ncbi.nlm.nih.gov/articles/PMC9652828/

At the time of guideline development, there were no treatment-specified approved therapies for FA.

D. Comparative Clinical Effectiveness: Supplemental Information

D1. Detailed Methods

PICOTS

Population

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

Data permitting, we evaluated 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
- Sociodemographic factors (e.g., sex, age, race, ethnicity)

Interventions

The full list of interventions is as follows:

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

Comparators

Data permitting, we compared these agents to each other and to usual care without any disease modifying therapy.

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 and education
    - Quality of Life
    - Need for a personal caregiver
    - Adverse events including
    - Serious Adverse Events (AEs)
    - Discontinuation due to AEs
    - AEs of interest
        - Anaphylaxis
        - Injection-site reactions
        - Liver injury
        - Cardiotoxicity
- Other Outcomes
    - Changes in FA biomarkers
    - Changes in cardiac function
    - A1c

Timing

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

Settings

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

Study Design

Randomized controlled trials and non-randomized controlled trials with any sample size were included. Comparative observational studies and non-comparative observational studies using historical controls were also included.

Table D1.1 PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item
TITLE		
Title	1	Identify the report as a systematic review.
ABSTRACT		
Abstract	2	See the PRISMA 2020 for Abstracts checklist.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of existing knowledge.
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.
METHODS		
Eligibility Criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.
Information Sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.
Search Strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.
Selection Process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.
Data Collection Process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.
Data Items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.
	10b	List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.
Study Risk of Bias Assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.
Effect Measures	12	Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.
Synthesis Methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.

	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression).
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.
Reporting Bias Assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).
Certainty Assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.
RESULTS		
Study Selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.
Study Characteristics	17	Cite each included study and present its characteristics.
Risk of Bias in Studies	18	Present assessments of risk of bias for each included study.
Results of Individual Studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.
Results of Syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.
	20c	Present results of all investigations of possible causes of heterogeneity among study results.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.
Reporting Biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.
Certainty of Evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.
DISCUSSION		
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.
	23b	Discuss any limitations of the evidence included in the review.
	23c	Discuss any limitations of the review processes used.
	23d	Discuss implications of the results for practice, policy, and future research.
OTHER INFORMATION		
Registration and Protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.

	24c	Describe and explain any amendments to information provided at registration or in the protocol.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.
Competing Interests	26	Declare any competing interests of review authors.
Availability of Data, Code, and Other Materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.

From: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *PLoS Med.* 2021;18(3):e1003583.

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on new therapies for Friedreich's ataxia followed established best research methods.[80,81] We reported the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[82] The PRISMA guidelines include a checklist of 27 items (see Table D1.1).

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see the Policy on Inclusion of Grey Literature in Evidence Reviews. Where feasible and deemed necessary, we also accepted data submitted by manufacturers "in-confidence," in accordance with ICER's published guidelines on acceptance and use of such data).

Table D1.2. Search Strategy of Medline 1946 to Present with Daily Update, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Review

1	("nomlabofusp" OR "cti 1601" OR "cti1601" OR "CTI-1601").ti,ab.
2	("omaveloxolone" OR " ABT-RTA 408" OR "rta 408" OR "rta408"OR "RTA-408" OR "skyclarys").ti,ab.
3	1 or 2
4	3 NOT (animals not (humans and animals)).sh.
5	4 NOT (addresses OR autobiography OR bibliography OR biography OR comment OR congresses OR consensus development conference OR dictionary OR directory OR duplicate publication OR editorial OR encyclopedia OR guideline OR interactive tutorial).pt
6	limit 5 to English language
7	Remove duplicates from 6

Search Ran: 7/7/26

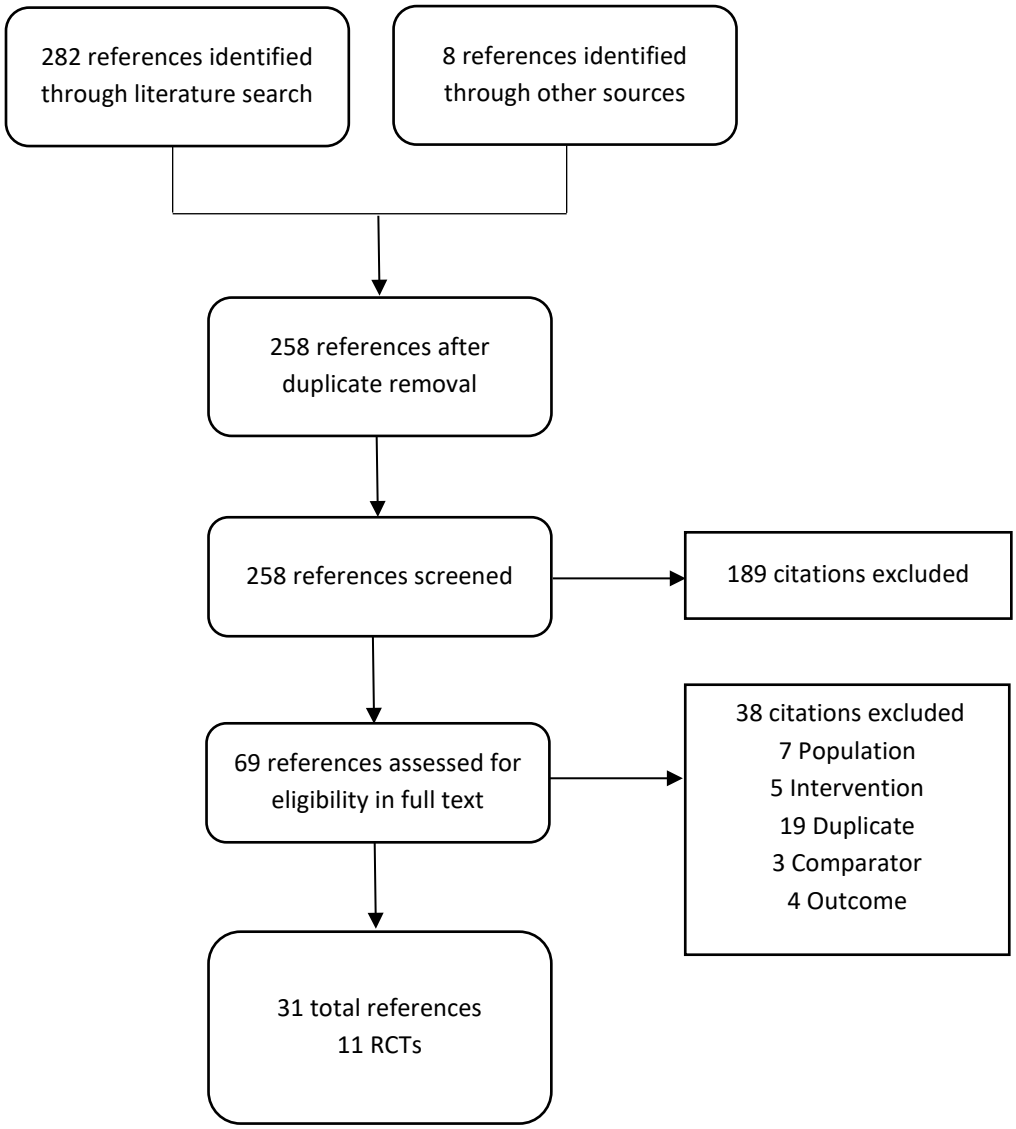
Table D1.3. Search Strategy of EMBASE

1	('nomlabofusp' OR 'cti 1601' OR 'cti1601' OR 'CTI-1601'):ti,ab

2	(‘omaveloxolone’ OR ‘ABT-RTA 408’ OR ‘rta 408’ OR ‘rta408’ OR ‘RTA-408’ OR ‘skyclarys’):ti,ab
3	#1 or #2
4	('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp
5	#3 NOT #4
6	#5 NOT ('chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
7	#6 AND [english]/lim
8	#7 NOT [medline]/lim

Search Ran: 7/7/26

Figure D1.1. PRISMA flow Chart Showing Results of Literature Search for Friedreich's Ataxia



Study Selection

We performed screening at both the abstract and full-text level. Two investigators independently screened all titles and abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier using Nested Knowledge (Nested Knowledge, Inc, St. Paul, Minnesota); a third reviewer worked with the initial two reviewers to resolve any issues of disagreement through consensus. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

We also included FDA documents related to omaveloxolone. These included the manufacturer's submission to the agency, internal FDA review documents, and the transcript of Advisory Committee deliberations and discussions. All literature that did not undergo a formal peer review process is described separately.

Data Extraction

Data were extracted into Microsoft Word and Microsoft Excel. The basic design and elements of the extraction forms followed those used for other ICER reports. Elements included a description of patient populations, sample size, duration of follow-up, funding source, study design features, interventions (agent, dosage, frequency, schedules), concomitant therapy allowed and used (agent, dosage, frequency, schedules), outcome assessments, results, and risk of bias for each study. The data extraction was performed in the following steps:

1. One reviewer extracted information from the full articles, and a second reviewer validated the extracted data.
2. Extracted data were reviewed for logic, and a random proportion of data were validated by a third investigator for additional quality assurance.

Risk of Bias Assessment

We examined the risk of bias for each randomized trial in this review using criteria published in the Cochrane Risk of Bias Assessment Tool Version 2.[81,83] Risk of bias was assessed by study outcome for each of the following aspects of the trials: randomization process, deviation from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported results, and overall risk of bias. Two reviewers independently assessed these domains. Any disagreements were resolved through discussion or by consulting a third reviewer. We did not assess the risk of bias in trials where we only had access to conference abstracts/presentations.

To assess the risk of bias in trials, we rated the categories as: "low risk of bias," "some concerns," or "high risk of bias." Guidance for risk of bias ratings using these criteria is presented below:

Low risk of bias*: The study is judged to be at low risk of bias for all domains for this result.*

Some concerns*: The study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.*

High risk of bias*: The study is judged to be at high risk of bias in at least one domain for this result or the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.*

We examined the risk of bias for mFARS, the primary outcome of the MOXIe trial (see Table D1.4). The main evidence base for nomlabofusp is from the single-arm JIVE open-label study and was not formally assessed using the Cochrane RoB-V2 tool.

Table D1.4. Risk of Bias Assessment

Studies	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk of Bias
Omaveloxolone						
MOXIe Part 2	Low	Low	Some Concerns	Low	Some Concerns	Some Concerns
	Comment: Double-blind, placebo-controlled trial. There were some differences in baseline characteristics between study arms related to % female, % with cardiomyopathy, etc. Primary efficacy analysis excluded participants with pes cavus (~20% of the trial participants) based on results observed in MOXIe Part 1. This protocol change was pre-specified but results, aside from one sensitivity analysis for the primary outcome, were reported for this "full analysis set" population and not the full intention-to-treat population. The primary outcome was change in mFARS which has measurement limitations related to ceiling effects which would impact both study arms but could potentially obscure treatment benefits for omaveloxolone.					

Evaluation of Clinical Trial Diversity

We evaluated the demographic diversity of clinical trials using the ICER-developed Clinical trial Diversity Rating (CDR) Tool.[40] However, the lack of prevalence estimates for this rare condition precluded the evaluation. As described in our Value Assessment Framework (VAF), trials of rare diseases with no reliable disease specific prevalence estimate will not be rated on clinical trial diversity. Instead, a qualitative description of the demographic characteristics of participants in the clinical trial will be presented. The demographic information for the pivotal trials of omaveloxolone (MOXIe Part 2) and nomlabofusp (JIVE) is described below.

In part 2 of the MOXIe trial, 103 participants were enrolled with a mean age of 24 (range: 16 to 40). In the omaveloxolone group, there were more female participants (61%) enrolled compared to male participants (39%). The participants were predominantly White (97%) (see Supplement Table D2.4).

The JIVE open-label study presented data for 41 participants from a March 2026 cut-off date. The mean age of the participants is 29 years old (range: 12 to 55). There were more female participants (58.5%) enrolled compared to male participants (41.5%). The trial did not report race (see Supplement Table D2.2).

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus.[84,85]

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for these newer treatments, we scanned the ClinicalTrials.gov site to identify studies completed more than two years ago. Search terms included: “nomlabofusp,” “omaveloxolone,” “Friedreich’s ataxia,” “cti 1601,” and “rta 408”.

We did not identify studies which would have met our inclusion criteria, and for which no findings have been published.

Data Synthesis and Statistical Analyses

Relevant data on key outcomes of the main studies were summarized qualitatively in the body of the Evidence Report and in evidence tables (Supplement Section D2).

D2. Evidence Tables

Table D2.1. Study Design

Trial Name (NCT)	Study Design & Duration of Follow-Up	Interventions (n) & Dosing Schedule	Key Inclusion & Exclusion Criteria	Key Outcomes
Nomlabofusp				
JIVE[31] **NCT06447025**	Phase II, ongoing open label study N=41	Arms: 1) 50 mg once daily (weight-based dose of 0.8 mg/kg up to a maximum of 50 mg in subjects ≥ 2 to 17 years of age) of nomlabofusp Antihistamines administered 5 days prior to first dose and for 90 days after the first dose.	Inclusion: ·Adolescents (12-17 yrs) from the PK run-in study ·Adult and adolescent participants not in prior studies ·Participants with a HbA1c ≤7% ·Must demonstrate sufficient dexterity and visual acuity or identify a caregiver to administer daily injections Exclusion: ·Subject has a Screening echocardiogram (ECHO) LVEF < 45%	·Skin FXN concentrations ·Safety and tolerability ·Long-term PK ·Clinical efficacy measures relative to reference population from FA-COMS database
Adolescent PK Run-in Study **NCT06681766**	Phase I adolescent PK run-in study N=14	Arms: 1)0.8 mg/kg (max 50mg) of nomlabofusp 2) Placebo	·12 to < 18 years with FA	·Safety & tolerability ·PK ·PD
Phase II Dose Exploration **NCT05579691**	Phase II, randomized, double-blind, placebo-controlled, dose exploration study N=28	All subjects were dosed once daily for 14 days followed by dosing every other day through Day 28 Cohort 1: 25 mg (9 on	·Ambulatory and non-ambulatory Friedreich's ataxia patients ≥18 years of age ·Nomlabofusp (CTI-1601) treatment naïve or	·Frataxin levels in peripheral tissue ·PK ·Safety and tolerability ·Number of participants with TEAEs

Trial Name (NCT)	Study Design & Duration of Follow-Up	Interventions (n) & Dosing Schedule	Key Inclusion & Exclusion Criteria	Key Outcomes
	Duration: 28 days	nomlabofusp, 4 on placebo) Cohort 2: 50 mg (10 on nomlabofusp, 5 on placebo)	participated (if eligible) in a previous Larimar study ·mFARS score ≥20 and be able to traverse a distance of 25 feet with or without an assistive device ·Must weigh >40 kg	
MAD **NCT04519567**	Phase I, double-blind, placebo-controlled study N=27	All cohorts received a single SC dose of nomlabofusp or placebo Cohort 1: 25 mg Cohort 2: 50 mg Cohort 3: 100 mg	Inclusion: · ≥18 years with a genetically confirmed diagnosis of FRDA ·mFARS score ≥20 ·Ability to traverse a distance of 25 feet with or without an assistive device (including a wheelchair) Exclusion: ·Patients with any condition, disease, or situation that, based on the investigator's judgment, could confound the study results or put the patient at undue risk Patients who experienced a serious, severe, or clinically significant adverse event (AE) in the SAD study	·Incidence of AEs, serious AEs, TEAEs, ·PK ·PD ·FXN levels
SAD **NCT04176991**	Phase I, double-blind, placebo-controlled study N=28	All cohorts received a single SC dose of nomlabofusp or placebo Cohort 1: 25 mg Cohort 2: 50 mg Cohort 3: 75 mg Cohort 4: 100 mg		
Omaveloxolone				

Trial Name (NCT)	Study Design & Duration of Follow-Up	Interventions (n) & Dosing Schedule	Key Inclusion & Exclusion Criteria	Key Outcomes
MOXIe Part 2 **NCT02255435** **Lynch. Annals of Neurology, 2021.**[9]	Phase II, international, multicenter, double-blind, randomized, placebo-controlled, parallel group N=103 Duration: 48 weeks	Arms: 1) Oral omaveloxolone 150 mg daily 2) Placebo	Inclusion: ·16-40yrs with genetically confirmed FA ·Baseline mFARS score between 20-80 ·Complete maximal exercise testing on a recumbent stationary bicycle ·eGFR≥ 60 mL/min/1.73 m^2 ·Left ventricular ejection fraction ≥ 40% Exclusion: · Uncontrolled diabetes ·Clinically significant cardiac disease ·Interfering medical conditions	·Change from baseline in mFARS score compared with placebo at 48 weeks
MOXIe Part 1 **NCT02255435** **Lynch. Annals of Clinical and Translational Neurology. 2018.**[23]	Phase II, randomized, double-blind, placebo-controlled, dose-ranging, multi-center study N=69 Duration: 12 weeks	3:1 randomization 2 cohorts: omaveloxolone 160 mg/day 2 cohorts: omaveloxolone 300 mg/day 1 cohort: omaveloxolone 300mg/day		·Mean change from baseline in peak work (watts/kg) at Week 12 (regardless of pes cavus status) ·Safety ·Tolerability

Trial Name (NCT)	Study Design & Duration of Follow-Up	Interventions (n) & Dosing Schedule	Key Inclusion & Exclusion Criteria	Key Outcomes
MOXIe Extension **NCT02255435** **Lynch. Movement Disorders. 2023.**[17]	Open-label extension study Duration: 144 weeks	All arms received 150 mg of omaveloxolone daily 1) omaveloxolone-omaveloxolone 2) Placebo- omaveloxolone Subjects who completed MOXIe part 1 and part 2 (including 48 weeks of treatment and a follow-up safety visit at 52 weeks)		·Difference in the initial placebo and initial omaveloxolone groups in the "delayed-start period" (extension week 72 change from baseline mFARS values) versus the initial omaveloxolone -placebo difference in the "placebo controlled period" (MOXIe part 2 week 48 change from baseline mFARS values)
MOXIe Propensity Matched **FA-COMS: NCT03090789** **MOXIe Extension: NCT02255435** **Lynch. Annals of Clinical and Translational Neurology. 2023.**[18]	Propensity matched comparison of omaveloxolone treatment to Friedreich ataxia natural history data N=136 Duration: 3 years	Arms: 1) FA-COMS patients matched 1:1 to MOXIe Extension patients 2) MOXIe Extension (treatment naïve & patients continuing treatment) received 150 mg of omaveloxolone once daily Subjects who completed MOXIe part 1 and 2 were eligible to enroll in the MOXIe extension	·Baseline mFARS ·≥1 post-baseline mFARS within 3 years after baseline ·Values for all propensity score model covariates (sex, baseline mFARS score, age at baseline, age of FRDA onset, baseline gait score) ·All patients were included regardless of pes cavus status	·Change in mFARS score from baseline at Year 3

Trial Name (NCT)	Study Design & Duration of Follow-Up	Interventions (n) & Dosing Schedule	Key Inclusion & Exclusion Criteria	Key Outcomes
Lima. Journal of Neurology. 2025.[20]	Single-center, observational, prospective study N=20 Duration: 24 weeks	Each patient received oral omaveloxolone at a dose of 150 mg/day, administered as three tablets of 50 mg per day	Inclusion: ·Patients age≥18 years diagnosed with FRDA treated with omaveloxolone ·mFARS score<80 at study initiation ·Minimum follow-up of 4 weeks from omaveloxolone start Exclusion: ·mFARS score ≥80 at study initiation ·Severe hepatic impairment (Child–Pugh class C) ·eGFR < 30 mL/ min ·Heart failure with New York Heart Association (NYHA)functional class>III	·Assessed with an anamnestic profile and blood tests at baseline, 12, and 24 weeks of treatment (including mFARS, FA-ADL, SARA)
Liu. The Cerebellum. 2025.[21]	Post-marketing study evaluating real-world safety data based on the FDA Adverse Event Reporting System (FAERS) N= 820 omaveloxolone-related AE reports	FAERS data from Q1 2023 to Q4 2024		

AE: adverse event, CFB: change from baseline, eGFR: Estimated glomerular filtration rate, FA-COMS: Friedreich's Ataxia Clinical Outcome Measures, FA-ADL: Friedreich's Ataxia – Activities of Daily Living, FRDA: Friedreich's ataxia, FXN: frataxin, HbA1c: k Hemoglobin A1, kg: kilogram, LVEF: Left ventricular ejection fraction, mFARS: modified Friedreich Ataxia Rating Scale, MAD: multiple ascending dose, mg: milligram, PD: pharmacodynamics, PK: pharmacokinetics, SAD: single ascending dose, SARA: Scale for the Assessment and Rating of Ataxia, SC: subcutaneous, TEAE: treatment emergent adverse event

Table D2.2. Baseline Characteristics for JIVE Phase II OL[31]

Intervention		Nomlabofusp	
Trial		JIVE Phase II OL	
Arm		Nomlabofusp	FA-COMS
N		41	362
Age	Mean (SD)	29.0 (11.3)	25.6 (9.55)
	Min, Max	12, 55	12, 55
	≥ 12 to <18, n (%)	8 (19.5)	NR
	≥ 18 yr, n (%)	33 (80.5)	NR
Age at Symptom Onset (Years)	Mean (SD)	12.4 (5.98)	12.6 (5.25)
	Min, Max	5, 30	5, 30
Sex, n (%)	Male	17 (41.5)	NR
Prior Exposure to Nomla	n (%)	31 (75.6)	NR
Prior Exposure to Omav	n (%)	20 (48.8)	NR
Baseline mFARS Total Score	Mean (SD)	55.0 (16.96)	50.6 (13.19)
	Min, Max	16.8, 85.5	24.0, 83.0
Baseline FA-ADL Overall Score	Mean (SD)	17.1 (7.1)	14.7 (5.3)
	Min, Max	0, 27	2, 27
Baseline 9-HPT Average Time of Dominant Hands	Mean (SD)	93.8 (65.5)	75.4 (42.25)
	Min, Max	36.0, 277.3	36.0, 262.1
Baseline MFIS Overall Score	Mean (SD)	34.5 (2, 79)	31.8 (15.6)
	Min, Max	2, 79	2, 78
Ambulatory	n (%)	21 (51.2)	NR
Gait Score, n (%)	1 - Mild Ataxia	4 (9.7)	NR
	2 - Walks with Definite Ataxia	4 (9.7)	NR
	3 - Moderate Ataxia	5 (12.2)	NR
	4 - Severe Ataxia	8 (19.5)	NR
	5 - Cannot Walk with Assistance (Wheelchair Bound)	20 (48.8)	NR

FA-COMS: Friedreich's Ataxia Clinical Outcome Measures Study, FA-ADL: Friedreich's Ataxia- Activities of Daily Living, mFARS: modified Friedreich Ataxia Rating Scale, MFIS: modified fatigue impact scale, n: number, NR: not reported, OL: open label, SD: standard deviation, 9-HPT: Nine-hole peg test

Table D2.3. Baseline Characteristics for Nomlabofusp Phase I Studies[10]

Intervention		Nomlabofusp								
Trial		Phase I MAD				Phase I SAD				
Arm		25 mg	50 mg	100 mg	Placebo	25 mg	50 mg	75 mg	100 mg	Placebo
N		6	7	7	7	4	4	5	5	10
Age	Median (Range)	37 (21, 65)	36 (19, 47)	24 (20, 44)	23 (20, 36)	25 (20, 33)	41 (24, 52)	34 (19, 69)	24 (20, 26)	31 (20, 64)
Age at Symptom Onset (Years)	Median (Range)	18 (12, 44)	19 (8, 28)	10 (5, 22)	15 (8, 23)	8 (8, 11)	16 (10, 41)	19 (14, 60)	15 (5, 18)	14.5 (7, 40)
Sex, n (%)	Male	3 (50)	4 (57.1)	3 (42.9)	5 (71.4)	3 (75)	4 (100)	2 (40)	4 (80)	4 (40)
Race, n (%)	White	6 (100)	6 (85.7)	6 (85.7)	6 (85.7)	4 (100)	4 (100)	5 (100)	5 (100)	10 (100)
	Asian	0	1 (14.3)	1 (14.3)	0	NR	NR	NR	NR	NR
	American Indian	0	0	0	1 (14.3)	NR	NR	NR	NR	NR
Ethnicity, n (%)	Non-Hispanic/Latino	6 (100)	7 (100)	7 (100)	5 (71.4)	4 (100)	4 (100)	5 (100)	5 (100)	8 (80)
BMI (kg/m^2)	Mean (SD)	25.4 (3.9)	25.2 (4.1)	26.9 (4.7)	24.3 (3.5)	22.8 (4.0)	24.2 (4.4)	23.2 (3.9)	26.0 (6.0)	23.1 (4.1)
Time Since Diagnosis, Years	Median (Range)	7.9 (0.9, 19.4)	8.6 (0.8, 16.7)	10.7 (6.8, 18.8)	5.5 (0.9, 15.4)	14.3 (3.8, 18.7)	13.8 (8, 21.5)	5.5 (2, 12.5)	4.8 (0.2, 18.5)	11.4 (0.4, 20.7)
Baseline mFARS Total Score	Median (Range)	33.6 (23, 65)	33.5 (23, 63)	54.5 (43, 68)	55 (19, 67)	62.0 (47, 67)	52.8 (24, 71)	33.5 (27, 69)	52.5 (13, 67)	46.5 (27, 70)
Baseline FA-ADL Overall Score	Median (Range)	17.3 (11, 24)	16 (8, 24)	17.5 (14, 24)	15.5 (10, 23)	20.8 (10, 26)	16.8 (15, 25)	16.5 (13, 20)	16 (8, 25)	16 (10, 22)

BMI: body mass index, FA-ADL: Friedreich's Ataxia – Activities of Daily Living, MAD: multiple ascending dose, mg: milligram, mFARS: modified Friedreich Ataxia Rating Scale, n: number, NR: not reported, SAD: single ascending dose, SD: standard deviation

Table D2.4. Baseline Characteristics for MOXIe Part 2[9,24,25,86]

Intervention		Omaveloxolone					
Trial		MOXIe Part 2					
Population		Primary Analyzed Subset		ARP		Pes Cavus	
Arm		Omav	Placebo	Omav	Placebo	Omav	Placebo
N		40	42	51	52	10	10
Age	Mean (SD)	24.2 (6.5)	23.6 (7.8)	23.4 (6.1)	24.1 (7.8)	19.9 (2.6)	26 (8.2)
	Median (Range)	23	21	22	21	20	27
	Min, Max	16,39	16,40	NR	NR	NR	NR
	<18 yr, n (%)	7 (18)	13 (31)	9 (18)	15 (29)	2 (20)	2 (20)
	≥ 18 yr, n (%)	33 (82)	29 (69)	NR	NR	NR	NR
Age at Symptom Onset (Years)	Mean (SD)	15.9 (5.7)	15.1 (5.3)	14.8 (5.7)	15.3 (5.3)	10.9 (3.6)	16.4 (5.3)
	Median (Range)	15	15	NR	NR	NR	NR
	Min, Max	7, 36	5, 30	NR	NR	NR	NR
Sex, n (%)	Female	24 (60)	14 (33.3)	31 (61)	17 (33)	7 (70)	3 (30)
	Male	16 (40)	28 (66.7)	20 (39)	35 (67)	3 (30)	7 (70)
Race, n (%)	White	40 (100)	40 (95.2)	50 (98)	50 (96.2)	9 (90)	10 (100)
	Unknown/Not Reported	NR	2 (4.8)	1 (2)	2 (3.8)	1 (10)	NR
Ethnicity, n (%)	Hispanic or Latino	1 (2.5)	3 (7.1)	2 (4)	3 (6)	NR	NR
	Non-Hispanic/Latino	39 (97.5)	39 (92.9)	49 (96)	49 (94)	NR	NR
	Not Reported	NR	NR	0	0	NR	NR
Weight (kg)	Mean (SD)	68.9 (18.4)	66.3 (17.9)	NR	NR	NR	NR
	Median	65.8	64.7	NR	NR	NR	NR
	Min, Max	42.2, 112.3	40.8, 127	NR	NR	NR	NR
BMI (kg/m^2)	Mean (SD)	23.6 (5.4)	22.9 (5.1)	NR	NR	NR	NR
	Median	23.2	21.9	NR	NR	NR	NR
	Min, Max	17.4, 43	15.6, 40.5	NR	NR	NR	NR
Duration of Disease	Mean (SD)	4.8 (4)	4.7 (4.7)	4.7 (3.8)	4.4 (4.4)	4.6 (3.2)	3 (2.7)
Baseline mFARS Total Score	Mean (SD)	40.9 (10.4)	38.8 (11)	40.8 (10.2)	37.9 (10.8)	41.1 (9.9)	34.4 (9.3)
	Median	39.15	35.7	NR	NR	NR	NR

	Min, Max	24.3, 59.3	19.8, 63	NR	NR	NR	NR
Baseline FA-ADL Overall Score	**Mean (SD)**	10.7 (4.8)	9.9 (4.8)	11 (4.5)	9.9 (4.7)	12.2 (3.4)	9.8 (4.4)
	Median	11.5	10	NR	NR	NR	NR
	Min, Max	2, 21	1, 20.5	NR	NR	NR	NR
Peak Work, W/kg	**Mean (SD)**	1.1 (0.5)	1.2 (0.6)	1.1 (0.6)	1.2 (0.6)	1.1 (0.8)	1.4 (0.7)
	Median	1.02	1.06	NR	NR	NR	NR
	Min, Max	0.16, 2.05	0.23, 2.65	NR	NR	NR	NR
GAA1 Repeat Length	**Mean (SD)**	739.2 (214.9)	693.8 (277.2)	736.8 (206.8)	676.2 (267.9)	736.6 (200.1)	585.6 (206.6)
	Median	700	684.5	NR	NR	NR	NR
	Min, Max	230, 1160	170, 1270	NR	NR	NR	NR
Ambulatory	**N (%)**	37 (93)	39 (93)	46 (90)	49 (94)	8 (80)	10 (100)
History of Cardiomyopathy	**N (%)**	19 (48)	12 (29)	25 (49)	15 (29)	6 (60)	3 (30)
History of Scoliosis	**N (%)**	29 (73)	32 (76)	39 (77)	37 (71)	10 (100)	5 (50)
Scoliosis Surgery	**N (%)**	12 (30)	7 (17)	16 (31)	10 (19)	4 (40)	3 (30)
eGFR, mL/min/1.73 m2 Mean (SD)	**All Patients**	NR	NR	113.4 ± 14.7	109.2 ± 21.7	NR	NR
	Pediatric	NR	NR	106.3 ± 15.6	99.1 ± 33.7	NR	NR

ARP: all randomized patients, BMI: body mass index, eGFR: estimated glomerular filtration rate, FA-ADL: Friedreich's Ataxia – Activities of Daily Living, mFARS: modified Friedreich Ataxia Rating Scale, n: number, NR: not reported, SD: standard deviation

Table D2.5. Baseline Characteristics for MOXIe Extension & Propensity Matching[17,18]

Intervention		**Omaveloxolone**			
Trial		**MOXIe Extension**		**MOXIe Propensity Matching**	
Population		**Primary Analyzed Subset**		**Primary Pooled Population**	
Arm		**Omav-Omav**	**Placebo-Omav**	**Matched FA-COMS**	**MOXIe Extension**
N		**40**	**42**	**136**	**136**
Age	**Mean (SD)**	24.2 (6.5)	23.6 (7.8)	26.2 (13.7)	26.6 (7.3)
	Median (Range)	23	21	NR	NR
	IQR	19, 28.5	17, 27	NR	NR
	Min, Max	NR	NR	6, 64	16, 41

Intervention		Omaveloxolone			
	<18 yr, n (%)	7 (18)	13 (31)	NR	NR
Age at Symptom Onset (Years)	**Mean (SD)**	15.9 (5.7)	15.1 (5.3)	15.2 (10.5)	15.5 (5.3)
	Median (Range)	15	15	NR	NR
	IQR	12, 19.5	12, 18	NR	NR
Sex, n (%)	**Female**	NR	NR	70 (51.5)	70 (51.5)
	Male	16 (40)	28 (67)	66 (48.5)	66 (48.5)
Race, n (%)	**White**	40 (100)	40 (95)	125 (96.2)	133 (97.8)
	Non-White	NR	NR	5 (3.8)	3 (2.2)
	P-Value	NR	NR	0.43	
Ethnicity, n (%)	**Hispanic or Latino**	NR	NR	6 (4.4)	6 (4.4)
	Non-Hispanic/Latino	39 (98)	39 (93)	129 (94.9)	130 (95.6)
	Not Reported	NR	NR	1 (0.7)	0
	P-Value	NR	NR	0.99	
Height (cm)	**Mean (SD)**	NR	NR	165.1 (14.7)	169.3 (10.4)
	P-Value	NR	NR	0.02	
Weight (kg)	**Mean (SD)**	68.9 (18.4)	66.3 (17.9)	61 (20.7)	69.1 (16.7)
	Median	65.8	64.7	NR	NR
	IQR	53.1, 80.9	51.5, 78.1	NR	NR
	P-Value	NR	NR	0.0018	
BMI (kg/m^2)	**Mean (SD)**	NR	NR	22 (5.7)	24 (5.2)
	P-Value	NR	NR	0.0069	
Baseline mFARS Total Score	**Mean (SD)**	40.9 (10.4)	38.8 (11)	41 (16.1)	42.2 (12.6)
	Median	39.2	35.7	NR	NR
	Min, Max	NR	NR	5.3, 77	8.2, 73.5
	IQR	31.1, 51.7	32.5, 47	NR	NR
Baseline FA-ADL Overall Score	**Mean (SD)**	10.7 (4.8)	9.9 (4.8)	11.8 (5.9)	12.5 (4.9)
	Median	11.5	10	NR	NR
	IQR	7.5, 13.8	6, 13.5	NR	NR
	P-Value	NR	NR	0.28	

Intervention		Omaveloxolone			
Baseline Gait (Assessment #7 in FARS Section E [Upright Stability])	**Mean (SD)**	NR	NR	2.7 (1.69)	2.8 (1.36)
GAA1 Repeat Length	**Mean (SD)**	739.2 (214.9)	693.8 (277.2)	590 (246)	721 (270)
	≥ 675, N (%)	NR	NR	54 (41.9)	66 (55.5)
	Median	700	684.5	NR	NR
	IQR	570, 933	500, 899.5	NR	NR
	P-Value	NR	NR	<0.0001	
GAA2 Repeat Length	**Mean (SD)**	NR	NR	863 (232)	728 (297)
	P-Value	NR	NR	0.0001	
Ambulatory	**N (%)**	37 (93)	39 (93)	NR	NR
History of Cardiomyopathy	**N (%)**	19 (48)	12 (29)	NR	NR
Systolic Blood Pressure (mmHg)	**Mean (SD)**	NR	NR	121.4 (15)	121.1 (13.5)
	P-Value	NR	NR	0.9	
Diastolic Blood Pressure (mmHg)	**Mean (SD)**	NR	NR	73.2 (10.5)	75.3 (8.7)
	P-Value	NR	NR	0.15	
Heart Rate (beats/min)	**Mean (SD)**	NR	NR	85.2 (15.4)	79.8 (12.6)
	P-Value	NR	NR	0.0089	

BMI: body mass index, IQR: interquartile range, FA-COMS: Friedreich's Ataxia Clinical Outcome Measures, FA-ADL: Friedreich's Ataxia- Activities of Daily Living, mFARS: modified Friedreich Ataxia Rating Scale, n: number, NR: not reported, SD: standard deviation

Table D2.6. Baseline Characteristics for Omaveloxolone Observational Studies[20,21]

Intervention		Omaveloxolone	
Trial		**Lima 2025**	**Liu 2025**
Arm		**Omaveloxolone**	**820 omaveloxolone-related AE reports**
N		**20**	
Age	**Mean (SD)**	40.6 (12.6)	NR
	0-15	NR	2 (0.2)
	16-39	NR	100 (12.1)

Intervention		Omaveloxolone	
	40-65	NR	54 (6.6)
	>65	NR	14 (1.7)
	Unknown	NR	650 (79.3)
Sex, n (%)	**Female**	13 (65)	287 (35)
	Male	NR	311 (37.9)
	Unknown	NR	222 (27.1)
Duration of Disease	**Mean (SD)**	24.9 (9.5)	NR
Baseline mFARS Total Score	**Mean (SD)**	59.1 (12.8)	NR
Baseline FA-ADL Overall Score	**Mean (SD)**	19.6 (5.8)	NR
Diabetes	**n (%)**	*1 (5)*	NR
History of Cardiomyopathy	**n (%)**	*4 (20)*	NR
History of Scoliosis	**n (%)**	*4 (20)*	NR
Pes Cavus	**n (%)**	*1 (5)*	NR
Gait Impairment	**n (%)**	18 (90)	NR

FA-ADL: Friedreich's Ataxia – Activities of Daily Living, mFARS: modified Friedreich Ataxia Rating Scale, n: number, NR: not reported, SD: standard deviation
Note: Italicized data has been digitized or calculated

Table D2.7. Baseline Characteristics for MOXIe Propensity Matched[18]

Omaveloxolone Propensity Matched					
Arm		**Placebo-Omav**		**Omav-Omav**	
Characteristic	**Statistic**	**Matched FA-COMS**	**MOXIe Extension**	**Matched FA-COMS**	**MOXIe Extension**
Age (Years)	**n**	95	95	41	41
	Mean (SD)	28.4 (15.1)	27.4 (7.5)	26.3 (14.4)	24.8 (6.3)
	Min, Max	6, 73	16, 41	7, 65	17, 40
	P-Value	NR	0.54	NR	0.54
Age at FRDA Onset	**n**	95	95	41	41
	Mean (SD)	16.1 (11.6)	15.5 (5.1)	15.6 (8.9)	15.3 (5.7)
	P-Value	NR	0.66	NR	0.85
Sex (n [%])	**n**	95	95	41	41

Omaveloxolone Propensity Matched					
	Female	43 (45.3%)	43 (45.3%)	27 (65.9%)	27 (65.9%)
	Male	52 (54.7%)	52 (54.7%)	14 (34.1%)	14 (34.1%)
	P-value	NR	1	NR	1
mFARS	**n**	95	95	41	41
	Mean (SD)	44.5 (18.0)	42.8 (12.8)	39.6 (16.8)	40.9 (12.2)
	Min, Max	8.5, 81.5	14.0, 73.5	13.0, 71.5	8.2, 62.0
	P-Value	NR	0.45	NR	0.71
Gait (Assessment #7 in FARS Section E [Upright Stability])	**n**	95	95	41	41
	Mean (SD)	3.0 (1.77)	2.9 (1.36)	2.6 (1.62)	2.7 (1.37)
	P-Value	NR	0.58	NR	0.88
Ethnicity (n [%])	**n**	93	95	41	41
	Hispanic or Latino	5 (5.4%)	5 (5.3%)	1 (2.4%)	1 (2.4%)
	Not Hispanic or Latino	86 (92.5%)	90 (94.7%)	39 (95.1%)	40 (97.6%)
	Not Reported	2 (2.2%)	0	1 (2.4%)	0
	P-Value	NR	0.94	NR	0.99
Race (n [%])	**n**	86	95	38	41
	White	83 (96.5%)	93 (97.9%)	37 (97.4%)	40 (97.6%)
	Non-White	3 (3.5%)	2 (2.1%)	1 (2.6%)	1 (2.4%)
	P-Value	NR	0.57	NR	0.96
Height (cm)	**n**	55	95	27	41
	Mean (SD)	164.6 (15.1)	169.6 (10.3)	159.4 (14.7)	168.6 (10.9)
	P-Value	NR	0.031	NR	0.0042
Weight (kg)	**n**	62	95	29	41
	Mean (SD)	63.0 (23.5)	69.7 (16.1)	59.1 (20.9)	67.6 (18.3)
	P-Value	NR	0.049	NR	0.077
BMI (kg/m^2)	**n**	55	95	27	41
	Mean (SD)	22.9 (6.3)	24.2 (5.1)	22.8 (6.0)	23.6 (5.5)
	P-Value	NR	0.18	NR	0.58
Systolic Blood Pressure (mmHg)	**n**	50	95	28	41
	Mean (SD)	122.1 (12.9)	123.9 (12.5)	120.6 (14.7)	114.6 (13.7)

Omaveloxolone Propensity Matched					
	P-Value	NR	0.4	NR	0.087
Diastolic Blood Pressure (mmHg)	**n**	50	95	28	41
	Mean (SD)	72.8 (9.6)	76.9 (8.5)	72.2 (9.6)	71.5 (7.9)
	P-Value	NR	0.0097	NR	0.75
Heart Rate (Beats/Min)	**n**	50	95	27	41
	Mean (SD)	83.0 (13.6)	79.6 (11.9)	82.2 (15.1)	80.4 (14.3)
	P-Value	NR	0.12	NR	0.62
ADL Total Score	**n**	87	95	37	41
	Mean (SD)	12.9 (6.8)	12.8 (4.8)	10.8 (5.9)	11.9 (5.2)
	P-Value	NR	0.9	NR	0.39
GAA1 Repeat Length	**n**	89	86	39	33
	Mean (SD)	618 (246)	717 (289)	591 (240)	732 (216)
	≥ 675, N (%)	39 (43.8%)	45 (52.3%)	19 (48.7%)	21 (63.6%)
	P-Value	NR	0.015	NR	0.011
GAA2 Repeat Length	**n**	87	84	37	32
	Mean (SD)	883 (223)	721 (294)	880 (239)	746 (308)
	P-Value	NR	<0.0001	NR	0.046

ADL: activities of daily living, BMI: body mass index, FRDA: Friedreich's Ataxia, mFARS: modified Friedreich's Ataxia Rating Scale, n: number, SD: standard deviation

Table D2.8. Functional Outcomes for JIVE Phase II OL[31]

Intervention			**Nomlabofusp**	
Trial			**JIVE Phase II OL**	
Arm			**Nomlabofusp**	**FA-COMS**
N			**41**	**362**
mFARS	**Baseline**	**n**	41	362
		Median (IQR)	54.75 (41.2, 71)	50.6 (24,83)
	CFB at 1 Year	**n**	13	189
		Mean (Range)	-1 (-6.5, 3.0)	1.6 (-15.7, 18.0)

Intervention			Nomlabofusp	
	CFB at 18 Months	**n**	7	NR
		Mean (Range)	-2.3 (-10, 4.5)	2.3*
FA-ADL	**Baseline**	**n**	41	362
		Median (IQR)	17.75 (13, 24.5)	14.5 (1.5, 27)
	CFB at 1 Year	**n**	13	211
		Mean (Range)	-1.1 (-9.0, 2.5)	1.5 (-5.5, 9.0)
	CFB at 18 Months	**n**	7	NA
		Mean (Range)	-0.3 (-1.5,1.0)	NA
9-HPT	**Baseline**	**n**	37	362
		Mean (Range), Seconds	93.8 (36.0, 277.3)	75.4 (36.0, 262.1)
	CFB at 1 Year	**n**	12	194
		Mean (Range)	-15.6 (-46.7, 15.4)	6.1 (-40.1, 203.7)
	CFB at 18 Months	**n**	7	NA
		Mean (Range)	-11.8 (-13.6, 6.5)	NA
MFIS [0-84]	**Baseline**	**n**	41	NA
		Mean (Range)	34.5 (2.0, 79.0)	NA
	CFB at 1 Year	**n**	13	NA
		Mean (Range)	-5.2 (-25.0, 10.0)	NA
	CFB at 18 months	**n**	7	NA
		Mean (Range)	0.6 (-16.0, 15.0)	NA

9-HPT: Nine-Hole Peg Test, CFB: change from baseline, FA-COMS: Friedreich's Ataxia Clinical Outcome Measures Study, FA-ADL: Friedreich's Ataxia- Activities of Daily Living, IQR: interquartile range, mFARS: modified Friedreich Ataxia Rating Scale, MFIS: modified fatigue impact scale, n: number, NA: not applicable, NR: Not reported

*Data collected annually in FA-COMS; 18-month value was interpolated using a linear equation constructed with annual data up to 3 years.

Table D2.9. Functional Outcomes for MOXIe Part 2[9,24]

Intervention			Omaveloxolone	
Trial			MOXIe Part 2	
Arm			Omaveloxolone	Placebo
N			40	42
mFARS	Baseline	Median (IQR)	40.9 (10.4)	38.8 (11)
	CFB at 48 Weeks	Mean ± SEM CFB (95% CI)	-1.55 ± 0.69 (-2.93, -0.18)	0.85 ± 0.64 (-0.43, 2.13)
		Difference v Placebo, % (95% CI); P-Value	-2.40 (0.96), (-4.31, -0.5); p=0.014	
		Improved*	16/34 (47)	11/41 (27)
		Worsened*	7/34 (21)	18/41 (44)
FA-ADL	Baseline	Median (IQR)	10.7 (4.8)	9.9 (4.8)
	CFB at 48 Weeks	LS Mean Change ± SE from Baseline	-0.17 (0.450), p=0.71	1.14 (0.42), p=0.009
		LS Mean Difference + SE Between Treatment Groups	−1.30 ± 0.629, p = 0.04	
		Improved	13/36 (36)	8/41 (20)
		Worsened	17/36 (47)	27/41 (66)
PGIC	CFB at 48 Weeks	LS Mean Change ± SE from Baseline	3.9	4.33
		LS Mean Difference + SE Between Treatment Groups	−0.43, p = 0.13	
		Improved	16/36 (44)	11/41 (27)
		Worsened	11/36 (31)	17/41 (42)
mFARS, FA-ADL, PGIC	CFB at 48 Weeks	All Improved	5/34 (15)	1/41 (2)
		None Worsened	13/34 (38)	7/41 (17)
9-HPT	CFB at 48 Weeks	LS Mean Change ± SE from Baseline	-0.0014 (0.0007), p=0.04	-0.0001 (0.0006), p=0.82
		LS Mean Difference + SE Between Treatment Groups	−0.0013 ± 0.0009, p = 0.18	
CGIC	CFB at 48 Weeks	LS Mean Change ± SE from Baseline	3.93	4.06
		LS Mean Difference + SE Between Treatment Groups	−0.13, p = 0.52	
T25-FW, 1/s	CFB at 48 Weeks	LS Mean Change ± SE from Baseline	-0.0169 (0.0056), p=0.004	-0.0226 (0.0053), p<0.0001
		LS Mean Difference + SE Between Treatment Groups	0.0058 ± 0.0078, p = 0.46	
Frequency of Falls	CFB at 48 Weeks	LS Mean Change ± SE from Baseline	3 (1, 89)	8.5 (0, 131)
		LS Mean Difference + SE Between Treatment Groups	0.30 ± 0.292, p = 0.30	

Peak Work, W/kg	**CFB at 48 Weeks**	**LS Mean Change ± SE from Baseline**	0.03 (0.035), p=0.33	0.090 (0.033), p=0.005
		LS Mean Difference + SE Between Treatment Groups	−0.06 ± 0.049, p = 0.22	

9-HPT: Nine-Hole Peg Test, CFB: change from baseline, CGIC: Clinical Global Impression of Change, FA-ADL: Friedreich's Ataxia- Activities of Daily Living, IQR: interquartile range, mFARS: modified Friedreich Ataxia Rating Scale, n: number, PGIC: Patient Global Impression of Change, T25-FW: Timed 25-Foot Walk

*Improvements were defined as changes from baseline ≤ −1.9 points for mFARS scores and ≤ −0.4 points for FA-ADL scores, and PGIC scores < 4. Worsening was defined as changes from baseline ≥ 1.9 points for mFARS scores and ≥ 0.4 points for FA-ADL scores, and PGIC scores > 4.

Table D2.10. Functional Outcomes for MOXIe Extension and Propensity Matched[17,18]

Intervention			**Omaveloxolone**			
Trial			**MOXIe Extension**		**Propensity Matched***	
Arm			**Omav-omav**	**Placebo-omav**	**Matched FA-COMS**	**MOXIe Extension**
N			**40**	**42**	**136**	**136**
mFARS	**Baseline**	**Mean (±SD)**	NR	NR	41 (16.1)	42.2 (12.6)
	CFB at 1 Year	**n**	NR	NR	108	133
		LS Mean (±SE)	*0.75 (0.8)*	*0.93 (0.88)*	2.11 (0.59)	0.015 (0.56)
		Difference btwn groups, LS Mean (±SE); P-Value	NR	NR	-2.1 (0.81); p=0.010	
	Year 2	**n**	NR	NR	103	102
		LS Mean (±SE)	*0.17 (0.83)*	*2.3 (1)*	4.58 (0.59)	1.18 (0.59)
		Difference Btwn Groups, LS Mean (±SE); P-Value	NR	NR	-3.41 (0.84);p<0.0001	
	CFB at 144 Weeks	**LS Mean (±SE)**	*2.8 (1)*	*5.4 (1)*	NR	NR
		Annualized Slope	0.45 ± 0.63 (-0.82, 1.71)	0.76 ± 0.28 (0.21, 1.31)	NR	NR
		Diff Btwn Groups, Mean ± SE (95% CI); P-Value	-0.31 ± 0.71 (-1.72, 1.1); p=0.66		NR	NR
	Year 3	**LS Mean (±SE)**	NR	NR	6.61 (0.65)	3 (0.66)
		Difference Btwn Groups, LS Mean (±SE); P-Value	NR	NR	-3.61 (0.93); p=0.0001	

CFB: change from baseline, FA-COMS: Friedreich's Ataxia Clinical Outcome Measures study, IQR: interquartile range, mFARS: modified Friedreich Ataxia Rating Scale, n: number, NR: not reported, SE: standard error

*Data from the primary pooled population.

Note: Italicized data has been digitized or calculated

Table D2.11. Additional Functional Outcomes for MOXIe Propensity Matched[18]

Omaveloxolone Propensity Matched						
Population			**Primary Placebo-Omav**		**Primary Omav-Omav**	
Arm			**Matched FA-COMS**	**MOXIe Extension**	**Matched FA-COMS**	**MOXIe Extension**
Change in mFARS	**Baseline**	**n**	**72**	**95**	**34**	**38**
		Mean (±SD)	44.5 (18)	42.8 (12.8)	39.6 (16.8)	40.9 (12.2)
	Year 1	**CFB LS Mean (±SE)**	2.32 (0.69)	-0.43 (0.63)	2.48 (1.12)	1.05 (1.09)
		Difference	-2.75 (0.94);p=0.0035		-1.43 (1.56);p=0.36	
	Year 2	**n**	71	69	33	33
		CFB LS Mean (±SE)	4.23 (0.68)	1.18 (0.69)	3.57 (1.13)	1.1 (1.13)
		Difference	-3.06 (0.97);p=0.0017		-2.47 (1.6); p=0.13	
	Year 3	**n**	95	95	41	41
		CFB LS Mean (±SE)	7.29 (0.72)	3.21 (0.76)	6.14 (1.24)	2.38 (1.33)
		Difference	-4.09 (1.05); p=0.0001		-3.76 (1.82); p=0.0400	

CFB: change from baseline, LS: least squares, mFARS: modified Friedreich Ataxia Rating Scale, n: number, SE: standard error

Table D2.12. Functional Outcomes for Omaveloxolone Observational Study [20]

Intervention			**Omaveloxolone**
Trial			**Lima 2025**
N			**20**
mFARS	**Baseline**	**Mean (SD)**	59.1 (12.8)
	Week 12	**Mean (SD)**	59.9 (10.3)
	Week 24	**Mean (SD)**	60.5 (10.4)
	P-Value		0.15
FA-ADL	**Baseline**	**Mean (SD)**	19.6 (5.8)
	Week 12	**Mean (SD)**	19.1 (5.4)
	Week 24	**Mean (SD)**	20.3 (5.8)
	P-Value		0.58

Intervention			Omaveloxolone
SARA	Baseline	Mean (SD)	25.8 (4.3)
	Week 12	Mean (SD)	25.3 (4.4)
	Week 24	Mean (SD)	25.8 (5.3)
	P-Value		0.96
9HPTl	Baseline	Mean (SD)	126.4 (90.6)
	Week 12	Mean (SD)	106.3 (40.9)
	Week 24	Mean (SD)	100 (34)
	P-Value		0.27
9HPTr	Baseline	Mean (SD)	88.4 (33.1)
	Week 12	Mean (SD)	85.8 (32)
	Week 24	Mean (SD)	89.3 (35.9)
	P-Value		0.84

9-HPTl: Nine-Hole Peg Test left, 9-HPTr: Nine-Hole Peg Test right, FA-ADL: Friedreich's Ataxia- Activities of Daily Living, mFARS: modified Friedreich Ataxia Rating Scale, SARA: Scale for the Assessment and Rating of Ataxia, SD: standard deviation

Table D2.13. Mean Changes in mFARS domains for MOXIe Part 2[25]

Trial			MOXIe Part 2	
Arm			Omaveloxolone	Placebo
mFARS Domains	Bulbar	Mean CFB	-0.18	-0.02
		P-Value	0.1112	
	Upper Limb Coordination	Mean CFB	-1.15	0.13
		P-Value	0.0397	
	Lower Limb Coordination	Mean CFB	-0.28	-0.1
		P-Value	0.6701	
	Upright Stability	Mean CFB	0.15	0.9
		P-Value	0.1365	

CFB: change from baseline, mFARS: modified Friedreich's Ataxia Rating Scale

Table D2.14. Noninferiority Testing for MOXIe Extension[17]

Trial		MOXIe Extension – Delayed Start	
Arm		Delayed start*	Placebo controlled†
Primary Analyzed Subset	Difference (LS Mean ± SE)	-2.91 ± 1.437 (p=0.0433)	-2.17 ± 1.089 (p=0.0471)
	Estimated (SE) = Δ2 –0.5 Δ1	-1.826 ± 1.3535	NA
	Upper Limit of 1-Sided 90% CI	-0.090	NA
All-Randomized	Difference (LS Mean ± SE)	-2.17 ± 1.382 (p=0.1172)	-1.81 ± 1.057 (p=0.0878)
	Estimated (SE) = Δ2 –0.5 Δ1	-1.264 ± 1.2637	NA
	Upper Limit of 1-Sided 90% CI	0.357	NA

CI: confidence interval, LS: least squares, NA: not applicable, SE; standard error

*MOXIe extension week 72 represent 124 weeks of total follow-up.

†The primary endpoint time for MOXIe part 2 was at week 48.

Table D2.15. Skin Frataxin Levels for JIVE Phase II OL[31]

Intervention			Nomlabofusp
Trial			JIVE Phase II OL
Participants with Skin FXN Levels >8.2 pg/ µg*	Baseline	n / N	1 / 27
		%	4%
	Month 1	n / N	10 / 26
		%	38%
	Month 3	n / N	10 / 20
		%	50%
	Month 6	n / N	9 / 11
		%	82%
	Month 12	n / N	9 / 9
		%	100%
	Month 18	n / N	3 / 3
		%	100%
Absolute Skin FXN Levels Increase Over Time†	Baseline	N	27
		Mean (Min, Max)	3.7 (1.5, 8.8)

Intervention			Nomlabofusp
		Median (IQR)	*3.4 (2.3, 4.6)*
	Month 1	**N**	26
		Mean (Min, Max)	8.9 (2.9, 22.9)
		Median (IQR)	*6.8 (5.4, 10.4)*
	Month 3	**N**	20
		Mean (Min, Max)	12.5 (5.6, 37.1)
		Median (IQR)	*8.9 (6.9, 14.3)*
	Month 6	**N**	11
		Mean (Min, Max)	12.3 (5.6, 26.7)
		Median (IQR)	*10.5 (8.7, 14.1)*
	Month 12	**N**	9
		Mean (Min, Max)	12.1 (8.1, 16.1)
		Median (IQR)	*12.5 (8.6, 13.7)*
	Month 18	**N**	3
		Mean (Min, Max)	10.7 (9.9, 11.8)
		Median (IQR)	NR
Change from Baseline in Skin FXN Levels	**Month 1**	**N**	26
		Median (IQR)	*2.9 (1.6, 5.6)*
		Mean	*5.2*
	Month 3	**N**	20
		Median (IQR)	*5.9 (4.3, 10.2)*
		Mean	*9.2*
	Month 6	**N**	11
		Median (IQR)	*8.3 (3.9, 11.1)*
		Mean	*8.9*
	Month 12	**N**	9
		Median (IQR)	*7.4 (6.7, 11.5)*
		Mean	*8.9*

FXN: frataxin, IQR: interquartile range, n: number, N: total number, pg/µg: picogram/microgram

Note: Italicized data has been digitized or calculated

*8.2 pg/µg represents 50% of the average FXN concentration levels of healthy volunteers, similar to levels in asymptomatic carriers.

†Data include all participants with quantifiable levels at each measurement point who had received 25 mg, 50 mg or had the dose increased from 25 mg to 50 mg. Data are presented as of the March 2026 cutoff date.

Table D2.16. Skin Frataxin Levels for Nomlabofusp Phase II[87]

Intervention		Nomlabofusp		
Trial		Phase II Dose Finding		
Arm		25 mg	50 mg	Placebo
N		NR	NR	NR
Change from Baseline in FXN Levels in Skin Cells, Median (IQR), pg/µg	Baseline	3.7	2.1	3.5
	Day 14	*2.8 (2.1, 3.3)*	*5.6 (4.3, 6.6)*	*-0.5 (-0.9, 0.6)*
	Day 28	*2.2 (0.1, 2.6)*	*3.1 (2.6, 3.6)*	*-0.3 (-0.7, 0.4)*

FXN: frataxin, IQR: interquartile range, mg: milligram, NR: not reported, pg/µg: picogram/microgram,

Note: Italicized data has been digitized or calculated

Table D2.17. Biomarkers for Omaveloxolone [20,86]

Intervention			Omaveloxolone				
Trial			Zaoui 2020				Lima 2025
Population			Overall		Pediatric		Overall
Arm			Omav	Placebo	Omav	Placebo	Omav
N			51	53	24		20
eGFR, mL/min/1.73 m^2	CFB at 48 weeks	Mean ± SEM CFB	7 ± 10.7	-4.4 ± 11	5.5 ± 14.5	-11.3 ± 14.3	NR
		Difference Between Groups	11.4		16.8		NR
	CFB at 52 weeks	Mean (SD)	0.9 ± 10.8*	-4.2 ± 10.9	NR	NR	NR
Aspartate Aminotransferase (U/L)	Baseline	Mean (SD)	NR	NR	NR	NR	23.8 (9.8)
	Week 12	Mean (SD)	NR	NR	NR	NR	38.3 (14.9)
	Week 24	Mean (SD)	NR	NR	NR	NR	34.3 (26.8)
	P-value		NR	NR	NR	NR	NR

Intervention			Omaveloxolone				
Alanine Aminotransferase (U/L)	**Baseline**	**Mean (SD)**	NR	NR	NR	NR	32 (29.3)
	Week 12	**Mean (SD)**	NR	NR	NR	NR	77.1 (33.9)
	Week 24	**Mean (SD)**	NR	NR	NR	NR	47.5 (20.4)
	P-Value		NR	NR	NR	NR	0.15

CFB: change from baseline, eGFR: estimated glomerular filtration rate, NR: not reported, SD: standard deviation, SEM: standard error of the mean, U/L: units per liter

*4 weeks off treatment

Table D2.18. Subgroup mFARS for MOXIe[9]

Intervention			Omaveloxolone	
Trial			**MOXIe Part 2**	
			N	**Difference (omaveloxolone - Placebo)**
Changes from Baseline in mFARS Score at Week 48	**Primary Efficacy**	**Primary Analyzed Subset**	**82**	-2.4 (-4.31, -0.5); p=0.01
		ARP	**103**	-1.93 (-3.7, -0.15); p=0.03
	Age Group	**<18**	**20**	-4.16 (-8.43, 0.12); p=0.06
		≥18	**62**	-1.6 (-3.78, 0.58); p=0.15
	Gender	**Female**	**38**	-1.6 (-4.62, 1.42) p=0.29
		Male	**44**	-3.17 (-5.9, -0.44); p=0.02
	GAA1 Repeat Length ≥ 675	**Yes**	**39**	-4.27 (6.96, -1.57); p≤0.01
		No	**28**	-1.94 (-5.19, 1.31); p=0.24
	Ambulatory Status	**Non-Ambulatory**	**6**	-4.57 (-11.42, 2.27); p=0.19
		Ambulatory	**76**	-2.19 (-4.22, -0.17); p=0.03

ARP: all randomized patients, mFARS: modified Friedreich's Ataxia Rating Scale, N: number

Table D2.19. Subgroup JIVE Phase II OL[31]

Intervention	Nomlabofusp			
Trial	**JIVE Phase II OL**			
Improvement / Worsening at 1 Year by Time in Disease Course				
Functional Outcome	**mFARS**	**FA-ADL**	**9-HPT**	**MFIS**

Intervention		Nomlabofusp			
Overall	**n**	13	13	13	13
	Improved	61.50%	61.50%	91.70%	61.50%
	Worsened	38.50%	38.50%	8.30%	38.50%
<12.5	**n**	4	4	4	4
	Improved	100%	75%	100%	75%
	Worsened	0	25%	0	25%
≥12.5 - <25	**n**	4	4	4	4
	Improved	50%	25%	100%	50%
	Worsened	50%	75%	0	50%
≥25	**n**	5	5	5	5
	Improved	40%	80%	80%	60%
	Worsened	60%	20%	20%	40%

9-HPT: Nine-Hole Peg Test, FA-ADL: Friedreich's Ataxia- Activities of Daily Living, mFARS: modified Friedreich Ataxia Rating Scale, MFIS: Modified Fatigue Impact Scale, N: number

Table D2.20. MOXIe Part 2 Post Hoc Analyses [9]

Omaveloxolone				
MOXIe Part 2				
N			**40**	**42**
MMRM	**Primary Analysis/Base Model**	**Mean Change from Baseline in mFARS**	-1.55	0.85
		Placebo-Corrected Difference Using MMRM	-2.4 (p=0.014)	
	History of Cardiomyopathy	**Mean Change from Baseline in mFARS**	-1.68	0.97
		Placebo-Corrected Difference Using MMRM	-2.65 (p=0.0064)	
	GAA1 Repeat Length	**Mean Change from Baseline in mFARS**	-1.95*	1.41†
		Placebo-Corrected Difference Using MMRM	-3.36 (p=0.0017)	
	Cardiomyopathy + GAA1	**Mean Change from Baseline in mFARS**	-2.02	1.46
		Placebo-Corrected Difference Using MMRM	-3.48 (p=0.0012)	
ANCOVA	**Primary Analysis/Base Model**	**Mean Change from Baseline in mFARS**	-1.66	1.17

Omaveloxolone				
		Placebo-Corrected Difference Using MMRM	-2.83 (p=0.0068)	
	History of Cardiomyopathy	**Mean Change from Baseline in mFARS**	-1.51	1.63
		Placebo-Corrected Difference Using MMRM	-3.14 (p=0.0024)	
	GAA1 Repeat Length	**Mean Change from Baseline in mFARS**	-1.98*	1.9†
		Placebo-Corrected Difference Using MMRM	-3.88 (p=0.0004)	
	Cardiomyopathy + GAA1	**Mean Change from Baseline in mFARS**	-1.96	2.15
		Placebo-Corrected Difference Using MMRM	-4.11 (p=0.0002)	

mFARS: modified Friedreich's Ataxia Rating Scale, MMRM: mixed model for repeated measures, N: number

*N=31

†N=36

Table D2.21. Nomlabofusp Phase I Safety [10]

		Nomlabofusp Phase I Studies								
		SAD					**MAD**			
		25 mg	**50 mg**	**75 mg**	**100 mg**	**Placebo**	**25 mg**	**50 mg**	**100 mg**	**Placebo**
N		**4**	**4**	**5**	**5**	**10**	**6**	**7**	**7**	**7**
Treatment Emergent Adverse Events	**TEAE**	4 (100)	4 (100)	5 (100)	5 (100)	6 (60)	6 (100)	7 (100)	7 (100)	7 (100)
	Related TEAE	4 (100)	4 (100)	5 (100)	5 (100)	2 (20)	6 (100)	7 (100)	7 (100)	3 (42.9)
	Serious TEAE	0	0	0	0	0	0	0	0	0
	Grade ≥3 TEAE	1 (25)§	0	0	0	0	1 (16.7)*	1 (14.3)†	0	0
	TEAE Leading to Study Withdrawal	0	0	0	0	0	1 (16.7)‡	1 (14.3)§	0	0
	Deaths	0	0	0	0	0	0	0	0	0
Treatment Related Adverse Events	**Injection Site Reaction**	4 (100)	4 (100)	5 (100)	5 (100)	1 (10)	6 (100)	7 (100)	7 (100)	3 (42.9)
	Nausea	0	1 (25)	2 (40)	0	0	1 (16.7)	1 (14.3)	1 (14.3)	1 (14.3)
	Dizziness	0	0	3 (60)	0	0	0	0	1 (14.3)	1 (14.3)
	Vomiting	0	1 (25)	1 (20)	0	0	0	1 (14.3)	1 (14.3)	0
	Headache	0	0	2 (40)	0	1 (10)	0	2 (28.6)	0	0
	Erythema	1 (25)	1 (25)	0	0	0	NR	NR	NR	NR
	Abdominal Pain	0	1 (25)	0	0	0	0	0	1 (14.3)	0

		Nomlabofusp Phase I Studies								
		SAD					MAD			
		25 mg	50 mg	75 mg	100 mg	Placebo	25 mg	50 mg	100 mg	Placebo
	Hepatic Enzyme Increase	1 (25)	0	0	0	0	NR	NR	NR	NR
	Presyncope	0	0	1 (20)	0	0	NR	NR	NR	NR
	Diarrhea	NR	NR	NR	NR	NR	0	0	3 (42.9)	1 (14.3)
	Flushing	NR	NR	NR	NR	NR	1 (16.7)	0	0	0
	Hyperhidrosis	NR	NR	NR	NR	NR	0	0	1 (14.3)	0
Injection Site Reactions	**≥1 injection site reaction**	4 (100)	4 (100)	5 (100)	5 (100)	1 (10)	6 (100)	7 (100)	7 (100)	3 (42.9)
	Erythema	4 (100)	4 (100)	4 (80)	5 (100)	0	6 (100)	7 (100)	7 (100)	3 (42.9)
	Pruritus	3 (75)	2 (50)	4 (80)	3 (60)	0	5 (83.3)	6 (85.7)	7 (100)	0
	Pain	2 (50)	1 (25)	3 (60)	2 (40)	1 (10)	4 (66.7)	6 (85.7)	6 (85.7)	2 (28.6)
	Induration	0	0	0	4 (80)	0	5 (83.3)	5 (71.4)	7 (100)	1 (14.3)
	Warmth	1 (25)	3 (75)	0	0	0	2 (33.3)	2 (28.6)	1 (14.3)	0
	Bruising	0	0	0	2 (40)	0	NR	NR	NR	NR
	Discomfort	0	1 (25)	0	1 (20)	0	NR	NR	NR	NR
	Swelling	0	0	1 (20)	1 (20)	0	0	0	1 (14.3)	0
	Laceration	0	1 (25)	0	0	0	NR	NR	NR	NR
	Paresthesia	0	1 (25)	0	0	0	NR	NR	NR	NR
	Discoloration	NR	NR	NR	NR	NR	1 (16.7)	0	0	0
	Hemorrhage	NR	NR	NR	NR	NR	0	1 (14.3)	4 (57.1)	0

MAD: multiple ascending dose, mg: milligram, N: number, NR: not reported, SAD: single ascending dose, TEAE: treatment emergent adverse event

*One grade 3 (severe) event of polycythemia; not related to study drug per investigator.

†One grade 3 (severe) event of rib fracture; not related to study drug per the investigator.

‡One patient experienced noncardiac chest pain and accelerated hypertension and was unable to receive the final dose of study drug but completed all follow-up visits.

§Transient grade 3 severe increase in associated hepatic enzymes, related to study drug per investigator

Table D2.22. MOXIe Trials Safety [9,17,23,24]

Intervention		Omaveloxolone					
Trial		MOXIe (Part 1)*		MOXIe (Part 2)§		MOXIe Extension	
Arm		Omav	Placebo	Omav	Placebo	Omav-omav	Placebo-omav
N		52	17	51	52	43	106
AE		NR	NR	51 (100)	52 (100)	40 (93)	103 (97.2)
SAE		0	2	5 (10)	3 (6)	5 (11.6)	8 (7.5)
≥1 Treatment-Related AE		NR	NR	NR	NR	0	0
Discontinuation Due to AE		1†	1‡	4 (8)	2 (4)	0	0
AEs Occurring in >10% of Patients	Contusion	NR	NR	17 (33)	19 (37)	4 (9.3)	14 (13.2)
	Headache	9 (17)	3 (18)	19 (37)	13 (25)	7 (16.3)	20 (18.9)
	Upper Respiratory Tract Infection	21 (40)	1 (6)	14 (28)	15 (29)	10 (23.2)	15 (14.2)
	Excoriation	NR	NR	13 (26)	12 (23)	2 (4.7)	16 (15.1)
	Nausea	5 (10)	1(6)	17 (33)	7 (14)	7 (16.3)	17 (16)
	Alanine Aminotransferase Increased	6 (12)	0	19 (37)	1 (2)	4 (9.3)	24 (22.6)
	Fatigue	4 (8)	2 (12)	11 (22)	7 (14)	6 (14)	14 (13.2)
	Diarrhea	6 (12)	1 (6)	10 (20)	5 (10)	4 (9.3)	15 (14.2)
	Abdominal Pain	1 (2)	3 (18)	11 (22)	3 (6)	7 (16.3)	9 (8.5)
	Aspartate Aminotransferase Increased	6 (12)	0	11 (22)	1 (2)	NR	NR
	Coronavirus Infection	NR	NR	NR	NR	8 (18.6)	20 (18.9)
	Arthralgia	5 (10)	0	NR	NR	5 (11.6)	13 (12.3)
	Ligament Sprain	1 (2)	2 (12)	NR	NR	3 (7)	14 (13.2)
	Vaccination Complication	NR	NR	NR	NR	6 (14)	9 (8.5)
	Muscle Spasms	NR	NR	NR	NR	2 (4.7)	12 (11.3)
	Nasopharyngitis	7 (14)	0	NR	NR	7 (16.3)	6 (5.7)
	Vomiting	NR	NR	NR	NR	5 (11.6)	7 (6.6)
	Back Pain	NR	NR	NR	NR	5 (11.6)	6 (5.7)
	Depression	NR	NR	NR	NR	5 (11.6)	4 (3.8)
	Constipation	1 (2)	2 (12)	NR	NR	5 (11.6)	3 (2.8)
SAEs	Atrial Fibrillation	NR	NR	1 (2)	1 (2)	NR	NR

Intervention		Omaveloxolone					
	Anemia	NR	NR	1 (2)	0	NR	NR
	Ankle Fracture	NR	NR	0	1 (2)	NR	NR
	Craniocerebral Injury	NR	NR	1 (2)[#]	0	NR	NR
	Gallbladder Disorder	NR	NR	0	1 (2)	NR	NR
	Laryngitis	NR	NR	1 (2)[¤]	0	NR	NR
	Noncardiac Chest Pain	NR	NR	1 (2)[¤]	0	NR	NR
	Palpitations	NR	NR	1 (2)[¤]	0	NR	NR
	Sinus Tachycardia	NR	NR	1 (2)[¤]	0	1 (2.3)	0
	Ventricular Tachycardia	NR	NR	1 (2)[#]	0	NR	NR
	Viral Upper Respiratory Tract Infection	NR	NR	1 (2)[¤]	0	0	1 (0.9)
	Cardiac Failure Congestive	NR	NR	NR	NR	1 (2.3)	0
	Myocarditis	NR	NR	NR	NR	0	1 (0.9)
	Constipation	NR	NR	NR	NR	1 (2.3)	0
	Pilonidal Cyst	NR	NR	NR	NR	1 (2.3)	0
	Upper Respiratory Tract Infection	NR	NR	NR	NR	1 (2.3)	0
	Gastroenteritis Norovirus	NR	NR	NR	NR	0	1 (0.9)
	Sepsis	NR	NR	NR	NR	0	1 (0.9)
	Facial Bones Fracture	NR	NR	NR	NR	0	1 (0.9)
	Hip Fracture	NR	NR	NR	NR	0	1 (0.9)
	Troponin Increased	NR	NR	NR	NR	0	1 (0.9)
	Back Pain	NR	NR	NR	NR	1 (2.3)	0
	Epilepsy	NR	NR	NR	NR	0	1 (0.9)
	Suicide Attempt	NR	NR	NR	NR	0	2 (1.9)
	Major Depression	NR	NR	NR	NR	0	1 (0.9)
	Depression	NR	NR	NR	NR	0	1 (0.9)
	Dyspnea	NR	NR	NR	NR	1 (2.3)	0

AE: adverse event, N: number, NR: not reported, SAE: serious adverse event

*All doses

†Only a single discontinuation, which occurred in a 40 mg/day patient who developed a skin rash

‡One placebo patient discontinued prematurely due to withdrawal of consent

§Adverse events occurring in ≥20% patients
#SAEs were reported in patients approximately 2 weeks after the last dose of study drug administration.
¤Multiple SAEs reported in a single patient

Table D2.23. Safety for Omaveloxolone Observational Study[20]

Intervention		Omaveloxolone
Trial		Lima 2025
Arm		Omav
N		20*
No Adverse Events		8 (40)
Adverse Events	Nausea	1 (5)
	Alanine Aminotransferase Increased	9 (45)
	Diarrhea	1 (5)
	Aspartate Aminotransferase Increased	1 (5)
	Transient Liver Enzyme Elevation	10 (50)
	Heartburn	3 (15)
	Dysmenorrhea	1 (5)
	Upper Limb Dysesthesia	1 (5)
	Urinary Incontinence	1 (5)
	Urinary Urgency	1 (5)
	Visual Disturbances	1 (5)

N: number
*Adverse events reported in 20 patients treated with omaveloxolone at the last available follow-up

Table D2.24. Safety for Omaveloxolone Observational Study[21]

Intervention		Omaveloxolone	
Trial		Liu 2025	
Arm		Case Reports	820 omaveloxolone-related AE reports
N			
Outcomes	Death	NR	28 (3.4)

Intervention		Omaveloxolone	
	Permanent Disability	NR	1 (0.1)
	Hospitalization - Initial or Prolonged	NR	164 (20)
	Life-Threatening	NR	2 (0.2)
	Other Serious	NR	91 (11.1)
	Unknown	NR	534 (65.1)
AE Occurrence Time-Medication Date (days)	**0-30**	NR	44 (34.1)
	31-60	NR	4 (3.1)
	61-90	NR	6 (4.7)
	91-120	NR	31 (24)
	121-150	NR	15 (11.6)
	151-180	NR	14 (10.9)
	181-360	NR	6 (4.7)
	>360	NR	9 (6.9)
AEs, ROR (95%CI)	**Hepatic Enzyme Increased**	89	29.24 (23.65, 36.15)
	Fatigue	86	2.53 (2.04, 3.14)
	Nausea	75	2.62 (2.08, 3.3)
	Headache	60	2.6 (2.01, 3.35)
	Blood Cholesterol Increased	45	23.61 (17.57, 31.73)
	Muscle Spasms	44	6.74 (5, 9.09)
	Abdominal Pain (Upper)	43	5.43 (4.02, 7.34)
	Urinary Tract Infection	36	4.66 (3.35, 6.47)
	Myalgia	29	4.78 (3.32, 6.9)
	Atrial Fibrillation	28	7.91 (5.45, 11.49)
	Alanine Aminotransferase Increased	22	11.11 (7.3, 16.91)
	Balance Disorder	20	6.72 (4.32, 10.43)
	Heart Rate Increased	18	4.47 (2.81, 7.12)
	Dyspepsia	16	4.36 (2.66, 7.12)
	Speech Disorder	16	9.22 (5.64, 15.09)
	Brain Natriuretic Peptide Increased	15	106.88 (63.86, 178.88)
	Cardiac Disorder	15	4.86 (2.93, 8.08)

Intervention		Omaveloxolone	
	Aspartate Aminotransferase Increased	15	8.8 (5.29, 14.63)
	Hepatic Cytolysis	15	10.77 (6.48, 17.9)
	Cardiac Failure	14	4.67 (2.76, 7.9)
	Dysphagia	13	3.47 (2.01, 5.99)
	Nephrolithiasis	13	6 (3.48, 10.35)
	Liver Function Test Increased	13	10.49 (6.08, 18.1)
	Blood Triglycerides Increased	11	23.08 (12.74, 41.8)
	Diabetes Mellitus	11	4.47 (2.47, 8.09)
	Gastroesophageal Reflux Disease	10	3.38 (1.82, 6.29)
	Arrhythmia	10	6.97 (3.74, 12.97)
	Brain Fog	8	3.83 (1.91, 7.67)
	Gastroenteritis Viral	8	8.73 (4.36, 17.5)
	Viral Infection	7	4.45 (2.12, 9.35)

AE: adverse event, N: number, ROR: reporting odds ratio

Table D2.25. MOXIe Part 2 Efficacy Results at Week 48 – ITT Population

		Omaveloxolone	Placebo
N		51[†]	52[†]
mFARS Total Score*	**LS Mean Change from Baseline (95% CI)**	-1.01 (-2.28, 0.27)	0.82 (-0.38, 2.01)
	LS Mean Difference (95% CI); P-Value	-1.82 (-3.59, -0.06); 0.0428	
mFARS Bulbar Domain*	**LS Mean Change from Baseline (95% CI)**	-0.08 (-0.18, 0.03)	-0.03 (-0.13, 0.07)
	LS Mean Difference (95% CI); P-Value	-0.05 (-0.19, 0.10); 0.5079	
mFARS Upper Limb Coordination Domain*	**LS Mean Change from Baseline (95% CI)**	-0.72 (-1.51, 0.07)	0.11 (-0.62, 0.84)
	LS Mean Difference (95% CI); P-Value	-0.83 (-1.91, 0.25); 0.1306	
mFARS Lower Limb Coordination Domain*	**LS Mean Change from Baseline (95% CI)**	-0.13 (-0.73, 0.48)	-0.30 (-0.86, 0.26)
	LS Mean Difference (95% CI); P-Value	0.17 (-0.66, 1.00); 0.6822	
mFARS Upright Stability Domain*	**LS Mean Change from Baseline (95% CI)**	-0.11 (-0.88, 0.67)	0.94 (0.22, 1.67)
	LS Mean Difference (95% CI); P-Value	-1.05 (-2.12, 0.02); 0.0551	
FA-ADL	**LS Mean Change from Baseline (95% CI)**	0.28 (-0.56, 1.12)	1.05 (0.27, 1.84)
	LS Mean Difference (95% CI); P-Value	-0.78 (-1.93, 0.38); 0.1865	
PGIC	**LS Mean Change from Baseline (95% CI)**	3.91 (3.44, 4.38)	4.47 (4.02, 4.92)
	LS Mean Difference (95% CI); P-Value	-0.56 (-1.06, -0.06); 0.0282	

		Omaveloxolone	Placebo
9-HPT (1/sec) Dominant Hand	**LS Mean Change from Baseline (95% CI)**	-0.0002 (-0.0011, 0.0008)	-0.0007 (-0.0016, 0.0002)
	LS Mean Difference (95% CI); P-Value	0.0005 (-0.0008, 0.0018); 0.4223	
T25-FW (1/sec)	**LS Mean Change from Baseline (95% CI)**	-0.02 (-0.03, -0.01)	-0.02 (-0.03, -0.01)
	LS Mean Difference (95% CI); P-Value	0.00 (-0.01, 0.02); 0.5042	
Total Number of Falls	**Mean (SD)**	11.24 (18.98)	15 (23.66)
SF-36 Mental Component	**LS Mean Change from Baseline (95% CI)**	-1.19 (-3.41, 1.03)	-0.18 (-2.24, 1.89)
	LS Mean Difference (95% CI); P-Value	-1.01 (-4.08, 2.05); 0.5132	
SF-36 Physical Component	**LS Mean Change from Baseline (95% CI)**	-1.33 (-3.23, 0.58)	-2.08 (-3.85, -0.30)
	LS Mean Difference (95% CI); P-Value	0.75 (-1.89, 3.39); 0.5726	

9-HPT: Nine-Hole Peg Test, CI: confidence interval, FA-ADL: Friedreich's Ataxia- Activities of Daily Living, LS: least squares, mFARS: modified Friedreich Ataxia Rating Scale, N: number, PGIC: Patient Global Impression of Change, SD: standard deviation, SF-36: 36-Item Short Form Health Survey, T25-FW: Timed 25-Foot Walk Test

* mFARS total and subdomain scores calculated using the 93-point rating scale

†N at week 48 may differ across outcomes because of missed or incomplete assessments, and across visits because of study or treatment discontinuation.

D3. Ongoing Studies

Table D3.1. Ongoing Studies

Title/Trial Sponsor	Study Design	Arms	Inclusion Criteria & Patient Population	Primary Outcomes	Estimated Completion Date
A Study to Learn More About the Effects and Long-Term Safety of BIIB141 (Omaveloxolone) in Participants with Friedreich's Ataxia Aged 2 to 15 Years Old (BRAVE) **NCT06953583**	Part 1: 52 week, randomized, double-blind, placebo-controlled study Part 2: Open-label extension (up to week 104) Estimated N=255	1)Omaveloxolone 2)Placebo	·2-15 years old with genetically confirmed FA ·Children 7 to < 16 years must also have an upright stability score (USS) score of 10 to ≤ 34 at baseline	·CFB in USS Subscale E of Modified Friedreich's Ataxia Rating Scale (mFARS) at Week 52	11/16/2027
Efficacy of Omaveloxolone Treatment for Dysphagia in French Patients With Friedreich's Ataxia **NCT07013292**	Retrospective cohort study Estimated N=40	1)150 mg of Omaveloxolone	·≥16 years with genetically confirmed FA ·Received omaveloxolone therapy between February 2024-May 2025 for at least 6 months	·Mean Sydney Swallow Questionnaire (SSQ) score [at the time of treatment initiation and after 6 months)	6/30/2026
Cardiac Output and Fatigue in Friedreich's Ataxia **NCT07444333**	Observational study Estimated N=30 Duration: 6 months	1)Home Aerobic training on omaveloxolone (recumbent exercise bike, 5 times a week) 2) Home Aerobic training off omaveloxolone	·Genetically confirmed FA ·Ability to safely ride a stationary bike (mFARS sitting posture sub-score <2)	·AEs (0, 3, 6 months) Maximal oxygen consumption (0, 3-, 6- months) Fatigue Severity scale (0, 3-, 6-months)	2/1/2028
A Study to Learn More About the Long-Term Safety of BIIB141 (Omaveloxolone) in Participants With Friedreich's Ataxia Who Are Prescribed it by Their Own	Prospective, observational, multinational, post-marketing registry Estimated N=300	1)Omaveloxolone Naïve Participants 2)Omaveloxolone Non-Naïve Cohort	·≥16 with documented diagnosis of FA ·Omaveloxolone naïve and initiating omaveloxolone treatment as per an approved label concurrent	·Number of participants with TESAEs ·Number of participants with drug-induced liver injury (DILI) and congestive	10/1/2029

Doctors **NCT06623890**	Duration: 5 Years		with enrolling in this study or initiated omaveloxolone as per an approved label less than 12 months prior to enrollment in this study ·Enrolled in Friedreich Ataxia Global Clinical Consortium UNIFIED Natural History Study (UNIFAI)	heart failure (CHF) AEs	
A Study to Evaluate the Efficacy and Safety of Subcutaneous Nomlabofusp in Subjects With Friedreich's Ataxia (FORWARD-FA) **NCT07778836**	Phase III, randomized, double-blind, placebo-controlled, multicenter study Estimated N= 150 Duration: 72 weeks	1)Nomlabofusp 2) Placebo	·12-40 years old with genetically confirmed FRDA ·mFARS score ≥ 20 and < 60 ·Complete the T25-FW test within 3 minutes ·Functional Staging for Ataxia score of ≤4 ·HbA1c ≤ 7.0%	·Change from baseline in USS subscale E of mFARS at week 72 [Baseline, Weeks 12, 24, 36, 48, 72] ·Change from baseline in total mFARS at week 72 [Baseline, Weeks 12, 24, 36, 48, 72]	12/1/2029
FA Clinical Outcome Measures (FA-COMS) **NCT03090789**	Multicenter natural history study Estimated N=2000 Duration: 15 years		·Males or females age 4-80 years with genetically confirmed diagnosis of FA	·mFARS score [once every year]	1/1/2030
A Study to Find Out How BIIB141 (Omaveloxolone) is Processed in the Body and to Learn More About Its Safety in Participants With Friedreich's Ataxia Aged 2 to 15 Years Old (BOLD)	Phase I, open-label study Estimated N=33	1)150 mg of Omaveloxolone	·2-15 years old with genetically confirmed FA ·Left ventricular ejection fraction ≥40%	·Part 1: PK of omaveloxolone ·Part 2: long term safety & tolerability of omaveloxolone	11/22/2030

NCT06054893					
A Study to Learn How BIIB141 (Omaveloxolone) Affects the Health of Participants With Friedrich's Ataxia Who Took it During Pregnancy and/or During Breastfeeding and About the Health of Their Babies **NCT06628687**	Phase IV, post-marketing, observational study Estimated N=10 Duration: 10 years	1)Exposed to omaveloxolone at any time during pregnancy (from 12 days prior to conception through the end of pregnancy outcome), and/or at any time during lactation (up to 1 year of infant age or weaning, whichever comes first)	·≥16 years old female FA patients	·Number of major congenital malformations [up to 10 years]	4/1/2035
Friedreich Ataxia Global Clinical Consortium UNIFIED Natural History Study (UNIFAI) **NCT06016946**	Global, multicenter, prospective, longitudinal, observational natural history study Estimated N=3000 Duration: 25 years		·Males and females of any age genetically diagnosed with FA	·Change in mFARS, SARA, ADL, USS [Year 1 to 25]	1/1/2048

ADL: Activities of daily living, AE: Adverse event, CFB: Change from baseline, FA: Friedreich's ataxia, FRDA: Friedreich's ataxia, HbA1c: Hemoglobin A1c, mFARS: modified Friedreich's Ataxia Rating Scale, PK: Pharmacokinetics, SARA: Scale for the Assessment of Rating of Ataxia, TESAEs: Treatment-emergent adverse events, T25-FW: Timed 25-Foot walk, USS: Upright Stability Score

Source: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

D4. Previous Systematic Reviews and Technology Assessments

We identified one health technology assessment (HTA) of omaveloxolone for the treatment of FA initiated by Canada's Drug Agency (CDA-AMC). The National Institute for Health and Care Excellence (NICE) terminated its assessment of omaveloxolone due to Biogen withdrawing an evidence submission. We also identified one Cochrane Systematic Review of pharmacological treatments for FA and one systematic review assessing treatment impacts on patient outcomes at the time of our review.

CDA-AMC 2025: Omaveloxolone[26]

The Canada Drug Agency (CDA-AMC) reviewed omaveloxolone (SKYCLARYS) for the treatment of Friedreich's ataxia in patients 16 years or older and recommended reimbursement if the patient under the care of a clinical expert and the cost of the drug is reduced. However, use of SKYCLARYSshould halt if a patient's mFARS score elevates by more than 2 points in a year or if their overall score reaches above 80. Based on the evidence presented in the pivotal MOXIe trial, there is moderate certainty that SKYCLARYS produces slower progression in mFARS score. The review underscores remaining evidence gaps, particularly for pediatric patients, patients with more severe disease, and long-term comparative efficacy. Discussions with the patient community illuminate the impact of a disease-modifying treatment but urge future studies to incorporate more meaningful outcomes. An assessment of the health economic evidence reflects low value to the health care system based on the public list price of SKYCLARYS, requiring a price reduction.

Cochrane Review 2026: Pharmacological Treatments for Friedreich Ataxia[88]

The Cochrane library conducted an updated review in 2026 to evaluate the effects of pharmacological treatments for people with Friedreich's ataxia after 12 months of treatment. A meta-analysis of 7 studies included 574 patients treated with epoetin alpha, CoQ10 and vitamin E, idebenone, leriglitazone, omaveloxolone and RT001. An ongoing study assessing nomlabofusp was identified but not included in the review. The study population ranges from 8 to 70 years, with 68% having severe ataxia and 32% being ambulatory at baseline. Using 12-month data, the analyses demonstrated little to no treatment difference in the ataxia rating scale (SMD 0.02, 95% CI −0.23 to 0.26; I2 = 42%; 7 studies, 513 participants; moderate-certainty evidence). Similar findings of the treatment effect were seen for changes in ADL (MD−0.59, 95% CI −1.39 to 0.21; I2 = 24%; 3 studies, 167 participants; very low-certainty evidence). The interventions appeared to improve upper limb dexterity after 12 months (Standardized mean difference [SMD] −0.42, 95% CI −0.73 to −0.11; I2 = 0%; 3 studies, 166 participants; moderate-certainty evidence). Regarding safety, the authors were very uncertain of the difference between treatment and placebo for treatment related adverse events (Risk ratio [RR] 0.88, 95% CI 0.63 to 1.22; I2 = 0%; 2 studies, 104 participants; very low-

certainty evidence) and events leading to medication cessation or death (RR 1.24, 95% CI 0.44 to 3.48; I2 = 0%; 6 studies, 313 participants; low-certainty evidence.

Key Interventions in Friedreich's Ataxia and Their Impact on Patient Outcomes: A Systematic Review[89]

This systematic review aimed to evaluate the alignment of pharmacological and nonpharmacological interventions for FA patients with essential patient and caregiver outcome domains. The review included 90 publications with a wide range of patient populations and majority of the studies had low-to-moderate risk of bias. The efficacy of pharmacological interventions had the greatest impact among younger, pediatric, ambulant patients. Contrasting with 42% of pharmacological RCTS deficient in demonstrating a significant positive effect on the primary outcomes, non-pharmacological interventions revealed a consistent positive outcome trend. Only 54% of the studies included patient-reported outcome measures (PROMS) and 6% of the studies provided a caregiver perspective. Among the studies included in the review, the most common patient outcome addressed fell within the physical health domain (42.3%), and clinical status followed (36.8%). Most of the studies failed to acknowledge mental health, healthcare service utilization, or cost effectiveness among other domains.

E. Long-Term Cost-Effectiveness: Supplemental Information

E1. Detailed Methods

Table E1.1. Impact Inventory

Sector	Type of Impact (Add additional domains, as relevant)	Included in This Analysis from […] Perspective?		Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	X	X	
Medical Costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	☐	☐	
	Future related medical costs	X	X	
	Future unrelated medical costs	X	X	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	☐	
	Unpaid caregiver-time costs	NA	X	
	Transportation costs	NA	☐	
Non-Health Care Sector				
Productivity	Labor market earnings lost	NA	X	
	Cost of unpaid lost productivity due to illness	NA	X	
	Cost of uncompensated household production	NA	X	
Consumption	Future consumption unrelated to health	NA	X	
Social Services	Cost of social services as part of intervention	NA	☐	
Legal/Criminal Justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of home improvements, remediation	NA	X	
Environment	Production of toxic waste pollution by intervention	NA	☐	
Other	Other impacts (if relevant)	NA	☐	

NA: not applicable

Adapted from Sanders et al[90]

Description of evLY Calculations

The equal value life year (evLY) considers any extension of life at the same "weight" no matter what treatment is being evaluated or what population is being modeled. Below are the stepwise calculations used to calculate the evLY.

1. First, we attribute a utility of 0.851, the age- and sex-adjusted utility of the general population in the US that are considered healthy.[91]
2. We calculate the evLY for each model cycle.
3. Within a model cycle, if using the intervention results in additional life years versus the primary comparator, we multiply the general population utility of 0.851 with the additional life years gained (ΔLY gained) within the cycle.
4. The life years shared between the intervention and the comparator use the conventional utility estimate for those life years within the cycle.
5. The total evLY for a cycle is calculated by summing steps 3 and 4.
6. The evLY for the comparator arm is equivalent to the QALY for each model cycle.
7. The total evLYs are then calculated as the sum of evLYs across all model cycles over the time horizon.

Finally, the evLYs gained is the incremental difference in evLYs between the intervention and the comparator arm.

Target Population

The population of focus for the economic evaluation included adolescents and adults living with FA. Since each age-of-onset subgroup was modeled separately to account for the heterogeneity, baseline characteristics were stratified by age of onset. Outcomes from each age-of-onset subgroup were weighted according to the overall population distribution to generate aggregate results, while subgroup-specific results were presented separately as subgroup analyses. The baseline characteristics were obtained from Rummey et al. (2022), a natural history study that included individuals living with FA enrolled in Friedreich's Ataxia Clinical Outcome Measures Study (FA-COMS).[52,53] FA-COMS is a multicenter, long-term natural history study that tracks disease progression in Friedreich ataxia (FA). The study has enrolled more than 1,250 patients from multiple sites across the US and several sites in other countries (e.g., Canada and Australia).

Table E1.2. Baseline Population Characteristics

Parameters	Age of Onset Subgroup				Source
	Early [Omaveloxolone / Nomlabofusp]	Typical	Intermediate	Late	
Age, Years*	16 / 12 years	19 years	30 years	49 years	Rummey 2022[52]
Female, %	47%	51%	52%	60%	
mFARS [0-93]†	60.0 / 51.2	49.1	44.9	43.2	
FA-ADL [0-36]‡	18.0 / 14.3	13.2	12.8	13.2	
Distribution, %	29%	39%	21%	11%	

FA-ADL: Friedreich's Ataxia Activities of Daily Living, mFARS: Modified Friedreich's ataxia rating scale

*Treatment initiation at age 16 years for omaveloxolone, consistent with its indication for patients aged ≥16 years, and at age 12 years for nomlabofusp, consistent with the age range studied in clinical trials; In Scenario C for nomlabofusp, treatment was instead assumed to begin at the age of disease onset, rather than the age at study participation. The corresponding treatment initiation ages were 11, 18 and 32 years for the typical-, intermediate-, and late-onset groups respectively. The treatment initiation age for the early-onset group remained unchanged because of the minimum age criterion for nomlabofusp described above.

†Higher scores indicate greater disease severity; The baseline mFARS score was adjusted upward for omaveloxolone using the average annual rates of increase in mFARS to account for potential differences in disease severity by age at treatment initiation; In Scenario C for nomlabofusp, treatment was assumed to begin at the age of disease onset. Accordingly, baseline mFARS scores were adjusted based on the annual rate of mFARS progression for each onset group, resulting in baseline scores of 37.1, 31.5, and 25.5 for the typical-, intermediate-, and late-onset groups, respectively.

‡ Higher scores indicate greater disease severity; The baseline FA-ADL score was adjusted upward for omaveloxolone using the average annual rates of increase in FA-ADL to account for potential differences in disease severity by age at treatment initiation; In Scenario C for nomlabofusp, treatment was assumed to begin at the age of disease onset. Accordingly, baseline FA-ADL scores were adjusted based on the annual rate of FA-ADL progression for each onset group, resulting in baseline scores of 6.4, 4.9, and 5.1 for the typical-, intermediate-, and late-onset groups, respectively.

Treatment Strategies

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which treatments to include. The full list of interventions is as follows: omaveloxolone (Skyclarys®, Biogen) and nomlabofusp. The comparator for these interventions is no disease-specific treatment or standard of care (SoC).

E2. Model Inputs and Assumptions

Key model assumptions are listed in Table 4.1. Additional assumptions are provided below.

- Patients with an LVEF of less than 50% were assumed to have HF: LVEF was used as a surrogate to define HF status, as changes from baseline in LVEF are included as a cardiac endpoint in the open-label study of nomlabofusp, and LVEF is the cardiac function measure most commonly reported in the published literature in FA.[56,92] For modeling purposes, patients with an LVEF <50% were assumed to have HF, consistent with commonly used guideline-based classifications of LVEF.[50]

- No direct treatment effects on diabetes, scoliosis, and dysphagia were modeled beyond the effects mediated through changes in function: There are currently no data supporting direct treatment effects on non-neurological complications, such as diabetes, scoliosis, and dysphagia. Therefore, these complications were not modeled explicitly. However, any indirect effects resulting from improvements in function were captured through the model's estimation of the overall impact of function on mortality, quality of life, and costs.

- In the base-case analysis for omaveloxolone, the annual discontinuation rate observed in year 3 was applied over the remainder of the lifetime horizon: There are no long-term discontinuation data available for omaveloxolone. Therefore, the discontinuation rate observed between year 1 and year 3 was used as a proxy for the long-term rate. However, clinical experts and patients noted that discontinuations of omaveloxolone primarily occur early after treatment initiation due to adverse effects, with discontinuation being uncommon after this initial period. Therefore, an alternative assumption, in which patients who remain on omaveloxolone for at least three years are assumed to remain on treatment for the duration of the model (i.e., 0% annual discontinuation after year 3), was used as a lower bound in a sensitivity analysis.

- The findings from the pivotal clinical trials and open label extension studies of omaveloxolone and nomlabofusp are generalizable to the overall FA population in the US: The study populations enrolled in the pivotal clinical trials and open-label extension studies of omaveloxolone and nomlabofusp may represent a narrower subset of the overall FA population and thus may not fully reflect the overall FA patient population. For example, the Phase II clinical trial of omaveloxolone primarily included individuals with mid-stage disease who were able to perform exercise testing, and nearly all participants were ambulatory.[41] Detailed information on the patient population enrolled in the nomlabofusp open-label study is not currently available, limiting the ability to assess its generalizability.[45]

Model Inputs

Clinical Inputs

Natural Disease Progression: mFARS, FA-ADL, and Disability Stages

Annual changes in mFARS and FA-ADL were derived from Rummey et al. (2022), which analyzed FA-COMS dataset, a longitudinal natural history dataset that includes measures of disease progression such as mFARS, FA-ADL, and disability stages among individuals with FA.[52,53] The study reported annual progression rates stratified by age-of-onset subgroup and ambulatory status (ambulatory vs. non-ambulatory), as shown in Table E2.1.

Disability stages were tracked over time by estimating the proportion of patients in each of seven disability stages. FARS Disability stages categorize patients into seven groups based on functional ability and independence: normal (stage 0), no disability (stage 1), minimal disability (stage 2), mild disability (stage 3), moderate disability (stage 4), severe disability (stage 5), and total disability (stage 6).[38,54] Because no clinical trial or natural history study has reported longitudinal transitions between disability stages, mFARS was used to approximate the distribution of patients across disability stages over time. Specifically, the relationship between disability stages and 10-point mFARS bands (e.g., 0-10, 11-20, 21-30) was estimated using the FA-COMS dataset and applied to project disability stage distributions over time (Table E2.2).[53,55] FA-COMS dataset tracks both mFARS scores and disability stages longitudinally among study participants, allowing the relationship between the two measures to be characterized.

Table E2.1. Natural Disease Progression: mFARS and FA-ADL

	Age of Onset Subgroup				Source
	Early	Typical	Intermediate	Late	
mFARS [0-93], Annual Change					
Ambulatory*	2.62	1.83	1.24	1.18	Rummey 2022[52]
Non-Ambulatory*	1.21	0.9	0.75	0.53	
FA-ADL [0-36], Annual Change					
Ambulatory*	1.06	1.05	0.74	0.48	Rummey 2022[52]
Non-Ambulatory*	0.65	0.47	0.40	0.46	

FA-ADL: Friedreich's ataxia activities of daily living, mFARS: Modified Friedreich's ataxia rating scale

*The proportion of ambulatory patients at each time point was informed by the distribution of disability stages based on mFARS scores, estimated using FA-COMS data. Table 2.4. Distribution of Patients Across Disability Stages Based on mFARS Scores

Table E2.2. Distribution of Patients Across Disability Stages Based on mFARS Scores

	10-Point mFARS Bands								
Disability Stage*	**0-9**	**10-19**	**20-29**	**30-39**	**40-49**	**50-59**	**60-69**	**70-79**	**80 and Higher**
Stage 0	9.62%	2.54%	0.13%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
Stage 1	78.85%	59.32%	27.56%	9.49%	1.69%	0.07%	0.00%	0.00%	0.00%
Stage 2	11.54%	32.63%	54.10%	46.50%	19.07%	2.85%	0.00%	0.00%	0.00%
Stage 3	0.00%	3.81%	15.13%	27.39%	27.30%	10.53%	1.00%	0.00%	0.23%
Stage 4	0.00%	1.69%	3.08%	15.12%	36.20%	35.60%	9.59%	1.21%	0.23%
Stage 5	0.00%	0.00%	0.00%	1.50%	15.74%	50.68%	86.41%	79.12%	35.55%
Stage 6	0.00%	0.00%	0.00%	0.00%	0.00%	0.27%	3.00%	19.67%	63.99%
Sum	100%	100%	100%	100%	100%	100%	100%	100%	100%
Source	FA-COMS data analysis[53,55]								

FA-COMS: Friedreich's Ataxia Clinical Outcome Measures Study, mFARS: Modified Friedreich's ataxia rating scale

Natural Disease Progression: Left Ventricular Ejection Fraction (LVEF)

Annual changes in LVEF were estimated based on Pousset et al. (2015), a long-term cardiac outcomes study among individuals with FA.[56] The study stratified participants into low- and high-risk groups based on their pattern of cardiac function progression and estimated separate 10-year LVEF trajectories for each group. Linear models were fitted to the risk group-specific trajectories to estimate the average annual change in LVEF for each group (Table E2.3). The proportion of individuals in the high- versus low-risk groups varied by age of onset. Specifically, the probability of being classified into the high-risk group in the overall study population was 21.4%, with a mean age of onset of 16 years. The study reported an odds ratio of 0.91 (95% CI: 0.83 to 0.99) for membership in the high-risk group per 1-year increase in age of onset, indicating that individuals with later disease onset had a lower likelihood of experiencing high-risk cardiac progression. For modeling purposes, an LVEF <50% was used as the threshold to define HF, consistent with commonly used guideline-based classifications of LVEF.[50]

Table E2.3. LVEF Trajectory Over Time Based on Pousset et al. (2015)

Parameters	Low-Risk Group	High-Risk Group
Baseline LVEF	70%	62%
Annual Change in LVEF	-0.42 percentage points	-1.87 percentage points
Odds Ratio for High-risk Group Per 1-Year Increase in Age of Onset*	0.91	
Source	Pousset 2015,[56] authors' calculations	

LVEF: Left ventricular ejection fraction

*To estimate the probability of being in a high-risk group, the following ages of disease onset were used for each age-of-onset subgroup, based on Rummey 2022: Early onset: 5 years old, typical onset: 11 years old, intermediate onset: 18 years old, and late onset: 32 years old.[52]

Treatment Efficacy: Omaveloxolone

The treatment efficacy data for omaveloxolone versus SoC were obtained from the MOXIe study, a Phase II randomized controlled trial (RCT) comparing omaveloxolone with placebo, and the open-label MOXIe extension study, in which patients receiving omaveloxolone in the extension phase were matched with FA-COMS patients using propensity score methods.[18,26,41]

The Phase II RCT (MOXIe study) showed that the changes from baseline in mFARS scores at week 48 differed between the omaveloxolone and placebo groups.[41] However, the results reported in the original publication of the MOXIe study were based on the 99-point mFARS, whereas the other studies used in the model are based on the 93-point mFARS (the newer, modified version). Therefore, we used the mean difference in mFARS between the two arms at year 1 that the manufacturer re-analyzed using the 93-point mFARS (-1.82, 95% CI: -3.59, -0.06).[26] For FA-ADL, the treatment effect was reported only for the full analysis set (FAS) in the MOXIe study. Therefore, we estimated the changes from baseline in FA-ADL scores at week 48 between the two groups among the ITT population by multiplying the mean difference in FA-ADL in the full analysis set (1.30) by the ratio of the mean difference in mFARS between the ITT and full analysis sets (1.93/2.40).[41] These effect estimates were applied as absolute changes to the mFARS and FA-ADL scores in the comparator arm to estimate the impact of omaveloxolone during the first year of treatment.

After the first year of treatment, the treatment effect of omaveloxolone on mFARS was informed by 5-year results from the open-label MOXIe extension study and the propensity score matching analysis using FA-COMS dataset.[19] The study results for the primary pooled population showed that the annual rate of mFARS progression was approximately 1.8 points per year (9.04/5 years) in the matched FA-COMS population and approximately 1.3 points per year ([5.11 − (−0.18)]/4 years) among study participants after year 1. This corresponds to a ratio of approximately 0.73 between the two progression rates, representing an approximately 27% reduction in the mFARS progression rate with omaveloxolone. This ratio was applied to the annual changes in mFARS scores to model the long-term effect of omaveloxolone in slowing disease progression post year 1.

In terms of the long-term treatment effect on FA-ADL, there are no propensity-matched results available from the same study. Therefore, we assumed no difference in the annual changes between the two arms. This assumption appeared to be consistent with the manufacturer-reported four-year follow-up data among patients who remained on omaveloxolone, in which the slope between years 1 and 4 appears to be similar to that observed in the natural history study.[29,93]

There is currently no data supporting the effect of omaveloxolone on cardiac function. Therefore, no treatment effect on cardiac outcomes was assumed in the model.

Treatment Efficacy: Nomlabofusp

For nomlabofusp, the clinical data were deemed insufficient to adequately inform a model. Therefore, exploratory analyses ranging from conservative to optimistic scenarios on the long-term treatment effects were presented in lieu of a base-case analysis.

As of now, some data are available to inform the short-term treatment efficacy of nomlabofusp, although these data have not yet been published. Specifically, the open-label study results for nomlabofusp (Datacut: March 2026) suggest improvements in mFARS through month 18 and FA-ADL through year 1. The study compared patients on nomlabofusp versus SoC and showed a mean difference in mFARS scores of 2.6 points at year 1 and 4.6 points at month 18, favoring nomlabofusp, among those who remained on the treatment.[45] These effect estimates were applied as absolute changes to the mFARS scores in the comparator arm to estimate the impact of nomlabofusp by the first and second year of the treatment, respectively. In terms of FA-ADL scores, the study reported a mean difference of 2.6 points between treatment arms at year 1; no comparative data were available at month 18. Therefore, the year 1 effect estimate was applied as an absolute change to FA-ADL scores in the SoC arm to estimate the impact of nomlabofusp at one year after treatment initiation.

However, there is substantial uncertainty regarding the long-term treatment effect of nomlabofusp due to limited available data. Since the clinical data were deemed insufficient to inform the long-term treatment effect and exploratory analyses were therefore conducted, several assumptions ranging from conservative to optimistic were explored. These included the following assumptions regarding treatment effects after the observed improvement in mFARS during the first two years of treatment and FA-ADL during the first year of treatment: (Scenario A) no treatment benefit is assumed after the short-term period, with disease progression occurring at the same rate as SoC, (Scenario B) disease progression is assumed to slow down by 27% for mFARS among those who remain on the treatment, informed by long-term data of omaveloxolone, (Scenario C) a disease-stabilizing effect, with no progression in mFARS, FA-ADL, or LVEF after the short-term period. Scenario C also assumed no treatment discontinuation and treatment initiation at disease onset.

No treatment effect of nomlabofusp on cardiac outcomes was assumed in Scenarios A and B due to the absence of supporting data, whereas Scenario C explored an optimistic assumption that treatment halts LVEF progression while patients remain on treatment.

Table E2.4. Treatment Effects on mFARS and FA-ADL

Time Period	Treatment Effects (vs. SoC)	Source
Omaveloxolone; mFARS		
Year 1	Absolute difference of -1.82 points*	Biogen GmbH 2025 [26]
After Year 1	27% reduction in the annual rate of change‡	Nachbauer 2025 [19]
Omaveloxolone; FA-ADL		
Year 1	Absolute difference of -1.05 points*	Lynch 2021[41]
After Year 1	No reduction in the annual rate of change‡	Assumption, Zesiewicz 2026[29]
Nomlabofusp; mFARS		
Year 1	Absolute difference of -2.6 points‡	Larimar's Press Release[45]
Year 2	Absolute difference of -4.6 points‡	Larimar's Press Release[45]
After Year 2†	Several assumptions as described in the text‡	Assumption
Nomlabofusp; FA-ADL		
Year 1	Absolute difference of -2.6 points‡	Larimar's Press Release[45]
After Year 1†	Several assumptions as described in the text‡	Assumption

FA-ADL: Friedreich's ataxia activities of daily living, mFARS: modified Friedreich's ataxia rating scale, SoC: standard of care

*Estimated among the intention to treat (ITT) population; For FA-ADL, the treatment effect was estimated by multiplying the mean difference in FA-ADL in the full analysis set (1.30) by the ratio of the mean difference in mFARS between the ITT and full analysis sets (1.93/2.40).

†Since the clinical data were deemed insufficient to inform the long-term treatment effect of nomlabofusp, exploratory analyses were conducted in lieu of a base-case analysis, using a range of assumptions from conservative to optimistic.

‡Applied only among patients who remain on treatment; not applied to those who discontinued treatment.

Treatment Discontinuation: Omaveloxolone

All-cause discontinuation observed among patients enrolled in the Phase II MOXIe trial and the open-label extension study was incorporated into the model (Table E2.5). No discontinuation data is available for omaveloxolone beyond three years after treatment initiation. Therefore, the annual discontinuation rate after year 3 was assumed to remain the same as the last observed discontinuation rate in year 3.

Treatment Discontinuation: Nomlabofusp

All-cause discontinuation observed among patients enrolled in nomlabofusp long-term open label study was incorporated into the model.[45] As of the current data cutoff (March 2026), 21 of 41 (51.2%) participants who received treatment had discontinued. Based on manufacturer input indicating that most discontinuations occurred early after treatment initiation, this discontinuation rate was assumed to apply during the first year of treatment. Please note that additional context regarding this short-term discontinuation rate is provided in Section 4.3, "Uncertainty and Controversies". Given the limited available data, the long-term discontinuation rate for omaveloxolone was applied starting after the first year.

For omaveloxolone, discontinuation affected only drug costs during the period when treatment efficacy estimates are based on the intention-to-treat (ITT) population, because the treatment effect estimates already incorporate the reduced treatment exposure resulting from discontinuation. In contrast, during the period when treatment efficacy estimates are based on the on-treatment population, discontinuation affected both treatment costs and effectiveness. For nomlabofusp, all treatment efficacy estimates were based on the on-treatment population; therefore, discontinuation rates affected both treatment costs and effectiveness.

Table E2.5. Annual Treatment Discontinuation Rates

Time Period	Annual Discontinuation Rates	Source
Omaveloxolone		
Year 0-1	13%	JNHB 2024,[46] Lynch 2021[41]
Year 1-3	5.6%	JNHB 2024[46], Lynch 2024[18]
Year 3+	5.6%	Assumption
Nomlabofusp		
Year 0-1	51.2%*	Larimar's Press Release[45]
Year 1+	5.6%	Assumption

*Additional context regarding this short-term discontinuation rate is provided in Section 4.3, "Uncertainty and Controversies"

Mortality

Mortality was determined based on four factors: age, sex, mFARS score, and LVEF (Table E2.6). Age- and sex-specific mortality for the overall FA population was estimated by applying the standardized mortality ratio (SMR) for FA to mortality rates from the US general population.[57] The SMR was derived from Perlman et al. (2025), which compared survival among individuals with FA with that of matched controls without FA.[58] This estimate represented the reference mortality for individuals with FA with average disease characteristics, defined as an mFARS score of 40–50 and LVEF >55%, based on the characteristics of the overall FA population.[52,56]

Reference mortality was then adjusted over time based on changes in mFARS scores and LVEF using hazard ratios associated with mFARS categories and LVEF levels. Hazard ratios for overall survival by 10-point mFARS score bands, relative to the overall FA population, were obtained from an HTA submission (Joint Nordic) by the manufacturer of omaveloxolone, which used FA-COMS data.[46] Due to a lack of data in the FA population, hazard ratios associated with LVEF levels were obtained from Angaran et al (2020), which evaluated the association between LVEF and mortality in the general population. The hazard ratios were applied to further adjust mortality based on cardiac function.[59]

The potential risk of double-counting mortality effects when mortality was modeled based on both mFARS and LVEF was addressed through scenario analysis and external validation against mortality studies in FA.[56,58,60,61]

Table E2.6. Mortality Inputs

Parameters	Value	Source
SMR for Individuals with FA vs. The General US Population	3.9	Perlman 2025[58]
OS HR Based on mFARS		
mFARS 0-10	0.26*	JNHB 2024,[46] authors' calculations
mFARS 10-20	0.30	
mFARS 20-30	0.41	
mFARS 30-40	0.58	
mFARS 40-50	Reference	
mFARS 50-60	1.80	
mFARS 60-70	2.60	
mFARS 70-80	3.65	
mFARS 80-90	5.19	
mFARS 90+	5.58	
OS HR Based on LVEF		
LVEF <25%	1.96	Angaran 2020[59]
LVEF 25-35%	1.53	
LVEF 36-45%	1.38	
LVEF 46-55%	1.18	
LVEF 55%+	Reference	

FA: Friedreich's ataxia, HR: Hazard ratio, LVEF: Left ventricular ejection fraction, mFARS: Modified Friedreich's ataxia rating scale, OS: Overall survival, SMR: Standardized mortality ratio

*The hazard ratio estimated based on JNHB 2024 for patients with an mFARS score of 0-10 is 0.18. However, applying this value directly results in implausible estimates as it would imply that patients with FA in this mFARS category have lower mortality than the US population (i.e., an overall FA SMR of 3.9 multiplied by 0.18 is less than 1). Therefore, the hazard ratio was adjusted upward so that mortality for patients with FA is no lower than that of the age-sex-matched US population (i.e., 3.9 multiplied by 0.26 is approximately 1).

Adverse Events

Serious adverse events were reported infrequently with omaveloxolone, and therefore, were not modeled. As for nomlabofusp, it was reported in its long-term open label study that 10 out of 41 participants experienced anaphylaxis.[45] Therefore, anaphylaxis was assumed to occur at most once during the first year of treatment in 24.4% of patients. Patients experiencing anaphylaxis discontinued treatment, and the associated disutility and costs were applied at the time of the event.

Utilities

Health-related quality of life depended on three factors in the model: neurological function, cardiac function, and adverse events (Table E2.7). How neurological function was mapped into the health-related quality of life is described in Section 4.2.

To reflect the impact of cardiac function on health-related quality of life, utility multipliers were applied to individuals with LVEF <50% on top of the utility values adjusted for neurological function.

Utility values were stratified into two categories: LVEF 40–50% and LVEF <40%.[94] Utility multipliers of 0.93 and 0.91 were applied to individuals with LVEF 40–50% and <40%, respectively, based on Sullivan et al. (2006) and Settergren et al. (2025).[64,95] The use of broader LVEF categories was considered reasonable given the limited and conflicting evidence, including studies reporting higher utility values at lower LVEF levels.[94] This approach is also consistent with patient input suggesting that cardiac dysfunction does not substantially affect day-to-day quality of life and that its impact is not necessarily gradual.

To account for the impact of adverse events on health-related quality of life, a disutility associated with anaphylactic reactions was applied for the average duration of the event. Based on a previous ICER report in peanut allergy, a disutility of 0.311 was assumed for a duration of three days per anaphylactic reaction.[96]

Table E2.7. Utility Values

Parameters	Value	Source
Utility Values Based on the 20-Score mFARS Bands	mFARS 0-19: 0.85 mFARS 20-39: 0.76 mFARS 40-59: 0.60 mFARS 60-79: 0.25 mFARS 80-93: -0.18	Deger 2026 [62]
Age-Specific Utility†	0.9442-0.0007 x age	Sullivan 2006[64]
Utility Decrement Per 1 Point FA-ADL Increase†	-0.0115	FA-COMS data analysis[53,55]
Utility Decrement Per 1 Point mFARS Increase†	-0.0038	
Utility Values Based on the Disability Stages†	Stage 0: 0.851 Stage 1: 0.759 Stage 2: 0.697 Stage 3: 0.614 Stage 4: 0.585 Stage 5: 0.550 Stage 6: 0.492	
Utility Multipliers Associated with LVEF Level	LVEF 40-50%: 0.93 LVEF < 40%: 0.91‡	Sullivan 2006,[64] Settergren 2025[95]
Disutility Associated with Anaphylaxis	0.311 (duration = 3 days)	ICER Peanut Allergy report[96]

†These parameters were used in scenario analyses only.

‡The multiplier for LVEF <40% was estimated by calculating the ratio of the average EQ-5D-VAS score among individuals with LVEF <40% (corresponding to heart failure with reduced ejection fraction) to that among individuals with LVEF 40–50% (corresponding to heart failure with mildly reduced ejection fraction) in Settergren et al. (2025). This ratio was then applied to the utility multiplier for LVEF 40–50% (i.e., 0.93) to derive the multiplier for LVEF <40%.

Economic Inputs

Drug Acquisition Costs

Detailed description of drug acquisition costs is provided in Section 4.2.

Table E2.8. Treatment Regimen Recommended Dosage

Generic Name	Omaveloxolone	Nomlabofusp
Brand Name	Skyclarys®	NA
Manufacturer	Biogen	Larimar Therapeutics
Route of Administration	Oral	Subcutaneous
Dosing	150 mg (3 capsules) once daily	50 mg daily: 5 mg on day 1, 25 mg daily days 2-30, 50 mg day 31+

NA: not applicable

Table E2.9. Drug Costs

Drug	Annual WAC Price	Discount	Annual Net or Placeholder Price	Source
Omaveloxolone	$413,904	23%	$318,706	Redbook,[67] SSR Health[66]
Nomlabofusp	NA	NA	$625,000*	IPD Analytics

NA: Not applicable, WAC: Wholesale acquisition cost

*Placeholder price; IPD Analytics estimated that the annual price of nomlabofusp will range from $500,000 to $750,000.

Non-drug Health Care Costs

A detailed description of non-drug health care costs associated with the management of FA is provided in Section 4.2.

Table E2.10. Annual Average Health Care Costs (in 2025 USD)

Parameters	Mostly Wheelchair-bound	Not Wheelchair-bound	Source
Homecare	$36,760	$0	Polek 2013[68]
Long-term Care Facility	$4,214	$0	
Hospital Admissions	$2,914	$386	
Medications	$2,025	$903	
Therapist Visits	$1,788	$2,663	
Physician Visits	$1,362	$1,163	
ED	$877	$260	
Laboratory Analyses	$46	$54	
Heart Failure (LVEF<50%)		$19,801	Kazi 2024[69]
Anaphylaxis (one-time)		$11,752	ICER Peanut Allergy report [96]

ED: Emergency Department, LVEF: Left ventricular ejection fraction, USD: United States dollars

Non-Health Care Costs

From a modified societal perspective, non-health care costs associated with FA management were included, such as costs for vehicle adaptations, assistive devices, and home modifications. Cost estimates were obtained from Polek et al. (2013) and stratified by whether patients are mostly wheelchair-bound or not, consistent with the stratification used for health care costs described above (Table E2.11).

Table E2.11. Annual Average Non-Health Care Costs (in 2025 USD)

Parameters	Mostly Wheelchair-Bound	Not Wheelchair-Bound	Source
Car Adaptations	$1,493	$183	Polek 2013[68]
Devices	$1,043	$354	
Home Adaptations	$833	$143	

Formal and Informal Patient and Caregiver Productivity

In addition to the non-health care costs associated with FA management, the monetary value of patient and caregiver productivity associated with FA was included in a modified societal perspective. Both for patients and caregivers, formal (labor market) and informal (non-work) productivity were captured.

In terms of patient formal productivity, we captured the number of hours patients spend working to account for the different treatment impacts on workforce participation, absenteeism (i.e., missed work hours), and presenteeism (i.e., reduced productivity while at work). Patient productivity was estimated based on Lawson et al. (2026), which quantified the productivity burden associated with FA in the US.[97] Based on Lawson et al. (2026), 55% of individuals with FA are employed, and employed individuals work an average of 24.3 hours per week. The study also reported that productivity while working was reduced by an average of 3.8 points on a 10-point scale, corresponding to a 38% reduction in productivity. Based on these estimates, we calculated the average annual productive hours in the labor market as 431 hours (55% × 24.3 hours/week × 52 weeks/year × [1 − 0.38]). The monetary value of formal productivity was estimated by multiplying patients' working hours by a marginal pre-tax wage rate plus fringe benefits of $48.05 per hour.[98] This productivity value was applied as a gain for patients who were alive and aged 18 - 65 years and subtracted from total costs. Patient productivity was modeled as a gain rather than a cost to avoid the potential productivity trap (i.e., Productivity costs accumulate while patients are alive, resulting in higher productivity costs for the intervention when it extends survival).[99]

We also captured the number of hours that patients spend productively outside of paid employment, drawing on data from Lawson et al. (2026) and the American Time Use Survey conducted by the US Bureau of Labor Statistics (BLS).[97,100] Lawson et al. (2026) reported that

productivity during regular daily activities was reduced by 4 points on a 10-point scale, corresponding to a 40% reduction in productivity. Based on BLS data, individuals in the US general population spend approximately 20.3 hours per week on primary daily activities, including household activities, educational activities, organizational, civic, and religious activities, and telephone calls, mail, and email, if aged 65 years or younger, and approximately 24.9 hours per week if older than 65 years. Applying the 40% productivity reduction reported by Lawson et al. (2026), we estimated annual informal productive hours at 633 hours for individuals aged 65 years or younger (20 hours/week × 52 weeks/year × [1 − 0.40]) and 775 hours for individuals older than 65 years (25 hours/week × 52 weeks/year × [1 − 0.40]), respectively. The monetary value of informal productivity was estimated by multiplying patients' working hours by a marginal pre-tax wage rate plus fringe benefits of $48.05 per hour.[98] This productivity value was applied as a gain for patients who were alive regardless of their age.

In terms of caregiver formal productivity, we estimated the number of productive work hours lost due to providing care for individuals with FA. According to Lawson et al. (2026), 65% of patients receive caregiver support, with an average of 1.4 caregivers per patient, and 90.9% of caregivers are employed. Among employed caregivers, 30% report missing work due to providing care for an individual with FA, with an average of 2 hours missed per week. Employed caregivers work an average of 37.4 hours per week and report a 4.3-point reduction in productivity on a 10-point scale due to providing care for an individual with FA. These inputs were used to estimate work hours lost among caregivers due to absenteeism and presenteeism as follows: 65% × 1.4 caregivers per patient × 90.9% × [(30% × 2 hours/week) + (43% × 37.4 hours/week)] × 52 weeks/year = 718 hours per year per patient. The monetized value of caregiver's formal productivity loss was estimated by multiplying a marginal pre-tax wage rate plus fringe benefits ($48.05 per hour) and was added to the total costs while patients are alive.

Regarding caregiver informal productivity, the loss of productivity in their daily activities due to providing care for individuals with FA was estimated using Lawson et al. (2026) and BLS data.[97,100] Based on Lawson et al. (2026), caregivers reported that their productivity during regular daily activities is reduced by 5.2 out of 10 due to caring for an individual with FA. Combining the number of hours for primary daily activities among the US general population derived from the BLS data, the total number of productive hours lost in caregiver's daily activities was estimated as follows: 65% × 1.4 caregivers per patient × 20 hours per week x 52% x 52 weeks/year = 499 hours per year per patient. All caregivers were assumed to be aged 65 years or younger. The monetized value of caregiver's formal productivity loss was estimated by multiplying a marginal pre-tax wage rate plus fringe benefits ($48.05 per hour) and was added to the total costs while patients are alive.

The productive hours among patients and caregivers reported in Lawson et al. (2026) were not stratified by disease severity, limiting the ability to capture the impact of treatment on disease severity and its downstream effects on societal costs. Therefore, the relative differences in societal

costs across disability levels were informed by Grobe-Einsler et al. (2026), a European study that estimated societal costs across five disability stages: no disability, minimal disability, mild disability, moderate disability, and severe disability.[101] The ratios of societal costs across disability stages were estimated and applied to the caregiver productivity costs described above to reflect differences in productivity losses by disease severity. For patient productivity gains, the inverse ratios were applied to reflect differences in productivity gains across disability stages. Productivity estimates from Lawson et al. (2026) were assumed to represent patients with severe disability, based on the characteristics of the study population. The monetized values of patient productivity gains and caregiver productivity costs by disease severity are presented in Table E2.12.

Table E2.12. Annual Formal and Informal Productivity Costs for Patients and Caregivers

FARS Disability Stages	Patient Formal Productivity Gains*	Patient Informal Productivity Gains*	Caregiver Formal Productivity Costs†	Caregiver Informal Productivity Costs†
Patients ≤65 Years Old				
Stages 0 and 1	$76,222‡	$50,672‡	$1,949	$1,356
Stage 2	$68,884	$50,672‡	$10,363	$7,207
Stage 3	$26,220	$38,503	$27,225	$18,934
Stage 4	$21,682	$31,839	$32,924	$22,896
Stages 5 and 6	$20,704	$30,403	$34,479	$23,978
Patients >65 Years Old				
Stages 0 and 1	$0	$62,090‡	$1,949	$1,356
Stage 2	$0	$62,090‡	$10,363	$7,207
Stage 3	$0	$47,179	$27,225	$18,934
Stage 4	$0	$39,014	$32,924	$22,896
Stages 5 and 6	$0	$37,254	$34,479	$23,978

* The monetary value of the hours patients spend productively working in the labor market (formal) and daily activities (informal). Patient productivity was modeled as a gain rather than a cost to avoid the potential productivity trap (i.e., productivity costs accumulate while patients are alive, resulting in higher productivity costs for the intervention when it extends survival).[99]

†The monetary value of productive hours lost among caregivers due to providing care to individuals with FA

‡ Applying the ratio derived from Grobe-Einsler et al. (2026) resulted in an estimated monetary value that exceeded the value of formal and informal productivity in the US general population. Based on BLS data, the average number of hours spent working and engaging in daily activities is 30.5 hours and 20.3 hours, respectively.[100] Therefore, the monetary value of productivity in the US general population was used.

E3. Results

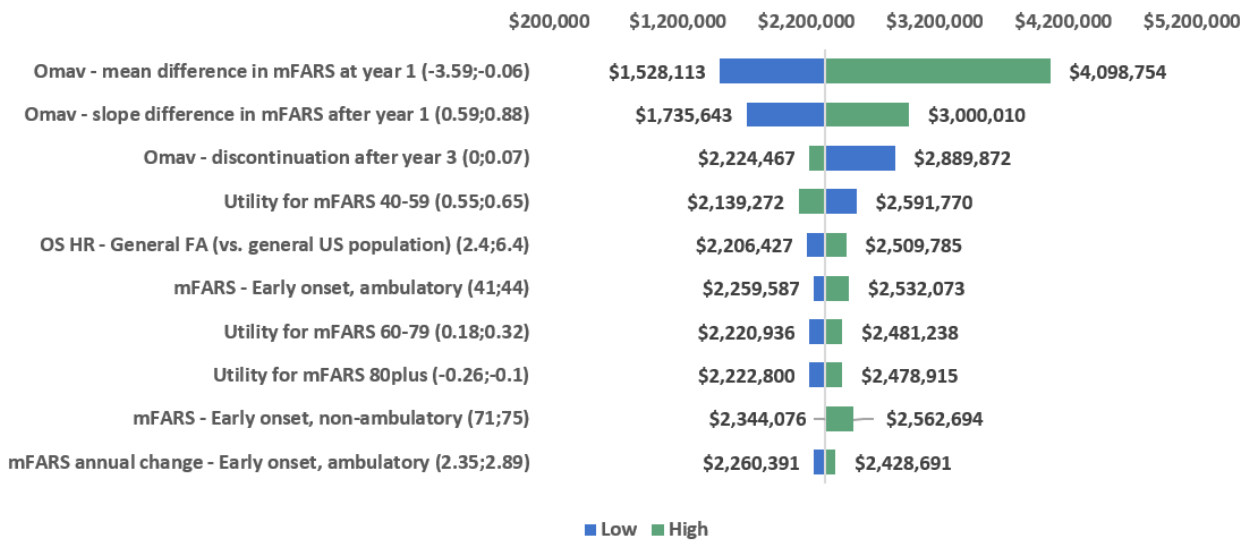
Primary analysis results are described in Section 4.3 of the report.

E4. Sensitivity Analyses

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges to evaluate changes in cost per additional QALY. Given that we conducted exploratory analyses for nomlabofusp, we did not conduct additional sensitivity analyses.

One way sensitivity results for omaveloxolone based on cost per evLY gained are displayed in Figure 4.2, and the corresponding results for cost per QALY gained are displayed in Figure E4.1. Probabilistic sensitivity results based on cost per evLY gained are presented in Table 4.9 and the corresponding results for cost per QALY gained are available in Table E4.1. The mean probabilistic sensitivity analysis results with 95% intervals for the outcomes are detailed in Table E4.2.

Figure E4.1. Tornado Diagram for the Base-Case Analysis of Omaveloxolone (Cost per QALY Gained)



FA: Friedreich's Ataxia, HR: Hazard Ratio, mFARS: modified Friedreich's Ataxia Rating Scale, Omav: Omaveloxolone, OS: Overall Survival, US: United States,

Table E4.1. Probabilistic Sensitivity Analysis for the Base-Case Analysis of Omaveloxolone versus SoC (Cost Per QALY Gained)

	Cost Effective at $50,000 per QALY Gained	Cost Effective at $100,000 per QALY Gained	Cost Effective at $150,000 per QALY Gained	Cost Effective at $200,000 per QALY Gained
Omaveloxolone	0%	0%	0%	0%

SoC: Standard of Care, QALY: quality-adjusted life year

Table E4.2. Mean and 95% CrI Results from the Probabilistic Sensitivity Analysis for Omaveloxolone versus SoC

	Omaveloxolone	SoC
Costs: Mean	$3,433,000	$770,000
QALYs: Mean	6.88	5.57
QALYs: 95% CrI	(5.79, 8)	(4.75, 6.43)
evLYs: Mean	7.27	5.57
evLYs: 95% CrI	(6.05, 8.44)	(4.75, 6.43)
Incremental CE Ratio per QALY	$2,000,000	Reference
Incremental CE Ratio per QALY	$1,600,000	Reference

CE: cost-effectiveness, CrI: credible interval, evLYs: equal-value life year, QALY: quality-adjusted life year

E5. Scenario Analyses

The details for each scenario analysis are provided below and the full results of the scenario analyses can be found in Tables E5.2-E5.7.

Scenario Analysis 1 – Modified Societal Perspective

This scenario adopts a modified societal perspective, incorporating patient and caregiver productivity costs associated with FA and non-health care costs associated with the management of FA. Details on the productivity costs and non-health care costs are provided in Section E2.

Scenario Analysis 2 – Exclusion of Unrelated Health Care Costs

Health care costs not attributable to FA (i.e., general health care costs derived from Jiao et al.[70]) were excluded.

Scenario Analysis 3 – Removal of Minimum Treatment Age

The average age at diagnosis for the early-onset group is approximately 10 years, based on Rummey et al. (2022), which is below the minimum age required to initiate treatment with omaveloxolone (16 years) or nomlabofusp (12 years) in the primary analysis. In contrast, the average age at diagnosis for the other groups is approximately 16 years or older, so patients in these groups are less likely to need to wait to become eligible for treatment.

In this scenario analysis, therefore, we assumed that patients in the early-onset group could initiate treatment at the average age of diagnosis (approximately 10 years). Because disease severity is expected to be lower at an earlier age, we adjusted the baseline mFARS and FA-ADL scores using the annual rate of change in mFARS and FA-ADL for each group.

Table E5.1. Parameters Modified in Scenario Analysis 3

Parameters	Base-case	Scenario	Source
Age at the Time of Treatment Initiation	16 years for omaveloxolone, 12 years for nomlabofusp	10 years*	Rummey 2022[52], calculations
mFARS Score at the Time of Treatment Initiation	60.0 for omaveloxolone, 51.2 for nomlabofusp	46.8†	Rummey 2022[52], calculations

*Estimated by subtracting time since diagnosis from the baseline age at the time of the study: 12 - 2.4 = 9.6 years.
†Expected mFARS score at age 10 years was estimated using the baseline mFARS score at age 12 years reported in Rummey et al. (2022) and the average annual change in mFARS scores for the early-onset group (2.21).

Scenario Analysis 4 – Assuming No Long-term Treatment Effect on mFARS (for omaveloxolone only)

In the base-case analysis, omaveloxolone reduces the rate of progression characterized by mFARS by 27%, after the first year based on its open label extension study. Because this estimate was based on a propensity score-matched analysis, which may be subject to residual confounding, we explored a more conservative scenario in which no treatment effect on mFARS was assumed after Year 1.

Scenario Analysis 5 – Alternative Approaches to Estimating Utilities

5-1: mFARS-Based Utilities Derived from FA-COMS Data

In the base-case analysis, the utility values based on mFARS scores were derived from Deger et al. (2026).[62] Because this study had not yet been published and was not specific to the US population, we explored the associated uncertainty in a scenario analysis using health utility values estimated from FA-COMS data. Details about this approach are provided in Sections 4.2 and E2.

5-2: FA-ADL-Based Utilities Derived from FA-COMS Data

In the base-case analysis, mFARS was used as the primary measure to map patient quality of life. In this scenario analysis, we used FA-ADL as an alternative approach for mapping utility values. Details about this approach are provided in Sections 4.2 and E2.

5-3: Disutility Stage-Based Utilities Derived from FA-COMS Data

In the base-case analysis, mFARS was used as the primary measure to map patient quality of life. In this scenario analysis, we used disability stages as an alternative approach for mapping utility values. Details are provided in Sections 4.2 and E2.

Scenario Analysis 6 – Cost-offset Using the Price of Omaveloxolone (for nomlabofusp only)

6-1: Cost-offset Using the Omaveloxolone Actual Net Price

In this scenario, nomlabofusp was assumed to eliminate the need for treatment with omaveloxolone. Therefore, the costs of omaveloxolone that would otherwise have been incurred were considered an avoided cost and offset against the cost of nomlabofusp. The net treatment cost therefore reflected the cost of nomlabofusp less the avoided costs of omaveloxolone based on the actual net price of omaveloxolone.

6-2: Cost-offset Using the Omaveloxolone Threshold Price at $150,000 per QALY Gained

This scenario is the same as Scenario Analysis 6-1, except that we used the threshold price of omaveloxolone at $150,000 per QALY gained instead of its actual net price.

Scenario Analysis 7 – Removal of Mortality Associated with LVEF

There is a potential risk of double counting mortality associated with cardiac and neurological function if the hazard ratios based on mFARS were estimated without adjustment for cardiac function (i.e., the higher mortality hazard ratios observed among patients with higher mFARS scores may partially reflect the impact of cardiac dysfunction). To assess the potential impact, we excluded the LVEF-based hazard ratio adjustment in this scenario analysis.

Scenario Analysis 8 – No Disease Modifying Effects

Instead of assuming that the mFARS progression rate reverts to that of SoC upon discontinuation, we assumed that the mFARS value itself would revert to that of SoC after discontinuation.

Scenario Analysis 9 – Pre-clinical Treatment (for nomlabofusp under Scenario C only)

We explored a hypothetical scenario in which patients were diagnosed preclinically (e.g., through screening at age 5), when their mFARS scores still matched those of the US general population, and initiated treatment upon diagnosis. Under Scenario C, we assumed that nomlabofusp completely halts the disease and that no one discontinues treatment; thus, the level of health of patients on nomlabofusp over time matches that of the US general population in this scenario.

Scenario Analysis 10 – Subgroup Analysis Based on the Age of Onset

In the main analysis, we reported model outcomes for the overall FA population by weighting four age-at-onset subgroups. In this analysis, we reported outcomes separately for each of the four age-at-onset subgroups: early, typical, intermediate, and late onset.

Full Results of Scenario Analyses

Tables E5.2-E5.7 show the full results of the scenario analyses.

For both omaveloxolone and nomlabofusp, the source of utility values had a substantial impact on the cost-effectiveness results. Deger et al. (2026), the study among the general population that was used as the primary source for the health state utilities, yielded relatively favorable results compared to using utility values derived from FA-COMS data, which include patients living with FA, because the differences in utility values estimated across disease severity levels are greater in Deger et al. (2026) than in FA-COMS data. The sensitivity of the model results to the source of utility values may reflect the parameter uncertainty that comes from multiple factors including, but not

limited to, different study populations (e.g., general population vs. patients living with FA) and different instruments to measure patient quality of life (e.g., time-trade-off (TTO) vs. SF-36).

In the cost-offset scenario, nomlabofusp was assumed to eliminate the need for treatment with omaveloxolone, and thus the costs of omaveloxolone were considered avoided costs and offset against the costs of nomlabofusp. The scenario analysis results showed that offsetting the actual net price of omaveloxolone was associated with a much more favorable cost per QALY or evLY gained for nomlabofusp. In particular, the cost-offset scenario, combined with Scenario C (where it is assumed that disease progression is halted with nomlabofusp and no patients discontinue treatment), represented the most optimistic scenario among all scenarios for nomlabofusp and resulted in a cost per QALY and evLY gained that were substantially lower than in other scenarios. However, the costs per QALY and evLY gained were still higher than the commonly used cost-effectiveness thresholds.

In a scenario assuming no disease-modifying effects of the interventions, the incremental health benefits of both interventions decreased considerably, thereby increasing the cost per QALY or evLY gained for both interventions. This is because discontinuers no longer retain any treatment benefit.

The cost per QALY and evLY increased and threshold prices decreased under the preclinical treatment scenario compared with Scenario C in the main exploratory analysis. Although this scenario resulted in greater total health benefits, treatment benefits on mFARS translated into smaller QALY gains at earlier disease stages, and benefits occurring later in life were more heavily discounted, resulting in fewer discounted QALYs gained relative to the additional years of treatment (Tables E5.5 - E5.7).

In the subgroup analysis by age of onset, the cost per QALY or evLY gained varied across age-of-onset subgroups. Under the base-case inputs and assumptions, the relationship was not necessarily monotonic, with typical-onset populations generally appearing to have more favorable cost-effectiveness results than the other subgroups. The non-monotonic relationship and variation in findings across analyses likely reflect the sensitivity of subgroup-specific results to multiple factors, including subgroup-specific inputs such as baseline age, baseline disease severity, and disease progression rates, as well as other model inputs that may affect subgroups differently, such as treatment effects. Therefore, the relationship between age of onset and cost-effectiveness may vary depending on other model inputs and assumptions, and these subgroup results should be interpreted with caution.

Table E5.2. Scenario Analysis Results for Omaveloxolone

Scenarios	Cost per QALY Gained	Cost per evLY Gained
Base-case	$2,300,000	$1,800,000
Modified Societal Perspective	$2,300,000	$1,800,000
Exclusion of Unrelated Health Care Costs	$2,300,000	$1,800,000
Removal of Minimum Treatment Age	$2,100,000	$1,600,000
Assuming No Long-term Treatment Effect on mFARS	$4,800,000	$3,700,000
Alternative Approaches to Estimating Utilities		
mFARS-Based Utilities Derived from FA-COMS Data	$4,800,000	$3,900,000
FA-ADL-Based Utilities Derived from FA-COMS Data	$5,300,000	$4,100,000
Disutility Stage-Based Utilities Derived from FA-COMS Data	$6,400,000	$4,500,000
Removal of Mortality Associated with LVEF	$2,300,000	$1,700,000
No Disease Modifying Effects	$3,600,000	$2,800,000
Subgroup Analysis Based on the Age of Onset		
Population: Early Onset (0-7 years)	$2,600,000	$2,000,000
Population: Typical Onset (8-14 years)	$1,900,000	$1,500,000
Population: Intermediate Onset (15-24 years)	$2,700,000	$2,100,000
Population: Late Onset (>24 years)	$3,200,000	$2,500,000

FA-ADL: Friedreich's ataxia activities of daily living, FA-COMS: Friedreich Ataxia Clinical Outcome Measures Study, LVEF: Left Ventricular Ejection Fraction, mFARS: Modified Friedreich's ataxia rating scale, SoC: Standard of care

Table E5.3. Scenario Analysis Results for Nomlabofusp – Scenario A

Scenarios	Cost per QALY Gained*	Cost per evLY Gained*
Base-case	$2,700,000	$2,100,000
Modified Societal Perspective	$2,700,000	$2,100,000
Exclusion of Unrelated Health Care Costs	$2,700,000	$2,100,000
Removal of Minimum Treatment Age	$3,000,000	$2,300,000
Alternative Approaches to Estimating Utilities		
mFARS-Based Utilities Derived from FA-COMS Data	$5,900,000	$4,800,000
FA-ADL-Based Utilities Derived from FA-COMS Data	$4,000,000	$3,400,000
Disutility Stage-Based Utilities Derived from FA-COMS Data	$7,400,000	$5,300,000
Cost-offset Using the Price of Omaveloxolone		
Cost-offset Using the Actual Net Price of Omaveloxolone	$1,300,000	$1,000,000
Cost-offset Using the Omaveloxolone Threshold Price at $150,000 per QALY Gained	$2,600,000	$2,000,000
Removal of Mortality Associated with LVEF	$2,700,000	$2,100,000
No Disease Modifying Effects	$5,300,000	$4,100,000
Subgroup Analysis Based on the Age of Onset		
Population: Early onset (0-7 years)	$2,500,000	$2,000,000
Population: Typical onset (8-14 years)	$2,400,000	$1,900,000
Population: Intermediate onset (15-24 years)	$3,700,000	$2,800,000
Population: Late onset (>24 years)	$4,000,000	$3,100,000

FA-ADL: Friedreich's ataxia activities of daily living, FA-COMS: Friedreich Ataxia Clinical Outcome Measures Study, LVEF: Left Ventricular Ejection Fraction, mFARS: Modified Friedreich's ataxia rating scale, SoC: Standard of care
*Based on placeholder price

Table E5.4. Scenario Analysis Results for Nomlabofusp – Scenario B

Scenarios	Cost per QALY Gained*	Cost per evLY Gained*
Base-case	$2,200,000	$1,700,000
Modified Societal Perspective	$2,100,000	$1,600,000
Exclusion of Unrelated Health Care Costs	$2,200,000	$1,700,000
Removal of Minimum Treatment Age	$2,200,000	$1,700,000
Alternative Approaches to Estimating Utilities		
mFARS-Based Utilities Derived from FA-COMS Data	$4,500,000	$3,600,000
FA-ADL-Based Utilities Derived from FA-COMS Data	$3,600,000	$3,000,000
Disutility Stage-Based Utilities Derived from FA-COMS Data	$5,800,000	$4,100,000
Cost-offset Using the Price of Omaveloxolone		
Cost-offset Using the Actual Net Price of Omaveloxolone	$1,000,000	$806,000
Cost-offset Using the Omaveloxolone Threshold Price at $150,000 per QALY Gained	$2,100,000	$1,600,000
Removal of Mortality Associated with LVEF	$2,100,000	$1,600,000
No Disease Modifying Effects	$3,400,000	$2,700,000
Subgroup Analysis Based on the Age of Onset		
Population: Early onset (0-7 years)	$2,100,000	$1,600,000
Population: Typical onset (8-14 years)	$1,900,000	$1,500,000
Population: Intermediate onset (15-24 years)	$2,600,000	$2,000,000
Population: Late onset (>24 years)	$3,300,000	$2,500,000

FA-ADL: Friedreich's ataxia activities of daily living, FA-COMS: Friedreich Ataxia Clinical Outcome Measures Study, LVEF: Left Ventricular Ejection Fraction, mFARS: Modified Friedreich's ataxia rating scale, SoC: Standard of care
*Based on placeholder price

Table E5.5. Scenario Analysis Results for Nomlabofusp – Scenario C

Scenarios	Cost per QALY Gained*	Cost per evLY Gained*
Base-case	$1,600,000	$1,500,000
Modified Societal Perspective	$1,500,000	$1,400,000
Exclusion of Unrelated Health Care Costs	$1,600,000	$1,500,000
Removal of Minimum Treatment Age	$1,600,000	$1,500,000
Alternative Approaches to Estimating Utilities		
mFARS-Based Utilities Derived from FA-COMS Data	$2,600,000	$2,400,000
FA-ADL-Based Utilities Derived from FA-COMS Data	$2,100,000	$2,100,000
Disutility Stage-Based Utilities Derived from FA-COMS Data	$3,000,000	$2,500,000
Cost-offset Using the Price of Omaveloxolone		
Cost-offset Using the Actual Net Price of Omaveloxolone	$781,000	$727,000
Cost-offset Using the Omaveloxolone Threshold Price at $150,000 per QALY Gained	$1,600,000	$1,500,000
Removal of Mortality Associated with LVEF	$1,600,000	$1,500,000
No Disease Modifying Effects	$1,600,000	$1,500,000
Pre-clinical Treatment	$2,200,000	$2,200,000
Subgroup Analysis Based on the Age of Onset		
Population: Early onset (0-7 years)	$1,500,000	$1,300,000

Population: Typical onset (8-14 years)	$1,400,000	$1,400,000
Population: Intermediate onset (15-24 years)	$2,000,000	$1,900,000
Population: Late onset (>24 years)	$3,000,000	$2,800,000

FA-ADL: Friedreich's ataxia activities of daily living, FA-COMS: Friedreich Ataxia Clinical Outcome Measures Study, LVEF: Left Ventricular Ejection Fraction, mFARS: Modified Friedreich's ataxia rating scale, SoC: Standard of care
*Based on placeholder price

Table E5.6. Results for the Pre-clinical Treatment Scenario for Nomlabofusp (Discounted)

Treatment	Intervention Acquisition Costs*	Non-Intervention Costs	Total Costs*	Life-Years with Ambulation	Life-Years Before HF Onset	QALYs	evLYs	Life Years
Nomlabofusp	$18,593,000	$319,000	$18,913,000	29.75	29.75	25.3	25.3	29.7
SoC	$0	$597,000	$597,000	20.20	16.17	16.8	16.8	24.5

*Based on placeholder price

Table E5.7. Threshold Prices Under the Preclinical Treatment Scenario for Nomlabofusp

	Annual Net or Placeholder Price*	Annual Price to Achieve $50,000 per evLY or QALY Gained	Annual Price to Achieve $100,000 per evLY or QALY Gained	Annual Price to Achieve $150,000 per evLY or QALY Gained	Annual Price to Achieve $200,000 per evLY or QALY Gained
Per evLY Gained	$625,000	$23,550	$37,761	$51,973	$66,185
Per QALY Gained	$625,000	$23,541	$37,744	$51,947	$66,150

*Based on placeholder price

E6. Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental Appendix materials). We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

Model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments.

E7. Prior Economic Models

Cost-effectiveness models of FA treatments published in academic journals are limited. However, the approval of omaveloxolone has prompted formal health technology assessments (HTAs) in several countries, including CDA-AMC (Canada), the Joint Nordic HTA bodies (JNHB; Denmark, Finland, Iceland, Norway, and Sweden), the National Centre of Pharmacoeconomics (NCPE; Ireland), and the Pharmaceutical Benefits Advisory Committee (PBAC; Australia).[46-49]

All four HTA models compared omaveloxolone with SoC over a lifetime horizon among patients with FA aged 16 years or older. The models were developed by the manufacturer of omaveloxolone and shared most of the key clinical features. Disease progression and treatment effects were modeled by tracking mFARS scores over time in the omaveloxolone and SoC arms. mFARS scores were then used to inform mortality, utilities, and costs. Treatment efficacy was modeled using mFARS data from the MOXIe open-label extension study with propensity score matching, with the assumption that omaveloxolone reduces the annual rate of mFARS progression by 55% relative to SoC. Utility values were derived from either SF-36 data from FA-COMS or EQ-5D data from EFACTS, depending on the alignment of the study population and the target population in each country. Another common feature was the modeling of age-at-onset subgroups separately to account for heterogeneity in disease progression, with overall outcomes estimated by weighting subgroup-specific outcomes. Drug and medical costs varied across countries and therefore were not directly comparable.

Across the four HTA submissions, the incremental discounted QALYs gained with omaveloxolone versus SoC ranged from approximately 0.3 to 2.6. Total discounted QALYs ranged from 10.5 to 16.2 in the omaveloxolone arm and from 9.4 to 13.7 in the SoC arm. The JNHB assessment found that incremental QALYs varied substantially depending on the assumed treatment effect on mFARS and highlighted that the 55% reduction in the annual mFARS progression rate is highly uncertain as it was based on an indirect comparison of non-randomized evidence involving a relatively small number of patients. In a scenario using the mean treatment effect across all three years of the MOXIe open-label extension study (the assumption used in the manufacturer's base-case), the incremental QALYs were 0.77. However, when the treatment effect was instead estimated using data from years 2-3 of the same study, incremental QALYs decreased to 0.32. The JNHB assessment also found that results were sensitive to the utility assumptions. In all four countries, the resulting ICERs were above the respective cost-effectiveness thresholds, indicating that discounts would be required for omaveloxolone to meet the applicable thresholds. Subgroup-specific results were limited, but the model submitted to the PBAC found that the typical-onset group has the highest incremental QALYs gained, followed by late-, intermediate-, and early-onset groups.

Our model shares several similarities with these previous models but differs in several important respects. First, our approach to modeling treatment effects differed from that of previous models.

Previous models assumed that treatment reduced the rate of disease progression beginning at treatment initiation and solely relied on the MOXIe open-label extension study to estimate this reduction. In contrast, we used both the MOXIe Phase II RCT and the MOXIe open-label extension study to inform treatment effect estimates. The RCT was used to inform the short-term treatment effect during the first year of treatment, whereas the open-label extension study was used to inform the long-term treatment effect. Unlike the open-label extension study, the RCT demonstrated a short-term improvement in both mFARS and FA-ADL, which was not explicitly captured in the previous models. Second, health state utilities for the main analysis were derived from a study of the general population, while utility values derived from patients with FA were explored in scenario analyses. These two sets of utility values differ substantially in the magnitude of utility decrements associated with disease progression. The general population-based utilities showed substantially larger decrements, ranging from 0.85 for an mFARS score of 0 to -0.18 for an mFARS score of 93. In contrast, utilities derived from patients with FA using FA-COMS data would range approximately from 0.85 to 0.50 across the corresponding mFARS range. Our scenario analyses showed that the source of health state utilities had a substantial impact on the model results. Due to these differences, the absolute QALYs associated with both omaveloxolone and SoC were lower than those reported in previous studies. However, consistent with previous models, our model estimated a modest incremental QALY gain with omaveloxolone versus SoC, and a cost per QALY gained well above commonly used cost-effectiveness thresholds.

F. Potential Budget Impact: Supplemental Information

Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over one- and five-year time horizons.

ICER's methods for estimating potential budget impact are described in detail in the Value Assessment Framework. The intent of our approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility.

As described in the Value Assessment Framework, this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent five-year period, and the contribution of spending on retail and facility-based drugs to total health care spending.

For 2025-2026, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $821 million per year for new drugs.