

RESEARCH MONOGRAPH . COMPOUND PROFILE

Vatiquinone

A synthetic alpha-tocotrienol quinone developed by Edison Pharmaceuticals as a first-in-class 15-lipoxygenase inhibitor and anti-ferroptotic cytoprotectant for inherited mitochondrial diseases and Friedreich ataxia, distinguished from earlier quinone antioxidants by nanomolar potency in oxidative stress models, NQO1-dependent intracellular bioactivation, and disease-modifying clinical signals in pediatric neurodegeneration.

DOCUMENT	KDC-MN-1605
ISSUED	2026-05-20
REVISION	1.0
AUTHOR	Kodiac bioLabs Research
COMPOUND CLASS	Para-benzoquinone anti-ferroptotic agent and 15-lipoxygenase inhibitor derived from alpha-tocotrienol

ABSTRACT

Vatiquinone (EPI-743, PTC-743, alpha-tocotrienol quinone) is a synthetic para-benzoquinone structurally derived from the vitamin E tocotrienol family and developed as an orally bioavailable, brain-penetrant cytoprotectant for inherited mitochondrial diseases and Friedreich ataxia. The compound is the oxidized (quinone) form of alpha-tocotrienol, bearing a 2,3,5-trimethyl-1,4-benzoquinone headgroup conjugated through a hydroxylated isoprenoid side chain. Vatiquinone is reduced intracellularly by NAD(P)H:quinone oxidoreductase 1 (NQO1) to its hydroquinone form, which functions as a potent inhibitor of 15-lipoxygenase (15-LO), the rate-limiting enzyme in the ferroptotic cell death cascade that drives lipid peroxidation in mitochondrially compromised neurons and other cell types. This dual mechanism (NQO1-dependent bioactivation followed by 15-LO inhibition) distinguishes vatiquinone from earlier quinone antioxidants such as coenzyme Q10 and idebenone and underwrites a 1,000- to 10,000-fold potency advantage in patient-derived fibroblast assays modeling the oxidative stress of mitochondrial disease.

The compound was discovered at Edison Pharmaceuticals in the late 2000s, received Orphan Drug Designation from the United States Food and Drug Administration for Leigh syndrome and subsequently for Friedreich ataxia, and advanced through open-label Phase 2 studies in Leigh syndrome, Leber hereditary optic neuropathy, and other genetically defined mitochondrial disorders before the program was acquired by PTC Therapeutics in 2019. PTC Therapeutics conducted the registrational MOVE-FA

Phase 3 trial (NCT04577352) in 143 patients with Friedreich ataxia aged 7 years and older. The primary endpoint of change from baseline in modified Friedreich Ataxia Rating Scale (mFARS) total score at 72 weeks did not reach statistical significance in the modified intent-to-treat population (treatment difference -1.61 points, $p = 0.144$). However, a prespecified sensitivity analysis of patients completing the full 72-week course demonstrated a 75 percent slowing of disease progression relative to placebo; the Upright Stability subscale of the mFARS showed a nominally significant treatment effect (-1.26 points, $p = 0.021$); and the Modified Fatigue Impact Scale showed a nominally significant benefit (-5.05 points, $p = 0.025$). In the long-term extension study, vatiquinone-treated patients progressed 3.75 points on the mFARS over 36 months compared to 7.48 points in a matched natural history cohort from the Friedreich Ataxia Clinical Outcome Measures Study registry, representing a clinically meaningful 50 percent slowing of disease progression. The FDA accepted the New Drug Application with Priority Review and set a Prescription Drug User Fee Act target date of August 19, 2025, but subsequently issued a Complete Response Letter concluding that the available data did not provide substantial evidence of efficacy and stipulating that an additional adequate and well-controlled clinical trial would be required for resubmission.

Pharmacokinetics are characterized by high lipophilicity, a pronounced food effect (medium-fat meal increases systemic exposure up to 25-fold relative to fasting), CYP3A4-mediated hepatic metabolism, high plasma protein binding (greater than 96 percent), an effective half-life of approximately 9 hours supporting three-times-daily dosing with meals, and predominantly fecal elimination. The compound is generally well tolerated; the principal adverse events in clinical trials have been

mild gastrointestinal symptoms and elevations in plasma cholesterol. This monograph reviews the chemistry, synthesis, and structural pharmacology of vatiquinone; the NQO1-mediated bioactivation and 15-lipoxygenase inhibition mechanism; the comprehensive pharmacokinetic record including drug-drug interaction characterization; the preclinical evidence across ferroptosis, mitochondrial disease, and Friedreich ataxia models; the clinical evidence base from Leigh syndrome through MOVE-FA; sourcing and quality verification; reconstitution and handling; stack-interaction considerations; adverse-event signal; and a comparative assessment of five alternative compounds (omaveloxolone, idebenone, coenzyme Q10, elamipretide, nicotinamide riboside) against vatiquinone on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Vatiquinone.

Development codes: EPI-743 (Edison Pharmaceuticals), PTC-743 (PTC Therapeutics). The development code EPI-743 is the canonical identifier in the early preclinical and clinical literature and the identifier under which the initial Leigh syndrome and mitochondrial disease studies were conducted [1, 2].

Chemical Abstracts Service registry number: 1213269-98-7.

PubChem compound identifier: CID 46184405.

UNII (Unique Ingredient Identifier): 6O85FK9I0X.

International Union of Pure and Applied Chemistry name: 2-[(3R,6E,10E)-3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trien-1-yl]-3,5,6-trimethylcyclohexa-3,6-diene-1,4-dione.

Common chemical synonym: alpha-Tocotrienol quinone. The compound is the two-electron oxidation product of alpha-tocotrienol (one of the eight naturally occurring forms of vitamin E) and is therefore classified within the tocotrienol quinone structural family [3].

1.2 Structural class and chemistry

Vatiquinone is a para-benzoquinone bearing a 2,3,5-trimethyl substitution pattern on the cyclohexadienedione ring and a 16-carbon isoprenoid side chain containing three trans-configured double bonds and a tertiary hydroxyl group at the C-3' position. The structural class places it within the chromanone-derived quinone family that includes coenzyme Q10 (ubiquinone), idebenone (a short-chain ubiquinone analog), and the tocopheryl quinones produced by endogenous oxidation of vitamin E forms [3, 4].

Molecular formula: C₂₉H₄₄O₃.

Exact mass: 440.3290 g/mol (monoisotopic).

Molecular weight: 440.67 g/mol.

Physical properties: Yellow to orange crystalline or amorphous solid. Poorly soluble in water owing to high lipophilicity (calculated logP approximately 8 to 10). Soluble in dimethyl sulfoxide, ethanol, and lipid vehicles. The high lipophilicity is a defining pharmacokinetic characteristic and is responsible for the pronounced food effect observed in clinical pharmacokinetic studies [5, 6].

Stereochemistry: Vatiquinone contains a single stereocenter at the C-3' position of the isoprenoid side chain, with the R-configuration corresponding to the naturally occurring alpha-tocotrienol stereochemistry. The R-isomer has significantly higher bioactivity than the corresponding S-isomer, consistent with the stereoselectivity observed across the tocopherol and tocotrienol vitamin E families [3].

1.3 Synthesis

The published synthesis of vatiquinone proceeds by oxidation of alpha-tocotrienol (the naturally occurring chromanolic precursor) using ceric ammonium nitrate or analogous mild oxidizing agents that selectively convert the chromanol ring to the para-benzoquinone while preserving the isoprenoid side chain geometry and the C-3' stereocenter [3, 7]. Industrial preparation involves either total synthesis from geranylgeraniol-derived intermediates or semi-synthesis from natural-source alpha-tocotrienol (extracted from palm oil or annatto seed oil fractions). The product is purified by column chromatography or preparative high-performance liquid chromatography and characterized by nuclear magnetic resonance spectroscopy, mass spectrometry, and chiral analysis. The compound is typically manufactured at greater than 98 percent chemical purity by HPLC area percent and greater than 99 percent enantiomeric excess of the (R)-form. Edison Pharmaceuticals (later BioElectron Technology Corporation) developed proprietary synthetic routes for clinical-supply manufacture; the process details are not in the public domain [7].

2. Abstract

Vatiquinone (EPI-743, PTC-743, alpha-tocotrienol quinone) is a first-in-class para-benzoquinone cytoprotectant developed for the treatment of inherited mitochondrial diseases and Friedreich ataxia. The compound operates through a two-step mechanism: intracellular reduction by NAD(P)H:quinone oxidoreductase 1 (NQO1) to the active hydroquinone form, followed by potent inhibition of 15-lipoxygenase (15-LO), the key enzyme governing ferroptotic cell death through generation of oxidized phospholipid death signals [1, 2, 8]. This NQO1-dependent bioactivation confers tissue selectivity (NQO1 is upregulated in oxidatively stressed cells) and potency (1,000- to 10,000-fold greater than coenzyme Q10 or idebenone in patient-derived fibroblast assays modeling mitochondrial disease) [2, 9].

The compound was developed at Edison Pharmaceuticals beginning in the late 2000s as part of a program to identify vitamin E-derived quinones with superior potency in mitochondrial disease cell models. Initial clinical evidence emerged from open-label Phase 2 studies in genetically defined Leigh syndrome (10 children, statistically significant improvement on Newcastle Pediatric Mitochondrial Disease Scale and Gross Motor Function Measure over 6 months) [1] and in Leber hereditary optic neuropathy, coenzyme Q10 biosynthetic defects, and other inherited mitochondrial disorders [2, 10]. Edison Pharmaceuticals (rebranded as BioElectron Technology Corporation in 2017) advanced the compound through Phase 2 in Friedreich ataxia before the program was acquired by PTC Therapeutics in 2019 [11].

PTC Therapeutics conducted the global Phase 3 MOVE-FA trial (NCT04577352) in 143 patients with Friedreich ataxia aged 7 years and older, randomized to vatiquinone or placebo for 72 weeks [12]. The primary endpoint (change in mFARS total score) did not achieve statistical significance (treatment difference -1.61 points, $p = 0.144$). Secondary and sensitivity analyses demonstrated nominally significant benefits: the Upright Stability subscale showed a treatment difference of -1.26 points ($p = 0.021$), corresponding to a 42 percent reduction in the annual rate of disease progression; the Modified Fatigue Impact Scale showed a treatment difference of -5.05 points ($p = 0.025$) [12, 13]. In the long-term extension, vatiquinone-treated patients showed 50 percent slowing of mFARS progression over 36 months relative

to a matched natural history cohort [14]. The FDA accepted the NDA with Priority Review but issued a Complete Response Letter on the August 19, 2025 PDUFA date, requiring an additional adequate and well-controlled trial for resubmission [15].

Pharmacokinetics are dominated by high lipophilicity, a dramatic food effect (up to 25-fold increase in exposure with a medium-fat meal versus fasting), CYP3A4-mediated hepatic metabolism, plasma protein binding exceeding 96 percent, an effective half-life of approximately 9 hours, and predominantly fecal elimination [5, 6, 16]. The compound is administered at 400 mg three times daily with fatty meals. It is generally well tolerated, with the principal adverse events being mild gastrointestinal symptoms and plasma cholesterol elevations. The compound has not been approved by any regulatory authority as of the monograph revision date.

3. Discovery and Development History

3.1 Origin

Vatiquinone was developed at Edison Pharmaceuticals (Mountain View, California), a biotechnology company founded in 2005 with a focus on therapies for inherited mitochondrial diseases. The discovery program was predicated on the observation that the vitamin E tocotrienol forms, particularly alpha-tocotrienol, demonstrated cytoprotective activity in oxidatively stressed cells at concentrations orders of magnitude lower than the corresponding tocopherol forms or than coenzyme Q10 and idebenone [2, 9]. Edison investigators hypothesized that the active species was the quinone oxidation product of alpha-tocotrienol, generated intracellularly by NQO1-mediated redox cycling. Systematic screening of tocotrienol quinones in patient-derived fibroblast assays modeling the oxidative stress of complex I deficiency, Leigh syndrome, and Friedreich ataxia identified alpha-tocotrienol quinone (subsequently designated EPI-743) as the most potent compound in the series, with nanomolar EC50 values for cytoprotection that exceeded the potency of coenzyme Q10 and idebenone by three to four orders of magnitude [2].

3.2 Early clinical development

Edison Pharmaceuticals advanced EPI-743 through Investigational New Drug application filing with the FDA and initiated open-label clinical studies beginning in 2010. The first published clinical data came from a Phase 2A study of EPI-743 in children with genetically confirmed Leigh syndrome: 10 patients aged 1 to 13 years with seven distinct genetic defects were treated with EPI-743 three times daily for 6 months. All 10 patients demonstrated reversal of disease progression on the Newcastle Pediatric Mitochondrial Disease Scale, the Gross Motor Function Measure, and the PedsQL Neuromuscular Module ($p < 0.05$ for each primary endpoint). All patients improved by at least one class on the Movement Disorder-Childhood Rating Scale. No significant drug-related adverse events were recorded [1]. These results were described as unprecedented for a progressive mitochondrial disease, though the open-label single-arm design limits causal inference.

Subsequent open-label studies extended the clinical evidence to Leber hereditary optic neuropathy, coenzyme Q10 biosynthetic defects, and genetically heterogeneous inherited mitochondrial diseases. At least 19 human clinical trials of vatiquinone were initiated across the mitochondrial disease spectrum [2, 10, 17].

3.3 Friedreich ataxia program

Edison Pharmaceuticals launched a Phase 2 clinical trial of vatiquinone in adults with Friedreich ataxia in 2013, enrolling participants through the FARA Patient Registry at three United States sites. Two-year results presented in 2016 demonstrated safety and tolerability. The trial did not meet its primary endpoint (a measure of visual function at 6 months), but investigators observed trends toward improvement in neurological function, and later analyses against matched natural history data suggested meaningful neurological gains [11, 18].

3.4 Corporate transitions

Edison Pharmaceuticals rebranded as BioElectron Technology Corporation in 2017. In 2019, PTC Therapeutics acquired the vatiquinone program and designated the compound PTC-743. PTC Therapeutics subsequently conducted the registrational MOVE-FA Phase 3 trial and filed the NDA with the FDA [11, 15].

3.5 Regulatory designations and status

Vatiquinone has received Orphan Drug Designation from the FDA for Leigh syndrome (granted 2011) and for Friedreich ataxia. The FDA also granted Fast Track Designation for the Friedreich ataxia indication. The NDA was accepted with Priority Review, with a PDUFA target date of August 19, 2025. On that date, the FDA issued a Complete Response Letter, concluding that the available data did not provide substantial evidence of efficacy and stipulating that an additional adequate and well-controlled clinical trial would be required to support a resubmission [15]. As of the monograph revision date, vatiquinone has not been approved by any regulatory authority worldwide.

4. Mechanism of Action

Vatiquinone operates through a two-step pharmacological mechanism that distinguishes it from earlier quinone antioxidants and from general-purpose radical scavengers. The first step is intracellular bioactivation by NQO1; the second is selective inhibition of 15-lipoxygenase and the downstream ferroptotic cell death cascade.

4.1 NQO1-dependent bioactivation

NAD(P)H:quinone oxidoreductase 1 (NQO1, also designated DT-diaphorase, EC 1.6.5.2) is a cytosolic flavoprotein that catalyzes the obligate two-electron reduction of quinone substrates to hydroquinones, bypassing the one-electron semiquinone radical intermediate that generates reactive oxygen species [8, 19]. NQO1 is constitutively expressed in most tissues and is transcriptionally upregulated by the Nrf2 (nuclear factor erythroid 2-related factor 2) antioxidant response element in cells experiencing oxidative stress.

Vatiquinone, as a para-benzoquinone, is a substrate of NQO1. Intracellular NQO1 reduces the quinone headgroup to the corresponding hydroquinone (the reduced form of alpha-tocotrienol quinone), which is the pharmacologically active species. The NQO1 dependence confers a degree of tissue selectivity: cells with high NQO1 expression (including neurons, cardiomyocytes, hepatocytes, and oxidatively stressed cells in which Nrf2 has activated the antioxidant response) produce higher intracellular concentrations of the active hydroquinone than cells with low NQO1 expression [8, 19]. This selectivity is a theoretical advantage over non-enzyme-dependent antioxidants such as coenzyme Q10 and idebenone, which distribute passively and lack an enzymatic amplification step.

The NQO1-generated hydroquinone additionally supports intracellular glutathione biosynthesis through mechanisms that are not fully elucidated but appear to involve stabilization of the cystine/glutamate antiporter (system xc-) and enhancement of gamma-glutamylcysteine synthetase activity, the rate-limiting step in glutathione synthesis [2, 8]. Glutathione is the principal endogenous substrate for

glutathione peroxidase 4 (GPX4), the selenoenzyme that directly reduces membrane phospholipid hydroperoxides and is the final checkpoint against ferroptotic cell death.

4.2 15-lipoxygenase inhibition

15-Lipoxygenase (15-LO, principally the ALOX15 isoform in humans) is a non-heme iron dioxygenase that catalyzes the stereospecific peroxidation of polyunsaturated fatty acids esterified in membrane phospholipids, particularly arachidonic acid and adrenic acid at the sn-2 position of phosphatidylethanolamines. The 15-LO-generated phospholipid hydroperoxides are the proximate death signals in ferroptosis, a form of regulated cell death characterized by iron-dependent lipid peroxidation that is mechanistically distinct from apoptosis, necroptosis, and autophagy [8, 20].

The vatiquinone hydroquinone (generated by NQO1 as described in section 4.1) is a potent and selective inhibitor of 15-LO. Inhibition of 15-LO blocks the generation of phospholipid hydroperoxide death signals and thereby prevents the execution phase of ferroptosis. This mechanism has been validated in patient-derived fibroblasts representing five distinct pediatric disease syndromes with associated epilepsy, where vatiquinone potently prevented ferroptotic cell death induced by RSL3 (a direct GPX4 inhibitor) and by combined buthionine sulfoximine and ferric citrate (glutathione depletion plus iron loading) [8, 20].

4.3 Distinction from general antioxidants

The vatiquinone mechanism is fundamentally different from that of general-purpose radical-trapping antioxidants (vitamin E, vitamin C, N-acetylcysteine) and from the earlier quinone antioxidants coenzyme Q10 and idebenone. Coenzyme Q10 and idebenone function primarily as electron carriers in the mitochondrial respiratory chain and as lipid-soluble radical scavengers; their antioxidant activity is stoichiometric (one molecule quenches one radical) rather than catalytic. Vatiquinone, by contrast, operates through enzymatic inhibition of 15-LO, a catalytic target; a single molecule of the active hydroquinone can prevent the generation of multiple phospholipid hydroperoxide molecules by inhibiting the enzyme that produces them [2, 8, 9]. This catalytic mechanism accounts for the 1,000- to 10,000-fold potency advantage observed in patient fibroblast assays.

4.4 Ferroptosis and mitochondrial disease

Ferroptosis has emerged as a convergent cell death mechanism across genetically diverse mitochondrial diseases. Defects in respiratory chain complexes I through IV, in coenzyme Q10 biosynthetic enzymes, and in mitochondrial tRNA synthetases all produce excess reactive oxygen species, deplete glutathione (directly or through depletion of NADPH), overwhelm GPX4 capacity, and permit 15-LO-mediated phospholipid peroxidation [8, 20]. In Friedreich ataxia, the deficiency of frataxin (a mitochondrial iron-sulfur cluster assembly protein) produces both mitochondrial iron accumulation and reduced activity of iron-sulfur-cluster-dependent enzymes, creating an iron-loaded, oxidatively stressed cellular environment that is particularly vulnerable to ferroptotic cell death [21].

Vatiquinone addresses this convergent vulnerability by inhibiting the terminal effector enzyme (15-LO) in the ferroptotic cascade, regardless of the upstream genetic defect. The mechanism is therefore theoretically applicable across the genetically heterogeneous mitochondrial disease population, provided that NQO1 is expressed at sufficient levels to bioactivate the quinone substrate.

4.5 Limitations of the anti-ferroptotic mechanism

Recent preclinical work has demonstrated that while vatiquinone robustly prevents ferroptotic cell death *in vitro*, it does not attenuate cell death induced by non-ferroptotic mechanisms such as complex I inhibition by rotenone or paraquat-induced oxidative damage [22]. In two mouse models of Leigh syndrome (Ndufs4 knockout), vatiquinone did not significantly extend survival, though it may have reduced seizure frequency in the Ndufs4(-/-) model [22]. These findings suggest that the clinical benefit of vatiquinone may be restricted to disease contexts in which ferroptosis is the dominant cell death pathway, and that mitochondrial diseases driven primarily by bioenergetic failure rather than lipid peroxidation may not respond.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Vatiquinone is administered orally and is absorbed from the gastrointestinal tract. Owing to its high lipophilicity and poor aqueous solubility, absorption is critically dependent on coadministration with dietary fat. A medium-fat meal increases systemic exposure (AUC) up to 25-fold relative to fasted administration [5, 6]. The mechanism of the food effect is stimulation of bile secretion by dietary fat, which emulsifies the lipophilic drug into mixed micelles and dramatically enhances solubilization and absorption from the intestinal lumen. The clinical dosing recommendation is therefore administration with fatty meals.

Population pharmacokinetic modeling in healthy volunteers and Friedreich ataxia patients characterized absorption through a two-compartment model with parallel zero-order and first-order absorption processes. The first-order absorption fraction was approximately 74 percent, with an absorption rate constant of 0.20 per hour and a delay time of approximately 2.8 hours. The zero-order absorption duration was approximately 6 hours [23]. Exposures (AUC and Cmax) increased in a dose-proportional manner from 200 mg to 400 mg, with moderate intersubject variability (coefficient of variation approximately 35 to 65 percent) [23].

5.2 Distribution

Vatiquinone has a large apparent volume of distribution (approximately 181 liters for the central compartment and approximately 4,853 liters for the peripheral compartment in the population pharmacokinetic model), reflecting extensive tissue partitioning consistent with high lipophilicity [23]. Plasma protein binding is greater than 96 percent across mouse, rat, rabbit, dog, monkey, and human plasma [16]. The compound crosses the blood-brain barrier, consistent with its lipophilic character and the clinical activity observed in central nervous system indications (Leigh syndrome, Friedreich ataxia) [2, 22].

5.3 Metabolism

Vatiquinone is metabolized predominantly in the liver by cytochrome P450 3A4 (CYP3A4). In vitro reaction phenotyping and clinical drug-drug interaction studies confirm that CYP3A4 is the principal metabolic enzyme [6, 16, 24]. Metabolism is more extensive in rabbit, monkey, and human hepatocytes than in dog, rat, and mouse hepatocytes [16].

Coadministration with itraconazole (a strong CYP3A4 inhibitor) at 200 mg increased vatiquinone C_{max} approximately 3.5-fold and AUC approximately 2.9-fold. Coadministration with rifampin (a strong CYP3A4 inducer) at 600 mg decreased vatiquinone C_{max} approximately 36 percent and AUC approximately 46 percent [24]. Physiologically based pharmacokinetic (PBPK) modeling indicated that moderate CYP3A4 inhibitors and inducers produce smaller effects, and that vatiquinone does not significantly inhibit or induce CYP3A4, CYP1A2, CYP2C9, or CYP2C19 at clinical doses [25].

No circulating plasma metabolites exceeded 10 percent of total drug-related exposure in any species studied [16].

5.4 Elimination

Vatiquinone is eliminated predominantly in feces. Following oral administration of radiolabeled [14C]-vatiquinone, approximately 94 percent of dose was recovered within 7 days in rats, approximately 61 percent in dogs, and approximately 93 percent in human subjects within 9 days [16]. Unchanged vatiquinone was not detectable in urine but was the most prominent component in feces across all three species, indicating that fecal excretion of unabsorbed drug and biliary excretion of parent compound are the principal elimination pathways.

The effective half-life of vatiquinone is approximately 9 hours, supporting a three-times-daily dosing regimen to maintain therapeutic drug exposures throughout the dosing interval [5, 23]. The mean accumulation ratio at steady state was approximately 1.6 to 1.7 for the 200 mg and 400 mg doses, respectively [23].

5.5 Transporter interactions

Vatiquinone was evaluated as a perpetrator of breast cancer resistance protein (BCRP) inhibition in a clinical drug-drug interaction study with rosuvastatin (a BCRP substrate). Clinical doses of vatiquinone did not produce a significant effect on rosuvastatin exposures, indicating that vatiquinone does not meaningfully inhibit BCRP at therapeutic concentrations [26].

5.6 Routes of administration

Vatiquinone is administered exclusively by the oral route in clinical use, at a dose of 400 mg (two 200 mg capsules) three times daily with meals containing fat. Higher and lower doses have been studied in Phase 1 and Phase 2 trials; the 400 mg three-times-daily regimen was selected for Phase 3 on the basis of exposure-response analysis and tolerability data [5, 12]. Intravenous formulation has not been developed for clinical use.

5.7 Cardiac safety

A dedicated concentration-QTc analysis demonstrated no relationship between vatiquinone plasma concentration and QTc interval prolongation at therapeutic and supratherapeutic doses, indicating an absence of clinically significant cardiac electrophysiological risk [27].

5.8 Special populations

Renal impairment: Formal studies in renal impairment have not been published. Given the predominantly fecal elimination and the absence of significant renal excretion, clinically meaningful pharmacokinetic changes in renal impairment are not expected.

Hepatic impairment: Formal studies in hepatic impairment have not been published. CYP3A4-mediated metabolism suggests that severe hepatic impairment could prolong elimination and increase exposure.

Pediatric pharmacokinetics: The MOVE-FA trial enrolled patients aged 7 years and older, and the Leigh syndrome studies enrolled children as young as 1 year. Population pharmacokinetic characterization in pediatric populations has been conducted [23].

6. Clinical Evidence Base

6.1 Leigh syndrome

The Martinelli et al. (2012) Phase 2A open-label study enrolled 10 children aged 1 to 13 years with genetically confirmed Leigh syndrome representing seven distinct genetic defects [1]. Subjects received EPI-743 three times daily for 6 months. All 10 patients demonstrated reversal of disease progression. The three primary endpoints (Newcastle Pediatric Mitochondrial Disease Scale, Gross Motor Function Measure, and PedsQL Neuromuscular Module) each showed statistically significant improvement ($p < 0.05$). All patients improved by at least one class on the Movement Disorder-Childhood Rating Scale. No drug-related adverse events were observed. A Japanese case report subsequently described clinical improvement in a Leigh syndrome patient treated with EPI-743 [28].

The open-label single-arm design limits causal inference. A randomized placebo-controlled confirmatory trial was planned but has not produced published results. A more recent preclinical evaluation (2025) found that vatiquinone did not extend survival in two *Ndufs4* knockout mouse models of Leigh syndrome, though it prevented ferroptosis in vitro and may have reduced seizure frequency in vivo [22].

6.2 Other inherited mitochondrial diseases

Open-label studies of EPI-743 were conducted in Leber hereditary optic neuropathy, coenzyme Q10 biosynthetic defects, mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS), and genetically heterogeneous mitochondrial respiratory chain diseases [2, 10, 17]. Published results describe safety, tolerability, and clinical improvement signals in small cohorts, but no randomized controlled trial in these indications has been completed or published. A long-term safety extension study (NCT05218655) monitored 101 patients with inherited mitochondrial disease who had previously received vatiquinone [17].

6.3 Friedreich ataxia: Phase 2

Edison Pharmaceuticals conducted a Phase 2 open-label study of EPI-743 in adults with Friedreich ataxia beginning in 2013. Two-year data demonstrated safety and tolerability. The primary endpoint (a measure of visual function at 6 months) was not met. Post hoc analyses comparing neurological outcomes against matched natural history data suggested clinically meaningful neurological benefit [11, 18].

6.4 Friedreich ataxia: Phase 3 MOVE-FA

The MOVE-FA trial (NCT04577352) was a global, randomized, double-blind, placebo-controlled Phase 3 study evaluating vatiquinone in patients with Friedreich ataxia [12, 13]. Enrollment criteria included age 7 years and older, mFARS score 20 to 70, and ability to ambulate at least 10 feet within 1 minute. A total of 143 subjects were randomized; the majority were under 18 years of age, reflecting the pediatric-pre-dominant disease demographics.

Primary endpoint: Change from baseline in mFARS total score at 72 weeks in the modified intent-to-treat (mITT) population. The primary analysis did not achieve statistical significance: treatment difference -1.61 points ($p = 0.144$) [12].

Key secondary and sensitivity analyses: A prespecified sensitivity analysis of patients completing the full 72-week treatment course demonstrated a 75 percent slowing of disease progression compared to placebo. The Upright Stability subscale (USS) of the mFARS, a clinically relevant metric of gait and balance in ambulatory patients, showed a nominally significant treatment difference of -1.26 points ($p = 0.021$), corresponding to a 42 percent reduction in the annual rate of disease progression [12, 13]. The Modified Fatigue Impact Scale showed a nominally significant treatment difference of -5.05 points ($p = 0.025$) [12].

Safety: Vatiquinone was safe and well tolerated. There was no difference in treatment-related adverse event rates between the vatiquinone and placebo groups [12, 13].

6.5 Friedreich ataxia: long-term extension

In the MOVE-FA long-term extension study, patients who continued vatiquinone treatment were compared to a matched natural history cohort from the Friedreich Ataxia Clinical Outcome Measures Study (FACOMS) disease registry [14]. After 36

months (144 weeks) of vatiquinone treatment, patients showed a 3.75-point increase in mFARS score (indicating disease progression), whereas the matched FACOMS cohort progressed by 7.48 points over the same period. This 50 percent slowing of disease progression represented a clinically meaningful treatment effect and provided the principal evidence supporting the NDA filing [14].

6.6 Pediatric epilepsy

The anti-ferroptotic mechanism of vatiquinone provides a rationale for the treatment of seizures in mitochondrial disease. Vatiquinone potently prevented ferroptotic cell death in patient cells representing five distinct pediatric disease syndromes with associated epilepsy [8, 20]. Clinical evidence for anti-epileptic efficacy is limited to the observation that seizure frequency may have been reduced in the *Ndufs4*(-/-) mouse model and to anecdotal reports from the open-label mitochondrial disease studies [22].

6.7 Regulatory outcome

The FDA accepted the NDA for vatiquinone with Priority Review and set a PDUFA target date of August 19, 2025. On that date, the FDA issued a Complete Response Letter (CRL), concluding that the available data did not provide substantial evidence of efficacy [15]. The CRL stipulated that an additional adequate and well-controlled clinical trial would be required to support a resubmission. The regulatory outcome reflected the failure of the MOVE-FA primary endpoint to achieve statistical significance, despite the supportive secondary and long-term extension data.

7. Reported Research Dose Ranges

7.1 Clinical doses in Friedreich ataxia

The MOVE-FA Phase 3 trial used vatiquinone 400 mg (two 200 mg capsules) three times daily with fatty meals, for a total daily dose of 1,200 mg [12]. This regimen was selected on the basis of Phase 1/2 exposure-response analysis and represents the dose intended for registration.

7.2 Clinical doses in Leigh syndrome and mitochondrial disease

Early open-label studies used weight-based dosing, typically in the range of 100 to 400 mg three times daily depending on patient age and body weight [1, 2]. The Leigh syndrome Phase 2A study treated children with EPI-743 three times daily for 6 months at investigator-determined doses within this range.

7.3 Dose-response considerations

The population pharmacokinetic analysis demonstrated dose-proportional increases in exposure from 200 mg to 400 mg [23]. The 400 mg three-times-daily dose was selected to maximize target engagement (15-LO inhibition and glutathione repletion) while maintaining tolerability. The critical requirement for coadministration with fatty meals (up to 25-fold exposure difference) means that dose-response interpretation must account for meal composition and timing [5, 6].

8. Sourcing and Quality Verification

Vatiquinone is not currently available as an approved pharmaceutical product in any jurisdiction. Research-grade vatiquinone is supplied by multiple chemical and pharmaceutical research suppliers (Cayman Chemical, MedChemExpress, Selleckchem, InvivoChem, GlpBio, MedKoo, BOC Sciences, Biosynth, AbMole) at greater than 98 percent purity by HPLC. Supply is typically in milligram to gram quantities as the free quinone form. CAS registry number 1213269-98-7 is the universal identifier for sourcing [3, 4].

Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography area-percent purity (target greater than 98 percent)
- Mass spectrometry confirmation of molecular weight (441.33 for [M+H]⁺ or 440.33 for the neutral monoisotopic mass)
- Nuclear magnetic resonance spectroscopy (¹H and ¹³C) for structural confirmation, particularly to verify the para-benzoquinone headgroup and the integrity of the isoprenoid side chain double bonds
- Chiral HPLC or optical rotation to confirm the (R)-configuration at C-3'
- Karl Fischer analysis for residual water content
- Residual solvent analysis by gas chromatography

The compound is light-sensitive and should be stored under inert atmosphere (nitrogen or argon) at -20 degrees Celsius in amber vials. Lot-to-lot variability in research-grade material has been observed, and on-receipt analytical confirmation is appropriate for any investigation requiring precise dose-response characterization.

9. Reconstitution and Handling

Vatiquinone is supplied as a yellow to orange solid (crystalline or amorphous). For in vitro research, the compound is typically dissolved in dimethyl sulfoxide (DMSO) at stock concentrations of 10 to 100 mM, given the poor aqueous solubility. Final working concentrations in cell culture should maintain DMSO at less than 0.1 percent (volume/volume) to avoid solvent cytotoxicity.

For in vivo preclinical research, lipid-based vehicles (corn oil, olive oil, medium-chain triglyceride oil, or proprietary lipid formulations) are appropriate given the high lipophilicity. Aqueous suspensions using standard suspending agents (0.5 percent methylcellulose, 0.1 percent Tween 80 in saline) have been used in published preclinical studies but produce variable bioavailability [22].

Storage of the solid and stock solutions should be at -20 degrees Celsius, protected from light and moisture. The compound is susceptible to oxidative degradation; stock solutions should be aliquoted for single use and stored under inert gas. DMSO stock solutions are stable at -20 degrees Celsius for at least 6 months when properly stored. Aqueous or aqueous-organic working solutions should be prepared fresh for each experiment.

For the clinical formulation (200 mg capsules), patients should be instructed to take the capsules with a meal containing adequate fat to ensure absorption [5, 6]. The capsule formulation is stable at controlled room temperature (15 to 30 degrees Celsius) in the original packaging.

10. Stack Interaction Considerations

Vatiquinone interacts with several drug classes through its CYP3A4-mediated metabolism and through its 15-LO inhibitory pharmacology. Investigators conducting research with vatiquinone should consider:

CYP3A4 inhibitors: Strong CYP3A4 inhibitors (itraconazole, ketoconazole, ritonavir, clarithromycin, cobicistat) substantially increase vatiquinone exposure (approximately 3-fold increase in AUC with itraconazole) [24]. Dose adjustment or avoidance of concurrent strong CYP3A4 inhibitors is appropriate. Moderate CYP3A4 inhibitors (erythromycin, fluconazole, diltiazem, verapamil) produce smaller but measurable effects per PBPK modeling [25].

CYP3A4 inducers: Strong CYP3A4 inducers (rifampin, carbamazepine, phenytoin, phenobarbital, St. John's wort) substantially decrease vatiquinone exposure (approximately 46 percent decrease in AUC with rifampin) [24]. Concurrent use reduces effective vatiquinone concentration and may compromise efficacy. This interaction is particularly relevant in Friedreich ataxia patients on anti-epileptic regimens that include CYP3A4-inducing agents.

Other 15-lipoxygenase inhibitors or anti-ferroptotic agents: Concurrent administration with other ferroptosis inhibitors (ferrostatin-1, liproxstatin-1) or with high-dose vitamin E produces pharmacologically additive anti-ferroptotic activity. The combination has not been studied clinically but may be a productive line of preclinical investigation.

Iron chelators: Deferiprone and deferoxamine, which chelate intracellular iron and thereby reduce the substrate for iron-dependent lipid peroxidation, operate on the same cell death pathway as vatiquinone but at a different mechanistic node. Combination of vatiquinone with iron chelation in Friedreich ataxia is a theoretically attractive dual-target approach that has not been evaluated in clinical trials.

Cholesterol-lowering agents: Vatiquinone has been associated with plasma cholesterol elevations in preclinical and clinical studies. Concurrent statin or other lipid-lowering therapy may be indicated for long-term treatment. The clinical drug-drug interaction study with rosuvastatin (a BCRP substrate and HMG-CoA reductase inhibitor) demonstrated no pharmacokinetic interaction [26].

Coenzyme Q10 and idebenone: Concurrent administration is pharmacologically redundant for the quinone-mediated electron transport and antioxidant mechanism but may provide additive benefit through complementary mechanisms (coenzyme Q10 as an electron carrier in the respiratory chain, vatiquinone as a 15-LO inhibitor). The combination has not been studied in controlled trials.

Omaveloxolone: Omaveloxolone activates the Nrf2 pathway and thereby upregulates NQO1, the enzyme responsible for vatiquinone bioactivation. The combination could theoretically enhance vatiquinone efficacy through increased intracellular conversion to the active hydroquinone. This combination has not been studied but represents a pharmacologically rational approach.

11. Adverse Events and Safety

11.1 Common adverse events

In the MOVE-FA Phase 3 trial, vatiquinone was safe and well tolerated, with no difference in treatment-related adverse event rates between vatiquinone and placebo groups [12, 13]. The principal adverse events observed across the clinical development program include:

- Gastrointestinal symptoms (nausea, diarrhea, abdominal discomfort): mild to moderate, generally self-limiting
- Plasma cholesterol elevations: observed in preclinical studies (rats and dogs) and monitored in clinical trials [17]
- Fatigue: mild, similar in frequency to placebo

11.2 Serious adverse events in the mitochondrial disease population

In the long-term safety extension study (NCT05218655) monitoring 101 patients with inherited mitochondrial disease, serious adverse events included acute respiratory failure (11 of 101, 10.89 percent), status epilepticus (3 of 101, 2.97 percent), epilepsy (2 of 101, 1.98 percent), seizure (2 of 101, 1.98 percent), respiratory failure (2 of 101, 1.98 percent), and respiratory distress (2 of 101, 1.98 percent) [17]. These events must be interpreted in the context of the severe underlying disease: inherited mitochondrial diseases are progressive, frequently fatal, and associated with high baseline rates of respiratory failure, seizures, and neurological deterioration. Attribution of these events to the study drug versus the underlying disease course is challenging in the absence of a concurrent placebo control.

11.3 Cardiac safety

Dedicated concentration-QTc analysis demonstrated no concentration-dependent QTc prolongation at therapeutic or supratherapeutic vatiquinone doses [27]. The absence of a cardiac electrophysiological signal distinguishes vatiquinone from some other quinone compounds and from the 5-HT₃ antagonist class.

11.4 Hepatic safety

Clinically significant hepatic enzyme elevations have not been reported as a class signal. Standard hepatic monitoring is appropriate during chronic dosing, particularly given the CYP3A4-mediated metabolism.

11.5 Pregnancy and lactation

Reproductive and developmental toxicology data have not been published. Given that vatiquinone has not been approved by any regulatory authority, formal pregnancy and lactation labeling does not exist. Use in pregnant or lactating individuals is not recommended in the absence of reproductive safety data.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five compounds against vatiquinone for the treatment of Friedreich ataxia and related mitochondrial oxidative stress conditions, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five comparators were selected as the principal therapeutic candidates with substantive clinical or preclinical evidence in Friedreich ataxia and mitochondrial disease.

12.1 Omaveloxolone (Skyclarys)

Mechanism: Semisynthetic oleanane triterpenoid activator of the Nrf2 (nuclear factor erythroid 2-related factor 2) transcriptional pathway. Omaveloxolone binds Keap1 (Kelch-like ECH-associated protein 1), the cytoplasmic repressor of Nrf2, releasing Nrf2 to translocate to the nucleus and activate antioxidant response element-driven transcription of glutathione synthesis enzymes, NQO1, heme oxygenase-1, and other cytoprotective proteins [29].

Development trajectory: Developed by Reata Pharmaceuticals (now acquired by Biogen). The MOXIe Phase 2 trial in 103 patients with Friedreich ataxia aged 16 to 40 demonstrated a statistically significant treatment effect on the mFARS total score at 48 weeks (treatment difference -2.40 points, $p = 0.014$) [29]. The FDA approved omaveloxolone (brand name Skyclarys) in February 2023 for Friedreich ataxia in patients aged 16 years and older, making it the first and, as of the monograph revision date, only FDA-approved treatment specifically for Friedreich ataxia [29, 30].

Novelty: Moderate. The Nrf2 activation mechanism is well established but was novel as a therapeutic approach in Friedreich ataxia at the time of development.

Effect size: The MOXIe trial reported a treatment difference of -2.40 points on the mFARS at 48 weeks. Long-term extension data showed that omaveloxolone-treated patients progressed 3 points on the mFARS over 3 years, compared to 6.6 points in matched untreated controls, representing approximately 55 percent slowing of progression [30].

Promising potential: High. The compound is FDA-approved and commercially available. It is the standard of care for Friedreich ataxia in patients aged 16 and older.

Side-effect profile: The principal adverse events are elevated liver transaminases (requiring regular hepatic monitoring), nausea, headache, fatigue, and decreased appetite. Hepatotoxicity risk necessitates periodic liver function testing. The compound carries a black box warning for hepatotoxicity in some prescribing labels [29].

Overall validation: High. The compound has passed the regulatory threshold for approval on the basis of a single positive Phase 2 trial with confirmatory long-term data.

Comparison to vatiquinone: Omaveloxolone achieved FDA approval with a statistically significant primary endpoint at 48 weeks in a smaller trial (103 patients), whereas vatiquinone failed its primary endpoint in a larger trial (143 patients) at 72 weeks. The mFARS treatment differences are of similar magnitude (omaveloxolone -2.40 at 48 weeks, vatiquinone -1.61 at 72 weeks, with the vatiquinone completers analysis showing a larger effect). The mechanisms are complementary: omaveloxolone activates Nrf2 to upregulate endogenous antioxidant defenses (including NQO1, which bioactivates vatiquinone), while vatiquinone directly inhibits the ferroptotic effector enzyme 15-LO. The combination has not been studied but is pharmacologically rational.

12.2 Idebenone

Mechanism: Short-chain synthetic analog of coenzyme Q10 (2,3-dimethoxy-5-methyl-6-(10-hydroxydecyl)-1,4-benzoquinone). Functions as a lipid-soluble antioxidant and mitochondrial electron carrier, shuttling electrons from complex I and complex II to complex III in the respiratory chain [31].

Development trajectory: Studied extensively in Friedreich ataxia, Leber hereditary optic neuropathy, Alzheimer's disease, and Duchenne muscular dystrophy. The MICONOS Phase 3 trial in 232 patients with Friedreich ataxia failed to meet its primary endpoint (change in International Cooperative Ataxia Rating Scale score at 12 months). A Cochrane systematic review concluded that the evidence for idebenone in Friedreich ataxia is insufficient to support clinical use [31, 32]. Idebenone is ap-

proved in the European Union for Leber hereditary optic neuropathy (brand name Raxone, Santhera Pharmaceuticals) but is not approved in the United States for any indication and is not approved anywhere specifically for Friedreich ataxia.

Novelty: Low. Coenzyme Q analogs are a well-established class with decades of clinical investigation.

Effect size: The MICONOS trial showed no significant effect on the primary endpoint. Subset analyses suggested possible benefit in non-ambulatory and cardiomyopathy subgroups, but these did not survive correction for multiplicity [32].

Promising potential: Low for Friedreich ataxia. The Phase 3 failure and the availability of approved alternatives (omaveloxolone) have reduced the clinical development rationale.

Side-effect profile: Generally well tolerated. The principal adverse events are gastrointestinal (nausea, diarrhea) and chromaturia (orange-brown discoloration of urine, cosmetically concerning but clinically insignificant).

Overall validation: Low for Friedreich ataxia; moderate for Leber hereditary optic neuropathy (EU approval).

Comparison to vatiquinone: Idebenone and vatiquinone are both para-benzoquinone compounds, but vatiquinone is 1,000- to 10,000-fold more potent in patient fibroblast assays. Idebenone functions primarily as a stoichiometric electron carrier and radical scavenger, whereas vatiquinone operates through catalytic 15-LO inhibition. Neither compound achieved a positive Phase 3 primary endpoint in Friedreich ataxia. Idebenone has a longer clinical history but a weaker evidence base.

12.3 Coenzyme Q10 (Ubiquinone)

Mechanism: Endogenous lipid-soluble quinone that functions as an obligate electron carrier between complexes I/II and complex III of the mitochondrial respiratory chain and as a membrane-embedded radical-trapping antioxidant [33].

Development trajectory: Studied as a dietary supplement and investigational product in Friedreich ataxia, typically in combination with vitamin E, at high oral doses (400 to 2,400 mg/day). Small open-label and pilot studies have reported mod-

est improvements in cardiac function and some neurological measures, but no randomized controlled trial of adequate size has demonstrated neurological benefit in Friedreich ataxia [33, 34].

Novelty: Low. CoQ10 supplementation has been studied for decades.

Effect size: Modest at best, based on small uncontrolled studies. No Phase 3 neurological efficacy demonstration.

Promising potential: Low as a monotherapy for Friedreich ataxia. Potential role as an adjunctive therapy.

Side-effect profile: Excellent. CoQ10 is well tolerated at high doses with minimal adverse events (occasional gastrointestinal symptoms). Widely available as a dietary supplement.

Overall validation: Low for Friedreich ataxia neurological endpoints. Moderate for CoQ10 deficiency syndromes (a genetically distinct group of mitochondrial diseases for which CoQ10 replacement is the rational treatment).

Comparison to vatiquinone: CoQ10 and vatiquinone are both quinone compounds that interact with the mitochondrial redox environment, but through distinct mechanisms. Vatiquinone is 1,000- to 10,000-fold more potent in fibroblast cytoprotection assays. CoQ10 has the advantages of excellent tolerability and widespread availability but the disadvantage of limited clinical evidence for neurological benefit in Friedreich ataxia.

12.4 Elamipretide (SS-31, Bendavia, MTP-131)

Mechanism: Mitochondria-targeted tetrapeptide (D-Arg-dimethylTyr-Lys-Phe-NH₂) that binds cardiolipin in the inner mitochondrial membrane, stabilizing the electron transport chain complexes and reducing electron leak and reactive oxygen species generation [35].

Development trajectory: Stealth BioTherapeutics developed elamipretide for multiple mitochondrial diseases and heart failure. A Phase 2 open-label study in Barth syndrome (a cardiolipin deficiency disease) produced FDA approval under the accelerated approval pathway (brand name Elamipretide, 2024). Trials in primary mitochondrial myopathy (MMPOWER Phase 3) failed to meet primary endpoints. A trial in Friedreich ataxia has been initiated [35, 36].

Novelty: High. The mitochondria-targeted peptide approach is mechanistically distinct from quinone-based therapies.

Effect size: Variable across indications. Positive in Barth syndrome (accelerated approval); negative in primary mitochondrial myopathy Phase 3.

Promising potential: Moderate for Friedreich ataxia. The Friedreich ataxia trial is in progress; efficacy data are pending.

Side-effect profile: Generally well tolerated. The principal adverse event is injection-site reaction (subcutaneous administration). Systemic adverse events have been mild.

Overall validation: Moderate. FDA-approved for Barth syndrome under accelerated pathway; Phase 3 failure in primary mitochondrial myopathy tempers enthusiasm.

Comparison to vatiquinone: Elamipretide targets upstream mitochondrial dysfunction (cardiolipin stabilization, electron transport chain optimization), while vatiquinone targets the downstream ferroptotic consequence (15-LO-mediated lipid peroxidation). The mechanisms are complementary. Elamipretide requires subcutaneous injection, whereas vatiquinone is orally bioavailable. Neither has produced a positive Phase 3 primary endpoint in a Friedreich ataxia or broad mitochondrial disease population.

12.5 Nicotinamide riboside

Mechanism: Nicotinamide adenine dinucleotide (NAD⁺) precursor. Oral nicotinamide riboside supplementation increases intracellular NAD⁺ levels, supporting mitochondrial bioenergetics, sirtuin-mediated deacetylation of mitochondrial proteins, and poly(ADP-ribose) polymerase activity for DNA repair [37].

Development trajectory: Studied as a dietary supplement and investigational product in mitochondrial myopathy, Friedreich ataxia, and age-related mitochondrial decline. A Phase 2 trial evaluating the combination of nicotinamide riboside and exercise in Friedreich ataxia is ongoing [37].

Novelty: Moderate. NAD⁺ precursor supplementation is a well-established concept, but the application to Friedreich ataxia is relatively recent.

Effect size: Preliminary. Controlled clinical data in Friedreich ataxia have not been published. Open-label studies in mitochondrial myopathy have reported improvements in mitochondrial biogenesis markers.

Promising potential: Moderate. The ongoing Friedreich ataxia trial and the broad scientific rationale for NAD⁺ repletion in mitochondrial disease support continued investigation.

Side-effect profile: Excellent. Nicotinamide riboside is well tolerated as a dietary supplement with minimal adverse events.

Overall validation: Low. No controlled clinical efficacy data in Friedreich ataxia.

Comparison to vatiquinone: Nicotinamide riboside and vatiquinone operate through entirely different mechanisms (NAD⁺ repletion versus 15-LO inhibition). The combination is theoretically attractive for dual targeting of bioenergetic deficit and ferroptotic cell death. Neither compound has produced a positive Phase 3 result in Friedreich ataxia.

12.6 Comparator summary

The five comparators occupy distinct positions in the Friedreich ataxia and mitochondrial disease therapeutic landscape. **Omaveloxolone** is the only FDA-approved treatment for Friedreich ataxia and represents the current standard of care; it achieved statistical significance on the mFARS primary endpoint in Phase 2 and has supportive long-term data showing approximately 55 percent slowing of progression over 3 years. **Idebenone** is a quinone analog with a negative Phase 3 in Friedreich ataxia and limited current development rationale for this indication. **Coenzyme Q10** is widely available and well tolerated but lacks controlled evidence for neurological benefit. **Elamipretide** is a mechanistically novel mitochondria-targeted peptide with approval in Barth syndrome but pending data in Friedreich ataxia. **Nicotinamide riboside** is an NAD⁺ precursor with an early-stage clinical program.

Vatiquinone occupies a distinctive position in this landscape: it is the most potent quinone-based cytoprotectant in preclinical assays (1,000- to 10,000-fold advantage over CoQ10 and idebenone), the only compound in the panel with a characterized 15-LO inhibitory mechanism that directly addresses ferroptotic cell death, and one of only two compounds (alongside omaveloxolone) to have completed a Phase 3 registration-directed trial in Friedreich ataxia with supportive long-term data

showing 50 percent slowing of disease progression. The primary endpoint failure in MOVE-FA and the subsequent FDA Complete Response Letter are significant setbacks. However, the nominally significant secondary endpoints (Upright Stability subscale, Modified Fatigue Impact Scale), the long-term extension data, the well-characterized mechanism, and the favorable safety profile support continued investigation. The pharmacologically rational combination of vatiquinone with omaveloxolone (Nrf2 activation to upregulate NQO1, enhancing vatiquinone bioactivation) represents an untested but scientifically grounded approach.

The principal practical question for the clinical positioning of vatiquinone is whether PTC Therapeutics will conduct the additional adequate and well-controlled trial stipulated by the FDA CRL and whether such a trial can be designed to demonstrate efficacy in an appropriately enriched population (e.g., younger ambulatory patients for whom the Upright Stability subscale may be the most sensitive endpoint). The compound remains investigational; investigators should obtain current regulatory and development status information before planning research that depends on future clinical supply.

13. References

1. Martinelli D, Catteruccia M, Piemonte F, et al. EPI-743 reverses the progression of the pediatric mitochondrial disease: genetically defined Leigh Syndrome. *Mol Genet Metab.* 2012;107(3):383-388.
2. Enns GM, Kinsman SL, Perlman SL, et al. Initial experience in the treatment of inherited mitochondrial disease with EPI-743. *Mol Genet Metab.* 2012;105(1):91-102.
3. PubChem. Vatiquinone. CID 46184405. National Library of Medicine.
4. Cayman Chemical. Vatiquinone (CAS 1213269-98-7). Product data sheet.
5. Lee JY, et al. Enhanced vatiquinone bioavailability with fatty meals and optimal dosing schedule. *J Clin Pharmacol.* 2026.
6. NCATS Inxight Drugs. Vatiquinone. National Center for Advancing Translational Sciences.
7. New Drug Approvals. Vatiquinone; alpha-tocotrienol quinone. [NewDrugApprovals.org](https://www.fda.gov/drugs/new-drugs-fda/new-drug-approvals.org).
8. Kahn-Kirby AH, Amagata A, Marier CI, et al. Targeting ferroptosis: a novel therapeutic strategy for the treatment of mitochondrial disease-related epilepsy. *PLoS One.* 2019;14(3):e0214250.
9. Enns GM, Cowan TM. Glutathione as a redox biomarker in mitochondrial disease: implications for therapy. *J Clin Med.* 2017;6(5):50.
10. Sadun AA, Chicani CF, Ross-Cisneros FN, et al. Effect of EPI-743 on the clinical course of the mitochondrial disease Leber hereditary optic neuropathy. *Arch Neurol.* 2012;69(3):331-338.
11. Friedreich's Ataxia Research Alliance. Vatiquinone (PTC-743). FARA Drug Development Pipeline. 2025.
12. PTC Therapeutics. PTC Therapeutics announces topline results from vatiquinone MOVE-FA registration-directed trial. Press release. 2024.

13. MDA Conference 2026. Safety and efficacy of vatiquinone treatment in Friedreich ataxia patients from MOVE-FA: a Phase 3, double-blind, placebo-controlled trial. Abstract.
14. NeurologyLive. Investigational vatiquinone slows Friedreich ataxia disease progression relative to FACOMS natural history cohort. 2025.
15. Rheumatology Advisor. FDA denies approval of vatiquinone for Friedreich ataxia. August 2025.
16. Dumrongprechachan V, et al. Absorption, distribution, metabolism and excretion of ¹⁴C-vatiquinone in rats, dogs, and human subjects. *Xenobiotica*. 2023;53(9):528-541.
17. ClinicalTrials.gov. A safety study for previously treated vatiquinone (PTC743) participants with inherited mitochondrial disease. NCT05218655.
18. Clinical Trials in Mitochondrial Disease: an update on EPI-743. *J Child Neurol*. 2017;32(14):1197-1203.
19. Dinkova-Kostova AT, Talalay P. NAD(P)H:quinone acceptor oxidoreductase 1 (NQO1), a multifunctional antioxidant enzyme and exceptionally versatile cytoprotector. *Arch Biochem Biophys*. 2010;501(1):116-123.
20. Stockwell BR, Friedmann Angeli JP, Bayir H, et al. Ferroptosis: a regulated cell death nexus linking metabolism, redox biology, and disease. *Cell*. 2017;171(2):273-285.
21. Cotticelli MG, Xia S, Lin D, et al. Ferroptosis as a novel therapeutic target for Friedreich's ataxia. *J Pharmacol Exp Ther*. 2019;369(1):47-54.
22. Stokes JC, Bornstein RL, et al. Evaluating the efficacy of vatiquinone in preclinical models of Leigh syndrome and GPX4 deficiency. *Orphanet J Rare Dis*. 2025;20(1):62.
23. Lee JY, et al. Characterizing population pharmacokinetics of vatiquinone in healthy volunteers and patients with Friedreich's ataxia. *J Clin Pharmacol*. 2025.
24. Lee JY, et al. Effect of itraconazole, a CYP3A4 inhibitor, and rifampin, a CYP3A4 inducer, on the pharmacokinetics of vatiquinone. *Clin Pharmacol Drug Dev*. 2024;13(8):901-909.

25. Lee JY, et al. Determination of vatiquinone drug-drug interactions, as CYP450 perpetrator and victim, using physiologically based pharmacokinetic (PBPK) modeling and simulation. *J Clin Pharmacol*. 2025;65(1):89-98.
26. Lee JY, et al. Clinical drug-drug interaction between vatiquinone, a 15-lipoxygenase inhibitor, and rosuvastatin, a breast cancer resistance protein substrate. *Clin Pharmacol Drug Dev*. 2023;12(4):432-439.
27. Lee JY, et al. Lack of concentration-QTc relationship and cardiac risk with vatiquinone therapeutic and suprathreshold doses. *Clin Pharmacol Drug Dev*. 2024;13(10):1189-1196.
28. Haginoya K, et al. Japanese Leigh syndrome case treated with EPI-743. *Brain Dev*. 2018;40(2):145-148.
29. Lynch DR, Chin MP, Delatycki MB, et al. Safety and efficacy of omaveloxolone in Friedreich ataxia (MOXIe study): a randomised, double-blind, placebo-controlled, Phase 2 trial. *Lancet Neurol*. 2021;20(5):339-352.
30. NeurologyLive. Long-term data suggest Friedreich ataxia agent omaveloxolone slows disease progression over 4 years. 2025.
31. Buyse G, Mertens L, Di Salvo G, et al. Idebenone treatment in Friedreich's ataxia: neurological, cardiac, and biochemical monitoring. *Neurology*. 2003;60(10):1679-1681.
32. Cochrane. Does taking medicine help people with Friedreich ataxia? Cochrane systematic review. 2024.
33. Lodi R, Hart PE, Rajagopalan B, et al. Antioxidant treatment improves in vivo cardiac and skeletal muscle bioenergetics in patients with Friedreich's ataxia. *Ann Neurol*. 2001;49(5):590-596.
34. Hart PE, Lodi R, Rajagopalan B, et al. Antioxidant treatment of patients with Friedreich ataxia: four-year follow-up. *Arch Neurol*. 2005;62(4):621-626.
35. Szeto HH. First-in-class cardiolipin-protective compound as a therapeutic agent to restore mitochondrial bioenergetics. *Br J Pharmacol*. 2014;171(8):2029-2050.
36. Stealth BioTherapeutics. Elamipretide clinical development program. Company pipeline. 2025.

37. Katsyuba E, Romani M, Hober D, Auwerx J. NAD⁺ homeostasis in health and disease. *Nat Metab.* 2020;2(1):9-31.
-

This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly. Vatiquinone is not approved by any regulatory authority worldwide as of the monograph revision date. The compound is available as a research-grade preparation; investigators should obtain analytical confirmation of identity and purity on every lot.