Clinical Management Guidelines for Friedreich Ataxia

Chapter 2. Potential disease modifying therapies for Friedreich ataxia

Contents

The original version of this chapter of the Clinical Management Guidelines for Friedreich Ataxia and the recommendations and best practice statements contained herein were endorsed by the authors and the Friedreich Ataxia Guidelines Panel in 2022. This chapter was updated in November 2024, including a new recommendation on the use of omaveloxolone that was endorsed by the authors and the Guidelines Panel.

Disclaimer

The Clinical Management Guidelines for Friedreich ataxia ('***Guidelines***') are protected by copyright owned by the authors who contributed to their development or said authors' assignees.

These Guidelines are systematically developed evidence statements incorporating data from a comprehensive literature review of the most recent studies available (up to the Guidelines submission date) and reviewed according to the Grading of Recommendations, Assessment Development and Evaluations (GRADE) framework © The Grade Working Group.

Guidelines users must seek out the most recent information that might supersede the diagnostic and treatment recommendations contained within these Guidelines and consider local variations in clinical settings, funding and resources that may impact on the implementation of the recommendations set out in these Guidelines.

The authors of these Guidelines disclaim all liability for the accuracy or completeness of the Guidelines, and disclaim all warranties, express or implied to their incorrect use.

Intended Use

These Guidelines are made available as general information only and do not constitute medical advice. These Guidelines are intended to assist qualified healthcare professionals make informed treatment decisions about the care of individuals with Friedreich ataxia. They are not intended as a sole source of guidance in managing issues related to Friedreich ataxia. Rather, they are designed to assist clinicians by providing an evidence-based framework for decision-making.

These Guidelines are not intended to replace clinical judgment and other approaches to diagnosing and managing problems associated with Friedreich ataxia which may be appropriate in specific circumstances. Ultimately, healthcare professionals must make their own treatment decisions on a case-by-case basis, after consultation with their patients, using their clinical judgment, knowledge and expertise.

Guidelines users must not edit or modify the Guidelines in any way – including removing any branding, acknowledgement, authorship or copyright notice.

Funding

The authors of this document gratefully acknowledge the support of the Friedreich Ataxia Research Alliance (**FARA)**. The views and opinions expressed in the Guidelines are solely those of the authors and do not necessarily reflect the official policy or position of FARA.

2. Potential disease modifying therapies for Friedreich ataxia

George Wilmot, Caterina Mariotti, David Lynch, Geneieve Tai and Massimo Pandolfo

2.1 History of examining modifying therapies

Since 1996, the year of the discovery of the genetic cause of Friedreich ataxia (FRDA), many pharmacological clinical trials have been conducted to explore potential medications and different strategies aimed at ameliorating or preventing cell damage due to reduced frataxin.

The first compounds tested in individuals with FRDA were medications that were already available – either supplements or drugs approved for other indications. Initially, medications used in clinical trials were compounds with antioxidant properties, including vitamin E, co-enzyme Q10 and idebenone. In particular, idebenone was the most tested drug, with numerous clinical trials conducted from 1998 to 2012. Administration of different dosages of idebenone was shown to be safe. However, the results of the most recent Phase III study did not confirm the efficacy of idebenone on neurological symptoms and it is still unclear whether idebenone provides any cardiac benefit (1).

Other compounds tested for their antioxidant and neuroprotective properties are EGb761, an extract of Ginkgo biloba leaves (EGb 761®, Tanaken, Ipsen, France), OX1 (indole-3-propionic acid, IPA) a naturally occurring small molecule, and A0001 or alpha-tocopherol quinone (Penwest-Edison Pharmaceuticals), a co-enzyme Q10 analogue (2, 3). Although these molecules have been demonstrated to improve mitochondrial function *in vitro*, their efficacy in ameliorating or stabilizing disease progression in individuals with FRDA has not been confirmed.

Pioglitazone hydrochloride (ACTOS®, Takeda Pharmaceuticals) has also been proposed as a potential treatment for FRDA because it was postulated to induce the expression of many enzymes involved in mitochondrial metabolism, including the superoxide dismutases. Pioglitazone is a thiazolidinedione oral antidiabetic agent, which may cause or worsen congestive heart failure and other cardiovascular problems in FRDA (4). Its efficacy in the treatment of FRDA has not been demonstrated (5).

A different therapeutic strategy came from the observation of iron overload in mitochondria of individuals with FRDA (6). The commercially available iron chelator deferiprone (Ferriprox®, Apopharma, Canada) has been tested in a double-blind placebo-controlled trial (sponsored by Apopharma) of 72 individuals with FRDA aged 7 to 35 years (7). The participants assigned to the high-dose arm (60 mg/kg/day) were prematurely discontinued due to worsening of ataxia. Participants receiving 40 mg/kg/day also had worsening Friedreich Ataxia Rating Scale (FARS) and the International Cooperative Ataxia Rating Scale (ICARS) scores, whereas participants receiving 20 mg/kg/day of deferiprone had no significant change in FARS, similar to the placebo-treated individuals. The lack of deterioration in the placebo arm impaired the ability to detect any potential protective effect of deferiprone. However, subgroup analyses in participants with less severe disease suggest a benefit of deferiprone at 20 mg/kg/day on ICARS, FARS, kinetic function, and 9-hole peg test (9HPT). Deferiprone-treated participants receiving 20 or 40 mg/kg/day showed a significant decline in the left ventricular mass index. Higher doses of deferiprone caused systemic iron depletion and anemia; however, only one participant treated with 20 mg/kg/day had to discontinue treatment because of this complication (7). The major risk with deferiprone is the sudden, idiosyncratic development of agranulocytosis, which may occur at any time, even after a few years of treatment. No cases of agranulocytosis occurred during this study, but one participant experienced neutropenia, which resolved upon discontinuation of deferiprone (7). This study

suggests that systemic iron depletion is deleterious in people with FRDA, possibly further impairing iron sulfur cluster biogenesis, but a low dose of a membrane penetrant chelator such as deferiprone may be beneficial by removing excess redox-active iron.

An anecdotal observation of an improvement in balance and coordination in patients treated with varenicline (Champix®, Pfizer), an agonist of nicotine receptors, to help quit smoking suggested the potential use of this drug for individuals with FRDA. However, a Phase II pilot study was stopped before completion due to concerns on safety and observations of worsening gait and imbalance. There was also insufficient evidence of efficacy. A complete report detailing study data will be issued shortly.

Other compounds have been tested for their *in vitro* property of increasing frataxin protein or enhancing frataxin gene transcription in cells from individuals with FRDA. Among these drugs, erythropoietin (EPO) and carbamylated EPO (C-EPO) were also tested in double-blind controlled studies, but neither neuro- nor cardio-protective properties were demonstrated *in vivo* (8-11).

Another drug tested for its property of increasing both frataxin messenger RNA (mRNA) and protein levels in a variety of cell types, including cells from individuals with FRDA, is the exogenous interferon gamma-1b (ACTIMMUNE). This drug was administered at different dosages via subcutaneous injection in an open-label study design. The twelve children with FRDA who received the treatment for 12 weeks improved in FARS scores without a clear relationship to changes in frataxin levels (12). The following double-blind placebo-controlled study performed in a much larger series of individuals with FRDA (n=92) did not demonstrate significant differences between interferon-treated and placebo-control groups after 6 months of treatment. No change was noted in buccal cell or whole blood frataxin levels (13).

Although a great scientific effort has been dedicated to selecting these drugs and testing their efficacy in clinical trials, most of these compounds have been removed from the list of potential therapeutic candidates for FRDA. While there is currently only one approved pharmacological treatment for FRDA, research into potential therapeutic agents has nevertheless advanced considerably in the past two decades. There are many other potential therapeutic candidates that have been proposed in the treatment of FRDA that have undergone or are in the process of undergoing clinical trial evaluation.

2.2 Potential targets for therapies

The research of therapies that could have clinically meaningful results leading to a cure for the disease is continuing, with new compounds and new clinical trials being designed, commenced and currently ongoing. The research of new strategies is still based on the evaluation of potential therapeutic effects of drugs that are already commercially available and approved for other diseases, as well as new compounds specifically intended for the cure of FRDA and not available for other indications.

2.2.1 Therapies that decrease oxidative stress and enhance mitochondrial function

The pathology of FRDA is characterized by mitochondrial dysfunction and oxidative stress, demonstrated in both cell and animal models of FRDA (6, 14). Respiratory chain dysfunction, accumulation of iron in the mitochondria and impaired antioxidant responses lead to increased production of reactive oxygen species (15). The use of antioxidants has therefore been investigated as a potential therapy for FRDA.

2.2.2 Anti-inflammatory therapy

Inflammation contributes to the pathology of FRDA and has been detected in animal models as well as in tissues of people with FRDA (16, 17). The anti-inflammatory properties of steroids may play a role in altering oxidative damage caused by frataxin deficiency. This hypothesis arose after an improvement in neurological symptoms was reported in an individual with FRDA following corticosteroid treatment (18). Methylprednisolone has thus been explored as a treatment in FRDA (19).

2.2.3 Modulators of frataxin-controlled metabolic pathways

FRDA is caused by the reduced expression of frataxin, a protein found mostly in the mitochondria (20, 21), where it acts as an activator of iron-sulfur (Fe-S) cluster biosynthesis. The resulting Fe-S deficiency impairs the activity of many cellular proteins, including respiratory chain subunits and Krebs cycle enzymes in the mitochondria, and triggers a homeostatic response that increases cellular and mitochondrial iron uptake (22). However, as the Fe-S cluster biosynthetic pathway is impaired, iron eventually accumulates in mitochondria where it may engage in redox reactions generating toxic free radicals, activate signaling pathways leading to neurodegeneration (23), and trigger cell death, in particular by ferroptosis (24).

It has been proposed that frataxin is also involved in various other pathways, including iron metabolism, transport and storage (25), as well as regulation of apoptosis (26). Furthermore, several metabolic pathways are perturbed because of frataxin deficiency, in particular those that control antioxidant responses and mitochondrial biogenesis. Therapies that modulate such pathways include nuclear factor erythroid-derived 2-related factor 2 (Nrf2) activators and peroxisome proliferator activated receptor (PPAR)-γ agonists.

2.2.4 Therapies that increase FRDA gene expression

Approximately 96% of individuals with FRDA have a homozygous mutation consisting of the expansion of GAA trinucleotide repeats within the first intron of the *FXN* gene (20), leading to the formation of heterochromatin (27). As a result, transcription of *FXN* mRNA is reduced (28, 29). Agents that counter heterochromatin formation can upregulate *FXN* mRNA, including histone deacetylase (HDAC) inhibitors (30, 31). Other agents directly boost *FXN* expression regardless of the presence of expanded GAA repeats. Those clinically tested include erythropoietin and derivatives, Interferon gamma (12, 32).

2.2.5 Frataxin replacement, stabilizers or enhancers

Frataxin replacement therapy has been proposed by pairing synthetic frataxin protein with a delivery system using a protein fragment called a trans-activator of transcription (TAT) to enable frataxin delivery into the mitochondria (33, 34). Another method of frataxin supplementation is through delivery of a normal copy of the *FXN* gene via gene replacement therapy (35-37).

Gene replacement and editing

Gene replacement therapy is perhaps the most promising in terms of correcting frataxin loss in FRDA, with numerous strategies currently being explored (https://curefa.org/pipeline). FRDA presents as a favorable candidate for gene replacement therapy due to several factors. About 96% of individuals with FRDA have the same single gene mutation which leads to gene silencing and a reduction of the frataxin protein levels. Because individuals with FRDA already produce frataxin, it is

less likely that an immune response will be produced. Furthermore, while carriers for FRDA possess one faulty copy of the gene and produce half the normal frataxin levels, these individuals do not exhibit any symptoms, indicating that even a small increase of frataxin has the likelihood to be beneficial.

There are several approaches to gene therapy (38). Adeno-associated viruses (AAV) are viral vectors that do not integrate into the host genome, avoiding genotoxicity. Their DNA persists for a long time in transfected cells as an episome, potentially lifelong. This makes AAV a vector of choice for perennial tissues such as the brain, spinal cord, and heart, which are most affected in FRDA. The potential efficacy of AAV-based gene therapy for FRDA was first demonstrated in a conditional cardiac and skeletal muscle *FXN* knockout mouse model (Mck-Cre-Fxn$^{L3/L}$ mice) that was treated intravenously with adeno-associated virus rh10 vector expressing human FXN, leading to prevention of cardiac disease onset if given early, as well as a complete reversal of cardiomyopathy when given after the development of symptoms (36). In a separate study, a parvalbumin-conditional *FXN* knockout mouse model (Pvalb cKO) with *FXN* delivered through an AAV9 vector resulted in a complete reversal of sensory ataxia but not of manifestations of central nervous system (CNS) disease (37).

There are, however, several issues that need to be resolved before AAV-based gene therapy becomes a reality in FRDA. Some naturally occurring AAVs, such as AAV9, can effectively cross the blood-brain barrier (BBB) after systemic administration, but only for a limited time after birth. For this reason, while AAV9-based gene therapy has been effective in treating diseases such as spinal muscular atrophy (SMA), that affects babies, there are ongoing efforts to generate new capsids that can penetrate the CNS in older children and adults after systemic administration (39). However, this may require very high intravenous doses of the vector, which, at least in the case of AAV9 and related capsids, may trigger a severe reaction with liver toxicity and cytokine release. While this reaction could be potentially lethal, it is at least partially preventable with immune suppressive treatment with steroids (40). Furthermore, an inflammatory reaction with neuron loss in the dorsal root ganglia (DRG) has been observed in some animal models (40). This is a particularly worrisome complication in FRDA, where DRG pathology is already present. Acquired immunity to AAVs, a common occurrence in the general population, is another problem, as neutralizing antibodies may inactivate the gene therapy vector and T cells may attack transfected cells presenting capsid fragments on their surface. This is also a major obstacle to re-administer AAV to patients who have previously received it. Overall, these difficulties impose the development of new capsids with improved biodistribution and ability to cross the BBB, as well as of strategies to control innate and acquired immune responses, allowing administration to individuals carrying anti-AAV antibodies and re-administration of a therapeutic vector if needed (41).

Proper control of transgene expression is also necessary. Frataxin expression must reach heterozygous carrier levels at least, but cannot be excessive, as it has demonstrated that very high levels are toxic, causing mitochondrial dysfunction and cardiac toxicity in mouse models (42). This requires a combination of appropriate vector biodistribution and promoter choice.

The possibility of dual routes of administration is an emerging option for what we may consider the first-generation gene therapy for FRDA, while “optimal” vectors are being developed. This approach aims at reaching peripheral organs (heart, pancreas, DRG, peripheral nerves, muscle) via a relatively low dose systemic administration, and the CNS via intrathecal or intraparenchymal administration, targeting key affected structures as the dentate nuclei in the cerebellum.

Other approaches may involve different viral vectors, such as Herpes virus-based, or non-viral vectors such as lipid nanoparticles. These are still in an early-preclinical phase.

Delivery of brain-derived neurotrophic factor (BDNF) is another approach to gene therapy in FRDA (43). BDNF has numerous neuroprotective properties including anti-apoptosis, antioxidation and autophagy suppression (44). The *stargazer* mouse model with severe cerebellar ataxia exhibited improved ataxia and motor impairment when crossed with mice overexpressing transgenic BDNF (45). In another study, a gene encoding BDNF was delivered via a herpesviral amplicon vector to a knockout mouse model which prevented the onset of cerebellar neuropathology and ataxia (46). Overexpression is an issue with BDNF as well, having been shown to cause learning and short-term memory impairment (47).

A lack of animal models that accurately depict FRDA is another barrier in the development of gene therapy in FRDA. Conditional knockout mouse models are useful in providing proof-of-concept, but models with a pathologically low systemic frataxin expression, as is the case in the human disease, are still unsatisfactory. A YG8JR mouse model carrying a human *FXN* gene with 800 GAA repeats has recently been developed and is the most genetically alike to individuals with FRDA. However, the phenotype of this model, as of other GAA repeat expansion-carrying mouse models, appears to be late disease onset and mild disease presentation. There is also a lack of models in larger animals which may be more useful with respect to translation to humans.

2.3 Therapies approved or under investigation

The sections below summarize the current approved therapies, drugs available off-label and drugs and gene therapies currently under investigation for use in FRDA (see also a recent publication describing the status of drug and gene therapy research in 2024 (48).

2.3.1 Drugs approved for use in Friedreich ataxia

Omaveloxolone (Skyclarys™)

Omaveloxolone was developed by Reata Pharmaceuticals to target activation of Nrf2, which is decreased in cells in individuals with FRDA. In a double-blind, randomized, placebo-controlled, multicenter study (MOXIe Part 2) of 103 individuals with FRDA, participants aged 16 to 40 years received either placebo or omaveloxolone at 150 mg per day (49). Individuals treated with omaveloxolone experienced a statistically significant, placebo-corrected mean improvement in mFARS, the primary outcome measure, of 2.4 points after 48 weeks of treatment ($p = 0.014$). This benefit was mostly recorded in patients without pes cavus, a common feature of FRDA associated with more severe disease, suggesting that patients with milder disease benefited the most. Omaveloxolone was reported to be safe and well tolerated (49).

After MOXIe Part 2, participants were enrolled in an open label extension (OLE) study to gather longer term safety and efficacy data. Two studies have been reported from the OLE study. In a delayed-start analysis, similar slopes in the mFARS were found for the placebo to omaveloxolone group (0.59 points per year) and the omaveloxolone to omaveloxolone group (0.41 points per year) (50). There was no significant difference in the rates of change between groups, demonstrating the disease modifying activity of omaveloxolone (50). A propensity matched study showed benefit from omaveloxolone over 3 years when compared to a matched cohort from an FRDA natural history study (51). The open-label extension study is ongoing with additional data collection and safety monitoring (https://www.clinicaltrials.gov/ct2/show/study/NCT02255435).

The most common adverse events (incidence ≥ 20% and greater than placebo) were elevated liver enzymes (alanine and aspartate aminotransferase; ALT/AST), headache, nausea, abdominal pain, fatigue, diarrhea, and musculoskeletal pain (49). Clinical experience shows that a number of patients

are experiencing raised cholesterol levels while using omaveloxolone. Therefore, ongoing monitoring by clinicians is necessary and cholesterol-lowering medication may be indicated.

In February 2023, the US FDA granted approval for the use of omaveloxolone (brand name Skyclarys™) for the treatment of FRDA in adults and adolescents aged 16 years and over (52). In December 2023, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) recommended marketing authorization for Skyclarys for the treatment of FRDA in individuals aged 16 and over in the European Union (EU). Following review by the European Commission, approval was announced in February 2024. (https://investors.biogen.com/news-releases/news-release-details/biogen-received-european-commission-approval-skyclarysr).

Omaveloxolone for the treatment of FRDA has not gained approval from drug regulatory bodies in other jurisdictions at this stage, although some countries (such as Canada) are able to prescribe omaveloxolone through Special Access Programs.

Dosing

Before prescribing omaveloxolone, please see https://www.fda.gov/drugsatfda for full current labelling information, including contraindications, drug interactions and use in specific populations. A summary of current dosing recommendations is given below.

The FDA-recommended dosage of omaveloxolone is 150 mg (3 capsules) taken orally once daily on an empty stomach. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, B-type natriuretic peptide (BNP), and lipid parameters should be monitored for elevated levels prior to initiating omaveloxolone and periodically during treatment. Omaveloxolone should be avoided for individuals with severe hepatic impairment. For those with moderate hepatic impairment, the recommended dosage of omaveloxolone is 100 mg once daily. However, if adverse reactions emerge, a dosage of 50 mg once daily is recommended.

Table 2.1 Summary of omaveloxolone – approved for use in Friedreich ataxia

Therapy	Proposed mechanism	Stage of development	Study outcomes
Omaveloxolone (RTA 408)	Nrf2 activator – reduces intracellular oxidative stress and mitochondrial damage, increases mitochondrial respiration and biogenesis.	Randomized double-blind placebo-controlled study completed. FDA approval for use in individuals with FRDA ≥16 years residing in the US and EC approval for use in individuals with FRDA ≥16 years residing in the EU. Open-label extension study: ongoing to collect long-term data. Two papers published so far. A Phase 1 trial for children with FRDA aged 2 to 15 years underway in the USA (https://clinicaltrials.gov/study/NCT06054893).	Improvement in primary outcome measure (mFARS) of 2.40 points after 48 weeks of treatment (p = 0.014). Reported to be safe and well tolerated. Results from the OLE study published so far: A delayed-start analysis demonstrated a persistent benefit of omaveloxolone on disease course through 144 weeks follow-up. A propensity matched study showed benefit from omaveloxolone over 3 years when compared to a matched cohort from an FRDA natural history cohort.

Recommendation

Grading for strength of recommendation and level of evidence

For the rating of the **strength** of the recommendation, in addition to evidence from studies in FRDA, evidence from like conditions, clinical experience and expert consensus are taken into account when published evidence is not available.

The **level of evidence** is based on published evidence from studies in FRDA. If there is no published evidence in FRDA, evidence from other like conditions or clinical expertise may have been used to make the recommendation – this is graded as 'very low' or in some cases 'low' level evidence. See the table below for an explanation of the symbols used to grade recommendations.

Strength of recommendation	Symbol	Level of evidence	Symbol
Strong for intervention	↑↑	High	⊕⊕⊕⊕
Conditional for intervention	↑	Moderate	⊕⊕⊕◯
Neither intervention nor comparison	—	Low	⊕⊕◯◯
Conditional against intervention	↓	Very low	⊕◯◯◯
Strong against intervention	↓↓		

Omaveloxolone treatment for individuals with FRDA aged 16 years and over

Should 150mg daily of omaveloxolone vs. none be used for providing neurological benefit for individuals with Friedreich ataxia aged 16 years and over?	**Strength**	**Level of evidence**
We recommend the use of 150mg daily of omaveloxolone administered according to regulatory guidelines over no omaveloxolone for providing neurological benefit for individuals with Friedreich ataxia aged 16 years and over.	↑↑	⊕⊕⊕◯
Justification: Given the landscape of the FRDA disease, the known trajectory of ongoing decline in neurological function, the absence of any other approved drug treatments to benefit neurological function and the low rate of adverse effects recorded in the RCTs, we believe individuals with FRDA aged 16 years and over residing in jurisdictions where regulatory approval has been granted would likely gain benefit from treatment with omaveloxolone. The current evidence therefore supports a strong recommendation for its use in individuals with FRDA aged 16 years and over when administered according to labeling guidelines. As is the case for any drug treatment, clinical experience indicates that individuals' perceptions of the magnitude of the desirable effects of omaveloxolone may vary according to factors such as prior (to treatment) expectations of the level of effect and the individual's stage of disease (whether in early stages or advanced). Ongoing clinical follow-up of patients suggests the beneficial effects are maintained beyond the duration of the studies. Early clinical experience is reinforcing the need for monitoring of both liver function enzymes and lipids and suggests a higher incidence of increased cholesterol levels which may require intervention with statin therapy.		
Subgroup considerations: Omaveloxolone is currently only approved for individuals aged 16 years and over. Efficacy of treatment for individuals aged <16 years and those with lower mobility and		

reduced cardiac function is unclear at this stage, but there is no obvious reason that omaveloxolone would not be beneficial for other groups of individuals with FRDA.

Clinicians need to be aware of the drug regulatory situation and labeling guidance in their jurisdiction. Regulatory approval for the use of omaveloxolone for FRDA (in those aged 16 years and over) has so far only been granted in the USA and the EU.

Lay summary

Lay summary of clinical recommendation for omaveloxolone use in Friedreich ataxia

Since 1996, the year of the discovery of the genetic cause of Friedreich ataxia, many clinical trials have been done to explore the potential benefit of various medications and other strategies for individuals with Friedreich ataxia. There is currently only one drug treatment approved for use in Friedreich ataxia, although other drugs and treatments are still under investigation in clinical trials.

Omaveloxolone (brand name Skyclarys™) is now available in countries that have regulatory approval, but only for individuals aged 16 years and over. Trials in younger people with Friedreich ataxia are ongoing.

Why these recommendations?

We recommend that omaveloxolone (150 mg daily) should be offered to individuals with Friedreich ataxia 16 years and over who live in areas where regulatory approval has been given. Randomized clinical trials have shown neurological benefit and few serious side effects. However, ongoing clinical follow-up of cholesterol levels and liver function are recommended while having treatment with omaveloxolone.

What does this mean for you as a person living with Friedreich ataxia or caring for someone living with Friedreich ataxia?

It is important for you to speak with your healthcare professional about the use of omaveloxolone in Friedreich ataxia, including about whether it is approved for use where you live and whether it might be helpful in your specific health circumstances.

Who are these recommendations specifically for?

These recommendations are for individuals with Friedreich ataxia aged 16 years and over.

2.3.2 Drugs available off-label

The current state of research into drugs available off-label as possible therapies for FRDA is summarized in Table 2.2 and details are given below. Only therapies currently under investigation are included (not those where trials have been undertaken in FRDA but have been discontinued for various reasons).

Etravirine

Etravirine is an antiviral drug approved in 2008 by the US Food and Drug Administration (FDA) and is currently in use for the treatment of HIV. Alfedi and colleagues (53) have shown that etravirine increased frataxin protein levels in fibroblasts and lymphoblasts derived from individuals with FRDA by increasing frataxin mRNA translation and restoring the activity of aconitase, the enzyme containing an Fe-S cluster that is decreased from frataxin deficiency and provides some resistance to oxidative stress in these tissues. The levels of frataxin in these cell lines were also found to be

comparable to frataxin levels in unaffected carrier cells (53). Based on these results, a pilot open-label phase 2 clinical trial was conducted in 35 individuals with FRDA over 4 months to explore safety and tolerability (54). The authors concluded that the treatment was safe, reasonably well tolerated and there was some improvement in neurological function and exercise performance, suggesting that testing the efficacy of etravirine in a randomized controlled clinical trial was warranted (54).

Dimethyl fumarate

Dimethyl fumarate (DMF) was identified through a drug discovery program by Cortopassi and colleagues who demonstrated this compound's ability to induce mitochondrial biogenesis through activation of the Nrf2 pathway in individuals with multiple sclerosis (55, 56). DMF was also found to increase mitochondrial gene expression and function in mice models of FRDA (57). The protocol for a clinical trial of DMF in individuals with FRDA has been published (58). The aim of the study is to investigate safety, tolerability and whether DMF can increase the expression of the FXN gene and frataxin protein and ameliorate mitochondrial dysfunction in FRDA (58).

Table 2.2 Summary of possible therapies: drugs available off-label

Therapy	Proposed mechanism	Stage of development	Study outcomes
Etravirine	Antiviral drug currently in use for HIV treatment. Appears to increase frataxin protein levels in fibroblasts and lymphoblasts derived from FRDA patients.	Safety and efficacy study conducted.	Safety and efficacy study (FAEST1) completed. Etravirine was found to be safe, reasonably well tolerated and there was some improvement in neurological function and exercise performance.
Dimethyl fumarate (DMF)	Approved for treatment of multiple sclerosis and psoriasis. Has been shown to induce mitochondrial biogenesis in multiple sclerosis via activation of Nrf2 pathway which could be beneficial in FRDA.	Phase II safety and tolerability RCT planned.	Study protocol published.

2.3.3 Drugs not available for other indications and under investigation for FRDA

The current state of research into drugs that are not available for other indications as possible therapies for FRDA is summarized in Table 2.3 and details are given below. Only therapies currently under investigation are included (not those where trials have been undertaken but have been discontinued for various reasons).

Vatiquinone (PTC-743)

PTC-743 (previously EPI-743), or vatiquinone, is a follow-on compound to EPI-A0001. Vatiquinone is an orally absorbed small molecule that readily crosses into the CNS. It works by targeting NADPH quinone oxidoreductase 1 (NQO1). Its mode of action is to synchronize energy generation in mitochondria with the need to counter cellular redox stress (59). Vatiquinone seems to be 1000- to 10,000-fold more potent than co-enzyme Q10 or idebenone in protecting cells subjected to oxidative stress in patient fibroblast assays modelling the effects of mitochondrial disease.

A 72-week randomized parallel-arm, double-blind, placebo-controlled study evaluating vatiquinone in children and young adults (aged 7 to 21 years) with FRDA has completed enrolment (MOVE-FA study; n=146). The 72-week placebo-controlled phase was followed by a 24-week open-label extension phase which is now continuing as an indefinite period open label extension study. In May 2023, PTC Therapeutics announced topline findings that the primary end point of change from baseline in mFARS was not met; however, vatiquinone did show benefit on key secondary endpoints assessing ambulation and activities of daily living (https://ir.ptcbio.com/news-releases/news-release-details/ptc-therapeutics-announces-topline-results-vatiquinone-move-fa). Specifically, there was no significant difference in change in mFARS score at 72 weeks, but significant differences between study groups were seen in fatigue (improvement) and upright stability (less decline). In a sub-population of those who completed all aspects of the study protocol (n=96), there was a statistically significant difference in change in the mFARS over 72 weeks compared to placebo. In addition, an open label study assessing the pharmacokinetics (PK) and safety of vatiquinone administered in children with FRDA younger than 7 years has commenced (https://www.clinicaltrials.gov/study/NCT05485987). An October 2024 update from PTC Therapeutics (https://ir.ptcbio.com/node/16936/pdf) reports results from the long-term extension study. For 70 individuals under treatment for 144 weeks, there was a 3.7-point benefit in the mFARS score ($p<0.0001$) compared to mFARS data from a natural history cohort. It was also reported that vatiquinone was safe and well tolerated with no serious treatment-related adverse events reported.

Earlier, a six-month placebo-controlled study of EPI-743 in 63 adults with FRDA was conducted, with participants receiving placebo, 600 mg/day EPI-743 or 1200 mg/day EPI-743 (60). This was followed by an 18-month open-label extension study where all participants were treated with EPI-743. While the primary endpoint of low contrast visual acuity assessment was not met, an improvement in the neurological examination subscale of the FARS was found in participants administered low-dose EPI-743 when compared to the placebo group ($p = 0.047$) at 6 months. There were significant improvements in neurological outcomes and treatment was well tolerated (61).

EPI-743 at 1200 mg/day has also been tested in people with FRDA who are compound heterozygous for a *FXN* GAA repeat expansion and a point mutation in an 18-month open-label study (62). There were significant improvements in neurological function as assessed by the FARS indicating potential benefit in this subgroup of individuals (62).

PTC Therapeutics plans to submit a New Drug Application (NDA) to the FDA for vatiquinone for the treatment of FRDA in late 2024 (https://ir.ptcbio.com/news-releases/news-release-details/ptc-therapeutics-provides-corporate-update-and-reports-first-2).

MIN-102 (leriglitazone)

MIN-102, or leriglitazone, is a metabolite of pioglitazone, which has previously been trialed in FRDA. Like pioglitazone, leriglitazone is a potent agonist of peroxisome proliferator-activated receptor-gamma (PPARγ). MIN-102 has been developed by Minoryx Therapeutics. Pre-clinical studies showed that leriglitazone increased frataxin protein levels in DRG neurons that were frataxin deficient (63). An improvement in motor function deficits in FRDA mouse models was also demonstrated. A Phase 1 clinical study demonstrated that MIN-102 was well tolerated and was able to cross the BBB and engage PPARγ within the CNS much more efficiently that pioglitazone (64).

The Phase 2 FRAMES clinical trial enrolled 39 individuals with FRDA and examined the effects of leriglitazone on biochemical, imaging, neurophysiological, and clinical outcome measures (65). PPARγ engagement was demonstrated in all participants, as assessed by the biomarker adiponectin. Although the primary endpoint of change in spinal cord area was not demonstrated, leriglitazone

significantly prevented iron accumulation in the dentate nucleus of individuals receiving treatment compared to placebo (ANCOVA p = 0.05). Numerical differences in favor of leriglitazone were also seen in magnetic resonance spectroscopic analysis of cervical spinal cord and in an upper-limb coordination measure. Leriglitazone was also well tolerated, with peripheral edema the most frequent adverse event (65). The results indicate that a larger study is warranted.

CTI-1601 (TAT-frataxin)

CTI-1601 (nomlabofusp) is a delivery system whereby a TAT protein fragment is used to transport synthetic frataxin directly into the mitochondria (33). When tested in mouse models, cardiac function (increased heart rate and improved diastolic function) was improved and mean lifespan in the mice was increased.

The first in-human study of CTI-1601 commenced in November 2019 (Larimar Therapeutics), exploring safety and dosage compared to placebo in individuals with FRDA. Following the completion of the single ascending dose (SAD) study (https://clinicaltrials.gov/ct2/show/NCT04176991), a multiple ascending dose (MAD) study began in late 2020 (https://www.clinicaltrials.gov/ct2/show/NCT04519567) and results have been published (66). Individuals received subcutaneous injections of either CTI-1601 or placebo at increasing dose levels and frequencies over 13 days. Dose-dependent increases in frataxin levels from baseline were demonstrated in buccal cells, skin biopsies and platelets of participants receiving CTI-1601 compared to those receiving placebo. CTI-1601 was generally well tolerated at doses of up to 100 mg/day for 13 days (66, 67). An open label extension study was planned for commencement in mid-2021. However, the FDA placed a hold on the CTI-1601 clinical program due to deaths at the highest dose levels in an ongoing 180-day non-human primate toxicology study. In September 2022, the FDA cleared the initiation of a 25 mg cohort of a Phase 2, 4-week trial. Preliminary Phase 2 data for the 25 mg cohort was submitted to FDA to initiate a 50 mg cohort in the Phase 2 trial. Daily subcutaneous injections of 25 mg CTI-1601 for 14 days led to increases in frataxin levels from baseline in skin and buccal cells, compared to placebo: median placebo-adjusted increases were 3.5 pg/µg in skin cells and 0.9 pg/µg in buccal cells. In July 2023, the FDA cleared the initiation of the 50 mg cohort – participants received daily dosing for the first 14 days followed by dosing every other day until day 28. A mean 59% increase in frataxin levels in skin cells was seen at 14 days and slightly lower levels at 28 days. Data for buccal cells were more variable, although the majority showed increases in frataxin.

The open label extension trial (OLE) was cleared for initiation by the FDA, whereby participants receive 25 mg of CTI-1601 daily. Participants who completed treatment in the Phase 2 dose exploration trial or a prior clinical trial of CTI-1601 are eligible to screen for the OLE study. (https://investors.larimartx.com/news-releases/news-release-details/larimar-therapeutics-receives-fda-clearance-proceed-50-mg-cohort). In March 2024, the first dosing (25 mg) of an individual with FRDA in the OLE study was announced. In May 2024, FDA changes allowed a 50 mg dose group to be added to the OLE. Safety and frataxin data will support a Biologics License Application submission for accelerated approval targeted for late 2025.

A pediatric (children and adolescents) MAD study has been approved and recruitment will commence at the end of 2024/start of 2025 (https://clinicaltrials.gov/study/NCT06681766).

GeneTAC (Syn-TEFS)

Synthetic transcription elongation factors (Syn-TEFs) are a novel class of compounds comprising programmable DNA binders that target desired genomic loci and ligands that engage transcription elongation machinery. Ansari and colleagues (68) have demonstrated that Syn-TEF was able to

restore frataxin levels in cell lines from individuals with FRDA to the levels in control cell lines. The company Design Therapeutics has developed derivatives of the initial molecule with greatly improved pharmacological properties (DT-216). Initial exploratory results from a multiple ascending dose study showed statistically significant, dose-related increase in frataxin mRNA levels in skeletal muscle ($p<0.05$). Injection site reactions were observed across dose cohorts leading to a re-formulation of DT-216. This new formulation (DT-216P2) must undergo preclinical testing, with GLP studies by the end of 2024 and a Phase 1/2 patient trial in 2025 (https://investors.designtx.com/news-releases/news-release-details/design-therapeutics-outlines-progress-across-genetactm-platform).

Table 2.3 Summary of possible therapies: drugs not available for other indications

Therapy	Proposed mechanism	Stage of development	Study outcomes
Vatiquinone (PTC-743)	Previously EPI-743. Similar to A0001 – improves mitochondrial function and prevents oxidative stress.	Phase 3, Randomized double-blind placebo-controlled study followed by open label extension phase. Commenced pharmacokinetics (PK) and safety in children with FRDA younger than 7 years.	Did not meet primary endpoint of statistically significant change in mFARS[1] score at 72 weeks, however significant benefit on secondary endpoints of fatigue and upright stability demonstrated. Data from the open label extension phase (ongoing) showed significant benefit in mFARS for those treated for 144 weeks compared to mFARS data from a natural history cohort.
MIN-102 (Leriglitazone)	Metabolite of pioglitazone, potent agonist of peroxisome proliferator-activated receptor-gamma (PPARγ).	Phase 2 randomized, double-blind, placebo-controlled study (FRAMES).	Primary endpoint of change in spinal cord area was not met. However, leriglitazone prevented iron accumulation in the dentate nucleus of individuals receiving treatment compared to placebo ($p = 0.05$).
CTI-1601 (Nomlabofusp)	Delivery system (trans-activator transcription, TAT) that transports synthetic frataxin directly into mitochondria.	Phase 2a, randomized, double-blind, placebo-controlled, dose exploration study. Open Label Extension (OLE) study to explore the long-term safety of Nomlabofusp and long-term changes in frataxin.	Phase 2a results - daily subcutaneous injections of 25 mg CTI-1601 for 14 days led to increases in frataxin levels from baseline in skin and buccal cells, compared to placebo: Skin cells showed a 33% mean increase in frataxin levels at

Therapy	Proposed mechanism	Stage of development	Study outcomes
			14 days with slightly lower levels at 28 days. The 50 mg cohort showed a 59% increase in frataxin levels in skin cells at 14 days and slightly lower at 28 days. Changes in buccal cell frataxin levels were more variable. First dosing of patient in OLE trial in March 2024, with interim data expected soon.
GeneTAC (Syn-TEFS) DT-2162P	A novel class of compounds called synthetic transcription elongation factors. Able to restore frataxin levels in cell lines in FRDA.	MAD[2] study conducted but injection site reactions led to re-formulating DT-216. New formulation (DT-216P2) to undergo preclinical testing with GLP[3] studies end 2024 and patient trials in 2025.	Initial results from MAD study showed statistically significant, dose-related increase in frataxin mRNA levels in skeletal muscle but muscle protein levels were variable.

[1] mFARS: modified Friedreich Ataxia Rating Scale; [2] MAD: multiple ascending dose [3] GLP: Good Laboratory Practice

Author details

David Lynch, MD, PhD
Professor of Neurology and Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA
Email: lynchd@mail.med.upenn.edu

Caterina Mariotti, MD
Neurologist, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy
Email: caterina.mariotti@istituto-besta.it

Massimo Pandolfo, MD
Professor (Clinical), McGill University, Montreal, Quebec, Canada
Email: massimo.pandolfo@mcgill.ca

Geneieve Tai, BBiomedSc(Hons)
Research Assistant, Murdoch Children's Research Institute, Parkville, Victoria, Australia.
Email: geneieve.tai@mcri.edu.au

George Wilmot, MD, PhD
Associate Professor, Department of Neurology, Emory University, Atlanta, Georgia, USA
Email: gwilmot@emory.edu

Conflict of Interest statements

George Wilmot serves on the Data Monitoring Committee for studies of nomlabofusp for Friedreich ataxia sponsored by Larimar Therapeutics.

David Lynch does not receive any funds or other items from for-profit entities. The Children's Hospital of Philadelphia, USA has received grant money for support for performance of clinical trials and other studies from PTC, FARA, NIH, FDA, MDA, Larimar, and Reata (a wholly owned subsidiary of Biogen).

Caterina Mariotti has received financial support for clinical trials from Roche Pharmaceutical, Biogen, and PTC Therapeutics. She has received research grants from Friedreich's Ataxia Research Alliance, CHDI Foundation and the Italian Ministry of Health. She has received a fee from Biogen for consultancy work and sitting on an advisory board.

Geneieve Tai has no conflict of interest to declare.

Massimo Pandolfo has received consultant fees from Larimar Therapeutics.

References

1. Parkinson MH, Schulz JB, Giunti P. Co-enzyme Q10 and idebenone use in Friedreich's ataxia. J Neurochem. 2013;126 Suppl 1:125-41.
2. Hawi A, Heald S, Sciascia T. Use of an adaptive study design in single ascending-dose pharmacokinetics of A0001 (alpha-tocopherylquinone) in healthy male subjects. J Clin Pharmacol. 2012;52(1):65-77.
3. Lynch DR, Willi SM, Wilson RB, Cotticelli MG, Brigatti KW, Deutsch EC, et al. A0001 in Friedreich ataxia: biochemical characterization and effects in a clinical trial. Mov Disord. 2012;27(8):1026-33.
4. Garcia-Gimenez JL, Sanchis-Gomar F, Pallardo FV. Could thiazolidinediones increase the risk of heart failure in Friedreich's ataxia patients? Mov Disord. 2011;26(5):769-71.
5. Coppola G, Marmolino D, Lu D, Wang Q, Cnop M, Rai M, et al. Functional genomic analysis of frataxin deficiency reveals tissue-specific alterations and identifies the PPARgamma pathway as a therapeutic target in Friedreich's ataxia. Hum Mol Genet. 2009;18(13):2452-61.
6. Delatycki MB, Camakaris J, Brooks H, Evans-Whipp T, Thorburn DR, Williamson R, et al. Direct evidence that mitochondrial iron accumulation occurs in Friedreich ataxia. Ann Neurol. 1999;45(5):673-5.
7. Pandolfo M, Arpa J, Delatycki MB, Le Quan Sang KH, Mariotti C, Munnich A, et al. Deferiprone in Friedreich ataxia: a 6-month randomized controlled trial. Ann Neurol. 2014;76(4):509-21.
8. Sturm B, Stupphann D, Kaun C, Boesch S, Schranzhofer M, Wojta J, et al. Recombinant human erythropoietin: effects on frataxin expression in vitro. Eur J Clin Invest. 2005;35(11):711-7.
9. Boesch S, Nachbauer W, Mariotti C, Sacca F, Filla A, Klockgether T, et al. Safety and tolerability of carbamylated erythropoietin in Friedreich's ataxia. Mov Disord. 2014;29(7):935-9.
10. Boesch S, Strum B, Hering S, Goldenberg H, Poewe W, Scheiber-Mojdehkar B. Friedreich's ataxia: clinical pilot trial with recombinant human erythropoietin. Ann Neurol. 2007;62(5):521-4.
11. Sacca F, Puorro G, Marsili A, Antenora A, Pane C, Casali C, et al. Long-term effect of epoetin alfa on clinical and biochemical markers in friedreich ataxia. Mov Disord. 2016;31(5):734-41.
12. Seyer L, Greeley N, Foerster D, Strawser C, Gelbard S, Dong Y, et al. Open-label pilot study of interferon gamma-1b in Friedreich ataxia. Acta Neurol Scand. 2015;132(1):7-15.
13. Lynch DR, Hauser L, McCormick A, Wells M, Dong YN, McCormack S, et al. Randomized, double-blind, placebo-controlled study of interferon-gamma 1b in Friedreich Ataxia. Ann Clin Transl Neurol. 2019;6(3):546-53.

14. Babcock M, de Silva D, Oaks R, Davis-Kaplan S, Jiralerspong S, Montermini L, et al. Regulation of mitochondrial iron accumulation by Yfh1p, a putative homolog of frataxin. Science. 1997;276(5319):1709-12.
15. Armstrong JS, Khdour O, Hecht S, M. Does oxidative stress contribute to the pathology of Friedreich's ataxia? A radical question. FASEB J. 2010;24:2152–63.
16. Shen Y, McMackin MZ, Shan Y, Raetz A, David S, Cortopassi G. Frataxin deficiency promotes excess microglial DNA damage and inflammation that Is rescued by PJ34. PLoS One. 2016;11(3):e0151026.
17. Koeppen AH, Ramirez RL, Becker AB, Mazurkiewicz JE. Dorsal root ganglia in Friedreich ataxia: satellite cell proliferation and inflammation. Acta Neuropathol Commun. 2016;4(1):46.
18. Shinnick JE, Isaacs CJ, Vivaldi S, Schadt K, Lynch DR. Friedreich ataxia and nephrotic syndrome: a series of two patients. BMC Neurol. 2016;16:3.
19. Patel M, Schadt K, McCormick A, Isaacs C, Dong YN, Lynch DR. Open-label pilot study of oral methylprednisolone for the treatment of patients with Friedreich ataxia. Muscle Nerve. 2019;60(5):571-5.
20. Campuzano V, Montermini L, Molto MD, Pianese L, Cossee M, Cavalcanti F, et al. Friedreich's ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion. Science. 1996;271(5254):1423-7.
21. Campuzano V, Montermini L, Lutz Y, Cova L, Hindelang C, Jiralerspong S, et al. Frataxin is reduced in Friedreich ataxia patients and is associated with mitochondrial membranes. Hum Mol Genet. 1997;6(11):1771-80.
22. Martelli A, Schmucker S, Reutenauer L, Mathieu JRR, Peyssonnaux C, Karim Z, et al. Iron regulatory protein 1 sustains mitochondrial iron loading and function in frataxin deficiency. Cell Metab. 2015;21(2):311-23.
23. Chen K, Lin G, Haelterman NA, Ho TS, Li T, Li Z, et al. Loss of Frataxin induces iron toxicity, sphingolipid synthesis, and Pdk1/Mef2 activation, leading to neurodegeneration. Elife. 2016;5.
24. Turchi R, Faraonio R, Lettieri-Barbato D, Aquilano K. An overview of the ferroptosis hallmarks in Friedreich's ataxia. Biomolecules. 2020;10(11).
25. Llorens JV, Soriano S, Calap-Quintana P, Gonzalez-Cabo P, Molto MD. The role of iron in Friedreich's ataxia: Insights from studies in human tissues and cellular and animal models. Front Neurosci. 2019;13:75.
26. Wong A, Yang J, Cavadini P, Gellera C, Lonnerdal B, Taroni F, et al. The Friedreich's ataxia mutation confers cellular sensitivity to oxidant stress which is rescued by chelators of iron and calcium and inhibitors of apoptosis. Hum Mol Genet. 1999;8(3):425-30.
27. Saveliev A, Everett C, Sharpe T, Webster Z, Festenstein R. DNA triplet repeats mediate heterochromatin-protein-1-sensitive variegated gene silencing. Nature. 2003;422(6934):909-13.
28. Gottesfeld JM, Rusche JR, Pandolfo M. Increasing frataxin gene expression with histone deacetylase inhibitors as a therapeutic approach for Friedreich's ataxia. J Neurochem. 2013;126 Suppl 1:147-54.
29. Silva AM, Brown JM, Buckle VJ, Wade-Martins R, Lufino MM. Expanded GAA repeats impair FXN gene expression and reposition the FXN locus to the nuclear lamina in single cells. Hum Mol Genet. 2015;24(12):3457-71.
30. Soragni E, Xu C, Cooper A, Plasterer HL, Rusche JR, Gottesfeld JM. Evaluation of histone deacetylase inhibitors as therapeutics for neurodegenerative diseases. Methods Mol Biol. 2011;793:495-508.
31. Rai M, Soragni E, Jenssen K, Burnett R, Herman D, Coppola G, et al. HDAC inhibitors correct frataxin deficiency in a Friedreich ataxia mouse model. PLoS One. 2008;3:e1958.
32. Marcotulli C, Fortuni S, Arcuri G, Tomassini B, Leonardi L, Pierelli F, et al. GIFT-1, a phase IIa clinical trial to test the safety and efficacy of IFNgamma administration in FRDA patients. Neurol Sci. 2016;37(3):361-4.

33. Vyas PM, Tomamichel WJ, Pride PM, Babbey CM, Wang Q, Mercier J, et al. A TAT-frataxin fusion protein increases lifespan and cardiac function in a conditional Friedreich's ataxia mouse model. Hum Mol Genet. 2012;21(6):1230-47.
34. Britti E, Delaspre F, Feldman A, Osborne M, Greif H, Tamarit J, et al. Frataxin-deficient neurons and mice models of Friedreich ataxia are improved by TAT-MTScs-FXN treatment. J Cell Mol Med. 2018;22(2):834-48.
35. Gerard C, Xiao X, Filali M, Coulombe Z, Arsenault M, Couet J, et al. An AAV9 coding for frataxin clearly improved the symptoms and prolonged the life of Friedreich ataxia mouse models. Mol Ther Methods Clin Dev. 2014;1:14044.
36. Perdomini M, Belbellaa B, Monassier L, Reutenauer L, Messaddeq N, Cartier N, et al. Prevention and reversal of severe mitochondrial cardiomyopathy by gene therapy in a mouse model of Friedreich's ataxia. Nat Med. 2014;20(5):542-7.
37. Piguet F, de Montigny C, Vaucamps N, Reutenauer L, Eisenmann A, Puccio H. Rapid and complete reversal of sensory ataxia by gene therapy in a novel model of Friedreich ataxia. Mol Ther. 2018;26(8):1940-52.
38. Ocana-Santero G, Diaz-Nido J, Herranz-Martin S. Future prospects of gene therapy for Friedreich's ataxia. Int J Mol Sci. 2021;22(4).
39. Liu D, Zhu M, Zhang Y, Diao Y. Crossing the blood-brain barrier with AAV vectors. Metab Brain Dis. 2021;36(1):45-52.
40. Hinderer C, Katz N, Buza EL, Dyer C, Goode T, Bell P, et al. Severe toxicity in nonhuman primates and piglets following high-dose intravenous administration of an adeno-associated virus vector expressing human SMN. Hum Gene Ther. 2018;29(3):285-98.
41. Muhuri M, Maeda Y, Ma H, Ram S, Fitzgerald KA, Tai PW, et al. Overcoming innate immune barriers that impede AAV gene therapy vectors. J Clin Invest. 2021;131(1).
42. Belbellaa B, Reutenauer L, Messaddeq N, Monassier L, Puccio H. High levels of frataxin overexpression lead to mitochondrial and cardiac toxicity in mouse models. Mol Ther Methods Clin Dev. 2020;19:120-38.
43. Misiorek JO, Schreiber AM, Urbanek-Trzeciak MO, Jazurek-Ciesiolka M, Hauser LA, Lynch DR, et al. A comprehensive transcriptome analysis identifies FXN and BDNF as novel targets of miRNAs in Friedreich's ataxia patients. Mol Neurobiol. 2020;57(6):2639-53.
44. Chen SD, Wu CL, Hwang WC, Yang DI. More insight into BDNF against neurodegeneration: anti-apoptosis, anti-oxidation, and suppression of autophagy. Int J Mol Sci. 2017;18(3).
45. Meng H, Larson SK, Gao R, Qiao X. BDNF transgene improves ataxic and motor behaviors in stargazer mice. Brain Res. 2007;1160:47-57.
46. Katsu-Jimenez Y, Loria F, Corona JC, Diaz-Nido J. Gene transfer of brain-derived neurotrophic factor (BDNF) prevents neurodegeneration triggered by FXN deficiency. Mol Ther. 2016;24(5):877-89.
47. Cunha C, Angelucci A, D'Antoni A, Dobrossy MD, Dunnett SB, Berardi N, et al. Brain-derived neurotrophic factor (BDNF) overexpression in the forebrain results in learning and memory impairments. Neurobiol Dis. 2009;33(3):358-68.
48. Scott V, Delatycki MB, Tai G, Corben LA. New and Emerging Drug and Gene Therapies for Friedreich Ataxia. CNS Drugs. 2024;38(10):791-805.
49. Lynch DR, Chin MP, Delatycki MB, Subramony SH, Corti M, Hoyle JC, et al. Safety and efficacy of omaveloxolone in Friedreich aAtaxia (MOXIe Study). Ann Neurol. 2021;89(2):212-25.
50. Lynch DR, Chin MP, Boesch S, Delatycki MB, Giunti P, Goldsberry A, et al. Efficacy of Omaveloxolone in Friedreich's Ataxia: Delayed-Start Analysis of the MOXIe Extension. Mov Disord. 2023;38(2):313-20.
51. Lynch DR, Goldsberry A, Rummey C, Farmer J, Boesch S, Delatycki MB, et al. Propensity matched comparison of omaveloxolone treatment to Friedreich ataxia natural history data. Ann Clin Transl Neurol. 2024;11(1):4-16.
52. Mullard A. FDA approves first Friedreich's ataxia drug. Nat Rev Drug Discov. 2023;22(4):258.

53. Alfedi G, Luffarelli R, Condo I, Pedini G, Mannucci L, Massaro DS, et al. Drug repositioning screening identifies etravirine as a potential therapeutic for Friedreich's ataxia. Mov Disord. 2019;34(3):323-34.
54. Paparella G, Straga C, Pesenti N, Dal Molin V, Martorel GA, Merotto V, et al. A Pilot Phase 2 Randomized Trial to Evaluate the Safety and Potential Efficacy of Etravirine in Friedreich Ataxia Patients. Children (Basel). 2024;11(8).
55. Jasoliya M, Sacca F, Sahdeo S, Chedin F, Pane C, Brescia Morra V, et al. Dimethyl fumarate dosing in humans increases frataxin expression: A potential therapy for Friedreich's Ataxia. PLoS One. 2019;14(6):e0217776.
56. McMackin MZ, Durbin-Johnson B, Napierala M, Napierala JS, Ruiz L, Napoli E, et al. Potential biomarker identification for Friedreich's ataxia using overlapping gene expression patterns in patient cells and mouse dorsal root ganglion. PLoS One. 2019;14(10):e0223209.
57. Hui CK, Dedkova EN, Montgomery C, Cortopassi G. Dimethyl fumarate dose-dependently increases mitochondrial gene expression and function in muscle and brain of Friedreich's ataxia model mice. Hum Mol Genet. 2021;29(24):3954-65.
58. Pane C, Marra AM, Aliberti L, Campanile M, Coscetta F, Crisci G, et al. Rationale and protocol of a double-blind, randomized, placebo-controlled trial to test the efficacy, safety, and tolerability of dimethyl fumarate in Friedreich Ataxia (DMF-FA-201). Front Neurosci. 2023;17:1260977.
59. Shrader WD, Amagata A, Barnes A, Enns GM, Hinman A, Jankowski O, et al. alpha-Tocotrienol quinone modulates oxidative stress response and the biochemistry of aging. Bioorg Med Chem Lett. 2011;21(12):3693-8.
60. Zesiewicz T, Salemi JL, Perlman S, Sullivan KL, Shaw JD, Huang Y, et al. Double-blind, randomized and controlled trial of EPI-743 in Friedreich's ataxia. Neurodegener Dis Manag. 2018;8(4):233-42.
61. Zesiewicz T, Sullivan K, Huang Y, Salemi J, Klein M, et al. EPI-743 (alpha-tocotrienol quinone) demonstrates long-term improvement in neurological function and disease progression in Friedreich's ataxia. Neurology. 2017;88.
62. Sullivan K, Shaw J, Gooch C, Huang Y, Klein M, et al. EPI-743 for Friedreich's ataxia patients with point mutations (P5.388). Neurology. 2016;86.
63. Rodriguez-Pascau L, Britti E, Calap-Quintana P, Dong YN, Vergara C, Delaspre F, et al. PPAR gamma agonist leriglitazone improves frataxin-loss impairments in cellular and animal models of Friedreich ataxia. Neurobiol Dis. 2021;148:105162.
64. Meya U, Pina G, Pascual S, Cerrada-Gimenez M, Pizcueta P, Martinell M, et al. A phase 1 study to assess the safety, tolerability, pharmacokinetics, and effects on biomarkers of MIN-102 (Leriglitazone) (4149) Neurology. 2020;94(15 Supplement):4149.
65. Pandolfo M, Reetz K, Darling A, Rodriguez de Rivera FJ, Henry PG, Joers J, et al. Efficacy and Safety of Leriglitazone in Patients With Friedreich Ataxia: A Phase 2 Double-Blind, Randomized Controlled Trial (FRAMES). Neurol Genet. 2022;8(6):e200034.
66. Clayton R, Galas T, Scherer N, Farmer J, Ruiz N, Hamdani M, et al. Safety, pharmacokinetics, and pharmacodynamics of nomlabofusp (CTI-1601) in Friedreich's ataxia. Ann Clin Transl Neurol. 2024;11(3):540-53.
67. Larimar Therapeutics reports positive topline phase 1 clinical trial data showing dose-dependent increases in frataxin levels in patients with Friedreich’s ataxia. 2021 [Available from: https://www.globenewswire.com/fr/news-release/2021/05/11/2227007/0/en/Larimar-Therapeutics-Reports-Positive-Topline-Phase-1-Clinical-Trial-Data-Showing-Dose-Dependent-Increases-in-Frataxin-Levels-in-Patients-with-Friedreich-s-Ataxia.html.
68. Erwin GS, Grieshop MP, Ali A, Qi J, Lawlor M, Kumar D, et al. Synthetic transcription elongation factors license transcription across repressive chromatin. Science. 2017;358(6370):1617-22.