CLINICAL PROTOCOL

A RANDOMIZED, PARALLEL-ARM, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY WITH OPEN-LABEL EXTENSION TO ASSESS THE EFFICACY AND SAFETY OF VATIQUINONE FOR THE TREATMENT OF FRIEDREICH ATAXIA (MOVE-FA)

PTC743-NEU-003-FA

21 MAY 2021

VERSION 5.0

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PROTOCOL IDENTIFIERS AND STUDY PERSONNEL

Project Code	PTC743-NEU
International Nonproprietary Name	Vatiquinone
Therapeutic Area	Friedreich Ataxia
PTC Therapeutics Substance Identifier	PTC743/Vatiquinone
IND Number	119220
EudraCT Number	2020-002812-36
Protocol Number	PTC743-NEU-003-FA
Protocol Version	5.0
Protocol Version Date	21 May 2021
Protocol Phase	2b/3
Protocol Title	A Randomized, Parallel-Arm, Double-Blind, Placebo-Controlled Study with Open-Label Extension to Assess the Efficacy and Safety of Vatiquinone for the Treatment of Friedreich Ataxia (MOVE-FA)
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The eSignature page is located on the last page.

PRINCIPAL INVESTIGATOR AGREEMENT AND SIGNATURE

I have read the protocol document and, on behalf of my institution, agree to comply with the protocol and all applicable regulations.

Principal Investigator	**Date**

Institution: _____

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SYNOPSIS

Study Number	PTC743-NEU-003-FA
Name of Investigational Product	Vatiquinone (PTC743)
Title of Study	A Randomized, Parallel-Arm, Double-Blind, Placebo-Controlled Study with Open-Label Extension to Assess the Efficacy and Safety of Vatiquinone for the Treatment of Friedreich Ataxia (MOVE-FA)
Proposed Indication	For the treatment of Friedreich ataxia
Number of Study Sites	Approximately ten sites globally
Trial Phase	Phase 2b/3
Study Objectives	***Primary*** The primary objective of the study is to evaluate the efficacy (using the modified Friedreich Ataxia Rating Scale [mFARS]) and safety of vatiquinone in subjects with Friedreich ataxia (FA). ***Secondary*** • Demonstrate the effects of vatiquinone on activities of daily living as assessed by the FA Rating Scale Activities of Daily Living (FARS-ADL) scale • Demonstrate the effects of vatiquinone on ambulation as assessed by the 1-minute walk test (1MWT) • Demonstrate the effects of vatiquinone on falls as assessed by a fall log ***Exploratory*** • Demonstrate the effects of vatiquinone on speech using Redenlab protocol • Demonstrate the effects of vatiquinone on fatigue as assessed by the Modified Fatigue Impact Scale (MFIS) • Demonstrate the effects of vatiquinone on health status using the EQ-5D-5L • Demonstrate the effects of vatiquinone on the Upright Stability subscale of the mFARS

Study Endpoints	***Primary*** Change from baseline in the mFARS at Week 72 ***Secondary*** Secondary endpoints will include change from baseline in the following assessments at Week 72: • FARS-ADL scale (key secondary endpoint) • 1MWT • Fall log ***Exploratory*** Exploratory endpoints will include change from baseline in the following assessments at Week 72: • Speech using Redenlab protocol • MFIS • EQ-5D-5L • Upright Stability subscale of the mFARS
Study Population	Subjects with FA aged 7 years and older
Sample Size	Based on the Phase 2 Study EPI-2010-006 data, vatiquinone demonstrated a change from baseline in mFARS score for 400 mg dose of -1.31 after 18 months of treatment, and natural history showed an estimated increase of 3.26 after 18 month of disease progression (Patel 2016). Assuming a common standard deviation of 6.76, with 1-sided type I error of 2.5% and 90% power, 47 subjects per group are required to detect a treatment difference of -4.57 in mFARS score. Assuming a dropout rate of 10%, a total of 106 subjects between 7 and 21 years of age will be randomized. The primary efficacy analysis will be based on change from baseline in mFARS score of subjects between 7 and 21 years old. In order to explore the treatment efficacy and safety, approximately an additional 20 subjects >21 years of age will be randomized for a total of approximately 126 subjects.

Methodology/ Study Design	This study will be a stratified, randomized, parallel-arm, double-blind, placebo-controlled trial. Stratification factors include baseline mFARS score (<40 versus ≥40), age of disease onset (<14 years versus ≥14 years old), and age at screening (≤21 versus >21 years old). Subjects will be randomized 1:1 to receive either vatiquinone or placebo using interactive response technology (IRT). Following completion of the randomized, double-blind, placebo-controlled phase (72 weeks), subjects will enter into an open-label (24 weeks) extension phase during which they will receive open-label treatment with vatiquinone. For subjects entering the extension phase who initially received vatiquinone, they will continue to receive the same dose of vatiquinone (unless there has been a change in weight of ±5 kg from the 25 kg dosing determination threshold or the subject's age changes from 11 to 12 years). For subjects entering the extension phase who initially received placebo, the dose of vatiquinone will be determined based on age and weight as described in the Study Treatment description below. The maximum duration of subject treatment will be 96 weeks (including the placebo-controlled phase and the extension phase). The overall study duration will be a maximum of approximately 106 weeks per subject. Subjects who complete the study may have the option to enter an open-label expanded access program to continue receiving vatiquinone.

Inclusion Criteria	1. mFARS ≥20 to ≤70 at baseline 2. Minimum age 7 years at the time of Screening Visit 3. Must be able to ambulate at least 10 feet in one minute with or without assistance (non-wheelchair) 4. Friedreich ataxia diagnosis (homozygous for guanine-adenine-adenine [GAA] repeat expansion in intron-1 of frataxin gene), confirmed by clinical genetic testing (Note: size of GAA repeat is not required for eligibility) 5. Consent to comply with study procedures. For subjects under the age of 18 (or age of consent), parent(s)/legal guardian(s) of the subject must agree to comply with the requirements of the study, including the need for frequent and prolonged follow-up; parent(s)/legal guardian(s) with custody of the subject must give their consent for subject to enroll in the study. 6. Difference in the mFARS between Screening and Baseline of no more than 4 points 7. Must be able to abstain from anticoagulants and any aspirin (including 81 mg) for 30 days prior to the Baseline Visit and for the duration of the study; any possible discontinuation of anticoagulants should be monitored and indicated by a specialist (eg, cardiologist, neurologist, or hematologist), and discontinuation will be noted by the prescribing physician (see Appendix 1). 8. Must be able to abstain from potent cytochrome P450 (CYP) 3A4 inducers/inhibitors (eg, ketoconazole, rifampin, St. John's wort, grapefruit juice or any grapefruit product) for at least 30 days prior to enrollment (see Appendix 1) 9. Must be able to swallow capsules 10. Males and females of childbearing potential must be willing to use an effective method of contraception (eg, implants, injectables, transdermal patch, combined oral contraceptives, barrier methods, and intrauterine devices) from the time consent is signed until 30 days after last dose of study drug or early termination visit. Male subjects must agree not to donate sperm during the study and for at least 30 days after the last dose of study drug or early termination visit. Note: Double-barrier method (ie, condom with spermicide) is required if no other methods of contraception are in use.

Exclusion Criteria	1. Individuals with clinical diagnosis of FA who have point mutations, deletions, or other non-GAA expansion mutations 2. Previous treatment with vatiquinone 3. Allergy to vatiquinone, sesame oil, gelatin (bovine and/or porcine), titanium dioxide, or red iron oxide 4. Ejection fraction <50% 5. Uncontrolled diabetes (HbA1c >7.0%) at the time of screening 6. Has current suicidal ideation based on Columbia-Suicide Severity Rating Scale (C-SSRS) within 3 months prior to screening or between screening and baseline at the Baseline Visit or suicidal behavior within the last year at the Screening Visit or between screening and baseline at the Baseline Visit. 7. Pregnant or lactating subjects or those sexually active subjects who are unwilling to comply with proper birth control methods; females of childbearing potential must have a negative pregnancy test at Screening and during the Baseline Visit 8. Aspartate aminotransferase or alanine aminotransferase ≥2×upper limit of normal (ULN) at time of screening 9. International normalized ratio ≥1.5×ULN at time of screening or clinically significant bleeding, as determined by the investigator 10. Serum creatinine ≥1.5×ULN at time of screening 11. Comorbidities that may confound study results (eg, fat malabsorption syndrome, other mitochondrial disorder) in the opinion of the investigator 12. Participation in any other interventional clinical trial or received any investigational drug in any other clinical trial within 60 days prior to the Baseline Visit. Subjects may be rescreened after the exclusionary period of 60 days has passed. 13. Concomitant use of interventional CoQ10, vitamin E, or any approved or non-approved medication for FA within 30 days prior to the Screening Visit (see Appendix 1). These prohibited medications can be discontinued at the Screening Visit; if this is the case, the mFARS assessment must be repeated to confirm inclusion eligibility after a minimum of 30 days post discontinuation, and there must be no more than a 4-point difference in mFARS assessed from the Post-Discontinuation Visit to the Baseline Visit. 14. Illicit drug use 30 days prior to screening and during the study is prohibited.

Study Treatment	Subjects meeting eligibility criteria will be randomized 1:1 to receive either vatiquinone or matching placebo during the placebo-controlled phase of the study. • Subjects will receive vatiquinone at a dose of 200 or 400 mg three times daily (tid). If randomized to vatiquinone, subjects will receive a dose of either 200 mg orally (PO) tid if <12 years of age and weighing <25 kg or 400 mg PO tid if ≥12 years of age and/or ≥25 kg. If randomized to placebo, subjects will receive placebo PO tid. Drug dosing will occur according to the schedule described under the placebo-controlled and long-term phases. Food with at least 25% fat (eg, yogurt, ice cream) is required for appropriate absorption of vatiquinone from the gastrointestinal tract. **Study Drug Description**: • Vatiquinone is manufactured as a 200 mg capsule (size 1 Swedish orange) unit dose for oral administration and is packaged in 97 count white high-density polyethylene (HDPE) bottles with a child resistant closure. Each bottle of 97 vatiquinone 200 mg capsules is enough for approximately one month when dosing 200 mg tid or approximately two weeks when dosing 400 mg tid. For this study, placebo will consist of a size 1 Swedish orange capsule containing sesame oil National Formulary (NF) and a colorant to match the appearance of both the capsule exterior and the contents of the vatiquinone 200 mg capsule. Blister packs may be approved for use in the open-label extension phase of the study.
Treatment Duration	Study duration will be approximately 106 weeks; 6 weeks at Screening; 72 weeks of double-blind, placebo-controlled treatment; 24 weeks of open-label extension treatment; and approximately 4 weeks posttreatment follow-up.
Safety Monitoring	Safety will be evaluated by physical examinations, vital signs assessments, echocardiograms, 12-lead electrocardiograms, routine clinical laboratory tests (including blood chemistry, hematology, and coagulation), and adverse event (AE) assessments from baseline through study completion. Suicide risk assessment will be performed throughout the study using the C-SSRS.
Serious Adverse Event Reporting	All serious adverse events (SAEs) should be reported via the SAE report form to PTC Therapeutics within 24 hours of becoming aware of the event(s).
Pharmacokinetic Sampling	Pharmacokinetic (PK) sampling will take place during each clinic visit from Baseline through the placebo-controlled phase just prior to the morning dose and >1 hour after the morning dose. PK sampling will take place just prior to the morning dose during all clinic visits in the open-label extension phase.

Statistical Methods	The primary efficacy variable is change from baseline to Week 72 in mFARS neurological exam score. Baseline of mFARS is defined as the mFARS score recorded before subject has received randomized study medication. The primary estimand is the treatment difference between vatiquinone and placebo in change from baseline to Week 72 in mFARS score attributable to the initially randomized treatment for randomized subjects who received at least 1 dose of study medication and between 7 and 21 years of age at screening. Missing mFARS score will be imputed as described below to form a complete set for analysis. Intermittent missing mFARS scores will be imputed using Monte Carlo Markov Chain (MCMC) method with adjustment for covariates (for example, but not limited to, treatment group, age, region, gender) to produce 5 monotone missing pattern datasets first. Missing data after dropout will be imputed assuming missing not at random using pattern mixture complete case missing value pattern. Approximately 1000 complete data sets will be produced. The change from baseline at each visit will be calculated using the completed data sets for analysis. The primary efficacy analysis will be performed for subjects between 7 and 21 years of age at screening, and will compare change from baseline in mFARS neurological score to Week 72 between vatiquinone- and placebo-treated subjects using mixed model repeated measure (MMRM) stratified by baseline mFARS score (<40 and ≥40) and age of disease onset (<14 and ≥14 years), with treatment and region as the main effects and baseline mFARS and age as covariates using an unstructured variance-covariance matrix structure. If the model fails to converge, other variance-covariance structure will be explored. The test will be performed using one-sided type I error of 2.5%. The results of MMRM analysis from each complete imputed dataset will be combined using Rubin's rule (Little 2002). Detail of the imputation will be specified in the Statistical Analysis Plan (SAP). Analysis in mFARS change from baseline to Week 72 in all subjects will be considered secondary analysis and will be described in the SAP.

Timing of Assessments	After subjects complete the baseline procedures on Day 1 and are eligible to be randomized, site staff will utilize an IRT to randomize each subject. Randomization will be 1:1 vatiquinone to placebo. During the Baseline Visit, subjects will be randomized to receive vatiquinone or matching placebo administered tid for 72 weeks (ie, the placebo-controlled phase). During the placebo-controlled phase, clinic visits will occur at Weeks 12, 24, 36, 48, 60, and 72 (±1 week), and study site staff will perform telephone assessments for AEs/SAEs and concomitant medications on Weeks 4, 8, 16, 20, 28, 32, 40, 44, 52, 56, 64, and 68. Following the 72-week placebo-controlled phase, subjects will enter into a 24-week open-label treatment phase with vatiquinone 200 mg or 400 mg tid. For subjects randomized to vatiquinone in the double-blind portion of the study, they will continue to receive the same dose of vatiquinone (unless there has been a change in weight of ±5 kg from the 25 kg dosing determination threshold or a change in age from 11 to 12 years). For subjects entering the open-label extension phase who initially received placebo, the dose of vatiquinone will be determined based on age and weight as outlined in the Study Treatment section above. In the open-label extension phase, in-person visits will occur every 12 weeks (±2 weeks) and there will be every 6 week (±2 weeks) telephone contact with the subject in between the in-person visits as measured from Baseline Visit date.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialized Term	Explanation
15-HpETE	15-Hydroperoxyeicosatetraenoic acid
15-LO	15-Lipoxygenase
1MWT	1-Minute walk test
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC_{0-8h}	Area under the plasma concentration-time curve from time zero to 8 hours
AUC_{0-24}	Area under the plasma concentration-time curve from time zero to 24 hours
bid	Twice daily
BSO	L-buthionine sulfoximine
BUN	Blood urea nitrogen
C_{max}	Maximum observed (plasma) concentration
CBC	Complete blood count
CFR	Code of Federal Regulations
CNS	Central nervous system
CO_2	Carbon dioxide
COVID-19	Coronavirus disease 2019
CS	Clinically significant
CTC	Common Terminology Criteria
CRO	Contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DSMB	Data Safety Monitoring Board
EC_{50}	Half maximal effective concentration
ECG	Electrocardiogram
eCRF	Electronic case report form
EQ-5D-5L	A self-assessed, health-related, quality of life questionnaire developed by the EuroQol Research Foundation
FA	Friedreich ataxia
FAC	Ferric ammonium citrate
FARS	Friedreich Ataxia Rating Scale
FARS-ADL	Friedreich Ataxia Rating Scale Activities of Daily Living
FAS	Full analysis set
FDA	Food and Drug Administration
FXN	Frataxin
GAA	Guanine-adenine-adenine
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practices
Gpx4	Glutathione peroxidase 4
GSH	Glutathione
HCG	Human chorionic gonadotropin
HDPE	High-density polyethylene
ICF	Informed consent form
ICH	International Council for Harmonisation
ID	Identification
IEC	Institutional Ethics Committee
IND	Investigational new drug application

Abbreviation or Specialized Term	Explanation
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive response technology
ITT	Intent-to-treat
LDH	Lactate dehydrogenase
MCMC	Monte Carlo Markov Chain
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mFARS	Modified Friedreich Ataxia Rating Scale
MFIS	Modified Fatigue Impact Scale
mITT	Modified intent-to-treat
MMRM	Mixed model repeated measure
NCS	Not clinically significant
NF	National Formulary
NOAEL	No-observed-adverse-effect level
Nrf2	Nuclear factor erythroid 2–related factor 2
OTC	Over-the-counter
PK	Pharmacokinetic
PO	Orally
PT	Preferred Term
PTC743	Vatiquinone
PTT	Partial thromboplastin time
PUFA	Polyunsaturated fatty acid
RBC	Red blood cell
RSI	Reference Safety Information
RSL3	RAS-selective lethal
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SEM	Standard error of the mean
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
tid	Three times daily
ULN	Upper limit of normal
USP	United States Pharmacopeia
WHO	World Health Organization
WOCBP	Women of childbearing potential
xCT	Cystine/glutamate antiporter

1. INTRODUCTION

PTC743 (vatiquinone) is a novel small molecule therapeutic in development for the treatment of mitochondrial disease and associated disorders of oxidative stress and inflammation. Vatiquinone targets oxidoreductase enzymes essential to inflammation, oxidation, and cell death. To date, vatiquinone has been evaluated for the treatment of mitochondrial diseases and has been demonstrated to improve long-term neurological and neuromuscular function in patients with Friedreich ataxia (FA). The purpose of this study is to evaluate the safety and efficacy of vatiquinone in patients with FA.

1.1. Study Rationale

Friedreich ataxia is an autosomal recessive, neurodegenerative disease that primarily affects the nervous system and heart. The disease was first described by Nicolaus Friedreich in the second half of the nineteenth century. In Western populations, the prevalence of FA varies between 1:20000 and 1:725000. Epidemiological studies gave evidence of a west to east prevalence gradient in Europe with highest levels in the South of France, North of Spain, and Ireland and lowest levels in Scandinavia and Russia. Carrier frequencies vary between 1:55 (North Spain) and 1:336 (Russia). Friedreich ataxia is a debilitating disease that causes severe morbidity and mortality in affected patients. The condition is characterized by progressive gait and limb ataxia, dysarthria, lower limb areflexia, decreased vibration sense, muscular weakness in the legs, and vision loss as well as non-neurological sequelae including hypertrophic cardiomyopathy and diabetes mellitus. Nearly all patients become paraplegic and eventually require wheelchairs. Typical disease onset occurs during puberty; however, both early-onset and late-onset variants exist and median age of death is 36.5 years. Currently, there are no approved treatments for FA in the United States or Europe (Burk 2017, Cook 2017).

More than 95 percent of patients are homozygous for a large expansion (60 to 1300) of a guanine-adenine-adenine (GAA) trinucleotide-repeat sequence located within the first intron of the gene for frataxin (FXN) on chromosome 9q21.21. The mutation causes a defect in transcription of the FXN protein, a 210-amino acid protein found in the mitochondria (Bencze 2006). Although there is a large body of literature on FXN, the precise mechanism of action underlying its function remains elusive. Because of the mitochondrial localization of FXN and significant role in mitochondrial enzyme integrity, the neurological and cardiac pathologies observed in FA result from mitochondrial dysfunction; hence, FA can be classified as a mitochondrial disease (Burk 2017).

In common with other inherited disorders that affect mitochondrial function, FA patients demonstrate biochemistry consistent with high levels of oxidative stress and glutathione (GSH) depletion (Piemonte 2001).

Recently, 15-lipoxygenase (15-LO) and ferroptosis, which regulate lipid oxidation and GSH levels, have been demonstrated to be important in the pathogenesis of FA (Seiler 2008, Cotticelli 2019). Ferroptosis was first described as a necrotic cell death pathway, triggered by iron and lipid peroxide accumulation, which causes morphologic and biochemical changes distinct from apoptosis and other necrotic pathways (Dixon 2012). By regulating the production of lipid peroxides, 15-LO is the key enzyme governor of ferroptosis (Shintoku 2017, Li 2018). Agents that target ferroptosis have been shown to be protective in various models of FA (Cotticelli 2019).

Therefore, the development of vatiquinone for the treatment of FA is based on the following:

- Vatiquinone mechanism of action: Vatiquinone targets 15-LO, a key regulator of ferroptosis and inflammation.
- Ferroptosis and FA: Oxidative stress inflammation, and specifically the products of 15-LO, have been demonstrated to be fundamental biochemical mechanisms underpinning FA pathogenesis.
- Vatiquinone in vitro validation: Vatiquinone is a potent rescue agent of patient cells in an in vitro ferroptosis test system mimicking FA.
- Clinical effect recorded in patients with FA

1.2. Name and Description of Investigational Product

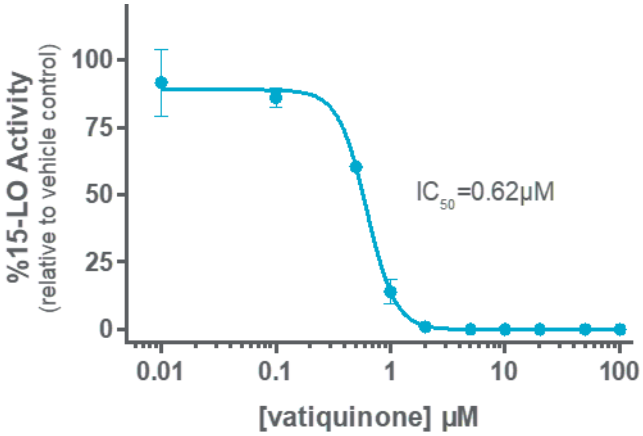
Vatiquinone is 2-[(3R,6E,10E)-3-hydroxy-3,7,11,15-tetramethyl-6,10,14-hexadecatrienyl]-3,5,6-trimethyl-2,5-cyclohexadiene-1,4-dione. Vatiquinone is the quinone oxidation product of alpha-tocotrienol, one of the eight naturally occurring forms of vitamin E. Vatiquinone is a viscous yellow oil and will be administered as a mixture with sesame oil National Formulary (NF)/ United States Pharmacopeia (USP) encapsulated in size 1 Swedish orange capsules.

1.3. Vatiquinone Mechanism of Action

Vatiquinone targets oxidoreductase enzymes critical to inflammation, oxidation, and cell death (ferroptosis) which have been shown to be associated with FA pathogenesis.

1. In a cell-free enzymatic assay, it has been demonstrated that vatiquinone dose-dependently inhibits 15-LO enzyme activity (half maximal inhibitory concentration [IC_{50}]=0.6 µM), as shown in Figure 1.

Figure 1: Vatiquinone Dose-Dependent Inhibition of 15-Lipoxygenase



Abbreviations: 15-LO, 15-lipoxygenase; IC_{50}, half maximal inhibitory concentration

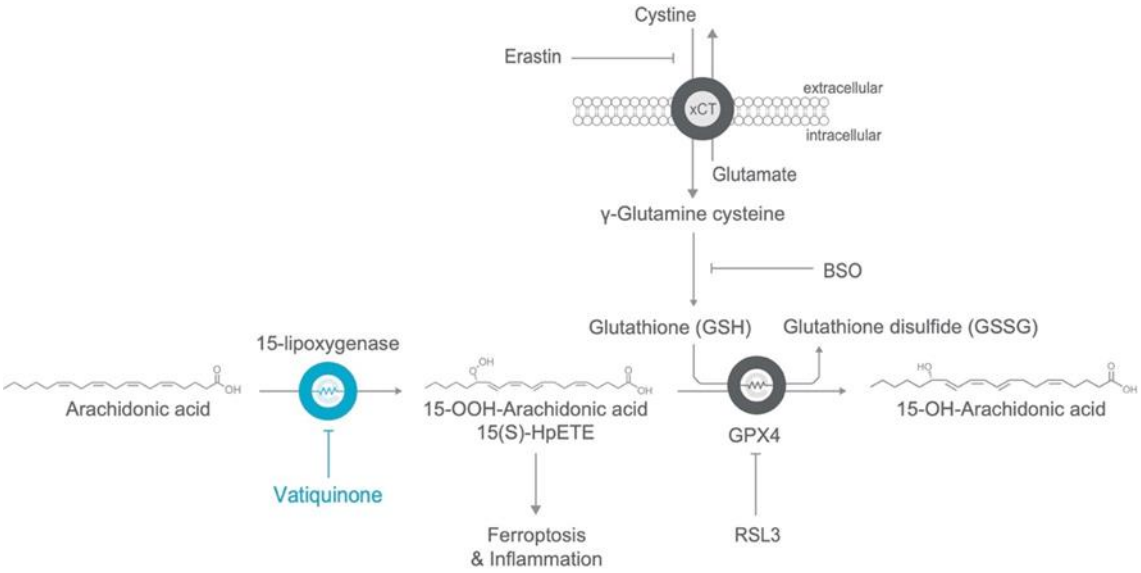
Cell-free 15-LO activity assay: Human 15-LO activity was determined by 15-hydroperoxyeicosatetraenoic acid (15-HpETE) formation, measured by liquid chromatography tandem mass spectrometry (LC-MS/MS). Mean ± standard error of the mean (SEM) from three independent experiments are shown above in Figure 1.

- 15-LO catalyzes the peroxidation of polyunsaturated fatty acids (PUFAs) to produce the lipid hydroperoxide 15-HpETE, a pro-inflammatory and pro-ferroptotic lipid signaling molecule.
- 15-HpETE and downstream metabolites, such as hydroxy-eicosatetraenoic acids (HETEs) and 4-hydroxy-2-nonenal (4-HNE), are clinical biomarkers that have been associated with FA .

Vatiquinone is an inhibitor for the enzyme 15-LO, a key governor of fatty acid oxidation and inflammation that underpin several neurological diseases, including FA.

2. Ferroptosis, the biochemical process regulated by 15-LO, has been demonstrated to be a key mechanism, shown in Figure 2, underpinning FA.

Figure 2: Overview of the Ferroptosis Pathway and Role of 15-Lipoxygenase as a Central Regulator of Lipid Oxidation, Inflammation, Glutathione Depletion, and Cell Death



Abbreviations: BSO, L-buthionine sulfoximine; GSH, glutathione; GSSG, glutathione disulfide; GPX4, glutathione peroxidase 4; HpETE, hydroperoxyeicosatetraenoic acid; RSL3, RAS-selective lethal

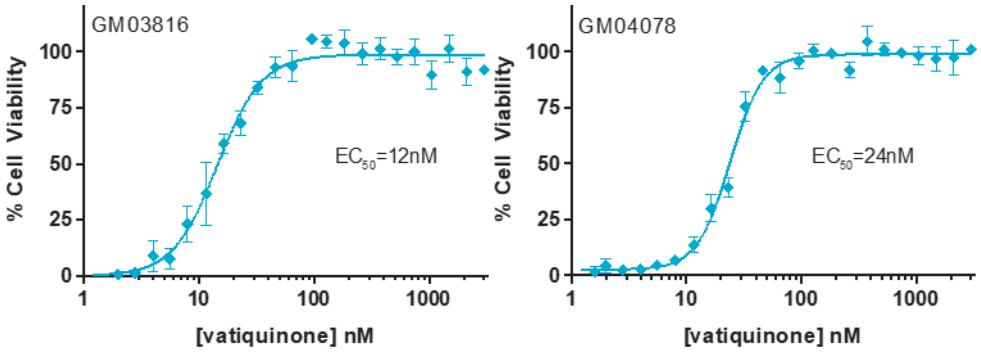
Ferroptosis pathway: Ferroptosis is regulated by 15-LO, and glutathione peroxidase 4 (Gpx4). Activation of 15-LO leads to the production of the lipid signaling molecule 15-OOH-arachindonic acid [15(S)-HpETE]. Gpx4 reduces 15(S)-HpETE to 15-OOH-arachindonic acid preventing inflammation and ferroptosis. Ferroptosis is experimentally induced by inhibition of Gpx4 (RAS-selective lethal [RSL3]), depletion of GSH (erastin or L-buthionine sulfoximine [BSO]) or excess arachidonic acid. Vatiquinone inhibits 15-LO and prevents ferroptosis under the four pro-ferroptotic conditions described above.

- Ferroptosis is a recently described form of regulated cell death (Dixon 2012, Stockwell 2017) mediated by lipid signaling molecules produced by 15-LO (Seiler 2008, Dixon 2012, Friedmann Angeli 2014).

- Under normal conditions, ferroptosis is prevented by the constitutive activity of the selenoenzyme, Gpx4, which utilizes GSH to reduce cellular lipid hydroperoxides (such as 15-HpETE) to their benign secondary alcohols .
- Depletion of cellular GSH, as has been observed in mitochondrial disease (Milder 2012, Enns 2014), including FA patients (Piemonte 2001), or inhibition of Gpx4 leads to the accumulation of 15-HpETE and rapidly induces ferroptotic cell death (Seiler 2008, Yang 2014, Kagan 2017).
- When patient fibroblasts or neuronal cells are depleted of endogenous GSH by an irreversible inhibitor of GSH synthesis (BSO), the result is rapid cell death that can be rescued by 15-LO inhibition (Seiler 2008).
- In biochemical analyses of patients with FA, there is a significant increase in the substrates for 15-LO as well as a decrease in the level of reduced GSH (Piemonte 2001).

3. In vitro validation: Vatiquinone is a potent rescue agent of FA patient cells in an in vitro test system mimicking ferroptosis-related disease pathology.
   - Fibroblasts collected from FA patients are more susceptible to a ferroptosis challenge compared to healthy control fibroblasts (Cotticelli 2019).
   - To determine the potential therapeutic benefit of vatiquinone and 15-LO inhibition, the sponsor developed an in vitro ferroptosis assay employing FA patient primary fibroblasts and Gpx4 inhibition.
   - Inhibition of cellular Gpx4 activity by RSL3, an irreversible small molecule inhibitor (Yang 2014), led to the rapid and nearly-complete death of FA patient fibroblasts.
   - Vatiquinone dose-dependently protected FA patient fibroblasts from RSL3-induced cell death, as shown in Figure 3.

Figure 3: Vatiquinone Rescues Friedreich Ataxia Patient Fibroblasts Following RSL3-Induced Ferroptosis Challenge

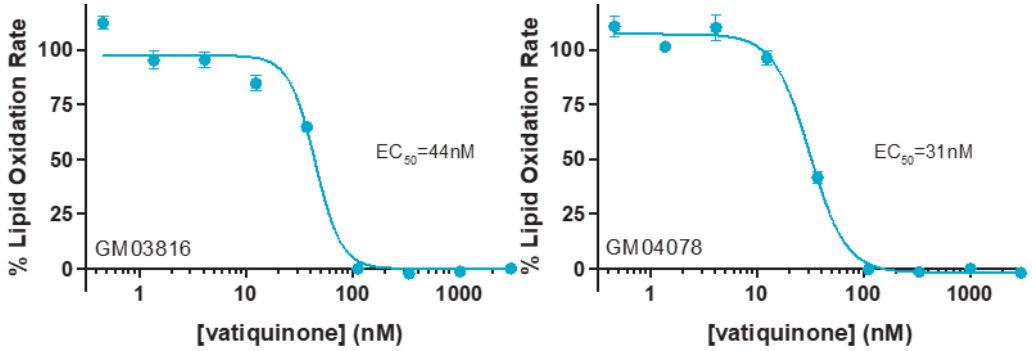


Abbreviations: EC_{50}, half maximal effective concentration; RSL3, RAS-selective lethal

Cell viability assay: Friedreich ataxia fibroblasts from two donors (GM03816-GAA repeats 380,330; GM04078-GAA repeats 541,420) were treated with RSL3 (2 µM) in combination with vatiquinone. Cell viability was assessed 18-hours later by CellTiter-Glo® 2.0 cell viability assay. Mean ± SEM (n=12 fields) from one experiment is shown above in Figure 3 and are representative of 3 independent experiments on two separate days.

- To confirm the mechanism by which vatiquinone protected cells from ferroptosis, it was demonstrated that vatiquinone dose-dependently prevented RSL3-induced formation of oxidized lipid signaling molecules in fibroblasts from two FA patients (measured using the BODIPY 581/591 C11 oxidation-sensitive fluorescent lipid probe) (Figure 4).

Figure 4: Vatiquinone Prevents Lipid Oxidation in Friedreich Ataxia Patient Fibroblasts Following RSL3-Induced Ferroptosis Challenge

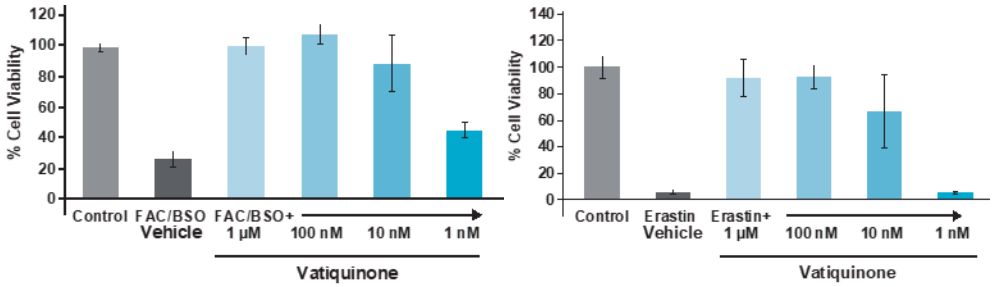


Abbreviations: EC_{50}, half maximal effective concentration; RSL3, RAS-selective lethal

Lipid oxidation assay: Friedreich ataxia fibroblasts from two donors (GM03816-GAA repeats 380,330; GM04078-GAA repeats 541,420) were treated with RSL3 (2 µM) in combination with vatiquinone. The initial (0-5 h) cell lipid oxidation rate was assessed by monitoring green fluorescence of BODIPY C11-labeled cells by quantitative time-lapse microscopy (IncuCyte). Mean ± SEM (n=12 fields) from one experiment is shown above in Figure 4 and are representative of 3 independent experiments on two separate days.

- To further confirm vatiquinone protected cells from ferroptosis, it was demonstrated that vatiquinone protected FA patient cells from ferroptosis induced using two additional approaches: 1) addition of ferric ammonium citrate plus the small molecule inhibitor of GSH synthesis - L-buthionine (S,R)-sulfoximine (BSO), and 2) preventing uptake of the GSH precursor cystine by the small molecule cystine/glutamate anti-porter (xCT) inhibitor erastin (Figure 5).

Figure 5: Vatiquinone Potently Rescues Friedreich Ataxia Patient Fibroblasts Following Two Different Ferroptosis Challenges



Abbreviations: BSO, L-buthionine sulfoximine; FAC, ferric ammonium citrate

Cell viability assay: Friedreich ataxia fibroblasts from a single donor (GM3665-GAA repeats 1357,790) were treated with either ferric ammonium citrate (FAC) and BSO for 48 hours and 24 hours respectively, or with erastin and vatiquinone added 2 hours later. Cell viability was assessed at 48 hours by the Promega® Cell-Glow.

Table 1: Summary of Vatiquinone Ferroptosis Rescue in Friedreich Ataxia Patient Fibroblasts

				Vatiquinone Potency (nM)			
Condition	**Gene**	**Cell ID**	**GAA Repeats**	**RSL3 Survival**	**RSL3 Lipid Oxidation**	**FAC/BSO Survival**	**Erastin Survival**
Friedreich ataxia	FXN	GM3816	380,330	12	44	-	-
Friedreich ataxia	FXN	GM4078	541,420	24	31	19	
Friedreich ataxia	FXN	GM3665	790,1357	-	-	10	10

Abbreviations: BSO, L-buthionine sulfoximine; FAC, ferric ammonium citrate; FXN, frataxin; GAA, guanine-adenine-adenine; ID, identification; RSL3, RAS-selective lethal

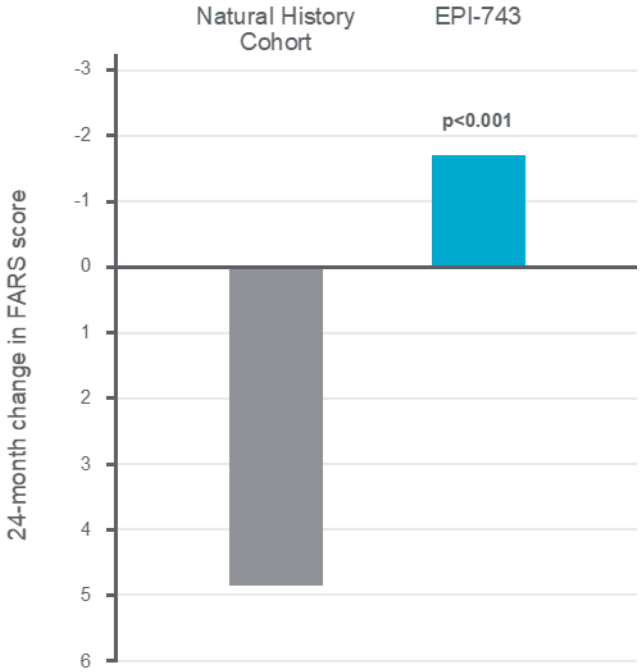
Ferroptosis challenge summary: Friedreich ataxia fibroblasts from FA donors were treated with RSL3 (2 µM) in combination with vatiquinone and cell viability and lipid peroxidation were determined as described above. In the FAC/BSO assay, cells were treated with FAC and BSO for 48 hours and 24 hours, respectively, and vatiquinone was added 2 hours after BSO. Cell viability was assessed at 48 hours by the Promega Cell-Glow. In the erastin assay, cells were treated with erastin and vatiquinone was added 2 hours later. Cell viability was assessed at 48 hours by the Promega Cell-Glow.

- In addition to increased markers of oxidative stress and GSH depletion, fibroblasts from FA patients show an increased sensitivity to pro-oxidant agents, which is thought to result in reduced nuclear factor erythroid 2–related factor 2 (Nrf2) activity (Paupe 2009, Shan 2013). The Nrf2 pathway is one of the major reactive oxygen species scavenging pathways which defends the cells against oxidative stress and regulates mitochondrial metabolism and function (Esteras 2016).
- It was demonstrated that vatiquinone increased the expression and activity of the antioxidant response master regulator Nrf2 in neural stem cells isolated from the embryonic cortex of the Frataxin knockin/knockout mouse.

Collectively, these in vitro mechanism-of-action studies in FA primary fibroblasts establish that vatiquinone potently prevents lipid oxidation and ferroptotic cell death via inhibition of 15-LO, and provides supportive mechanistic rationale for the use of vatiquinone to treat FA patients.

4. Clinical effect: In compassionate use and a Phase 2b study, treatment with vatiquinone was associated with improvement in a number of disease symptoms and an improvement in overall disease progression as assessed by the validated Friedreich Ataxia Rating Scale (FARS).
    - In patients receiving vatiquinone as part of an expanded access protocol, it was demonstrated that vatiquinone treatment resulted in an increase in brain GSH levels in patients with FA (Blankenberg 2012).
    - Supporting the clinical relevance of the target and mechanism-of-action of vatiquinone, increases in brain GSH were linearly correlated to an improvement in disease severity scores in FA patients (Blankenberg 2012).
    - In a Phase 2b clinical trial, posthoc analysis showed that long-term vatiquinone treatment was associated with a significant improvement in neurological function as assessed by the validated FARS scale relative to natural history (Figure 6) (Zesiewicz 2018).

Figure 6: Long-Term Vatiquinone Treatment in Friedreich Ataxia Patients Led to a Significant Reduction in Disease Progression



Phase 2b clinical study: Patients receiving vatiquinone for 24 months demonstrated a significant improvement in the FARS compared to a natural history cohort group matched 2:1 for the following: age, sex, and disease severity. In this posthoc analysis, vatiquinone treatment was associated with a statistically significant improvement in disease severity as assessed by the FARS-Neuro score with evidence of reversal of disease progression (Zesiewicz 2018).

Collectively, clinical studies in FA patients establish that vatiquinone increases brain GSH levels and positively affects disease progression supporting the further clinical development of vatiquinone for FA (Blankenberg 2012, Zesiewicz 2018).

Based on the vatiquinone mechanism of action, the understood biochemical mechanisms underpinning FA, the in vitro evidence of vatiquinone benefit, and clinical data collected to date, there is a valid rationale for the study of vatiquinone in patients with FA.

1.4. Nonclinical Experience with Vatiquinone

Vatiquinone has been evaluated in a comprehensive battery of nonclinical safety and toxicology studies. Vatiquinone is an orally available compound that has been demonstrated in vitro and in vivo to cross the blood-brain-barrier. In 6-month and 9-month repeat-dose toxicity studies in rat and dog, respectively, the no-observed-adverse-effect level (NOAEL) was 30 mg/kg/day, corresponding to Day 180 and Day 273 combined mean maximum observed plasma concentrations (C_{max}) values of 8828 ng/mL (rat) and 12854 ng/mL (dog) and area under the plasma concentration-time curve from time zero to 24 hours (AUC_{0-24}) values of 48786 (rat) and 107426 ng×h/mL (dog). The dose-limiting adverse event (AE) in both rat and dog studies was anticoagulation as demonstrated by prolonged prothrombin time and activated partial thromboplastin time that most likely results from weak vitamin K antagonism exhibited by this class of compounds (Studies 1660-045 and 1660-046).

Vatiquinone was negative in the Good Laboratory Practices (GLP) battery of genotoxicity assays including the bacterial reverse mutation Ames assay, the in vitro micronucleus assay in human peripheral blood lymphocytes, and the in vivo micronucleus assay in rat.

Safety pharmacology data collected in the 28-day toxicity studies in rat and dog and during the 6-month and 9-month toxicity studies in rat and dog, respectively, demonstrated that vatiquinone did not affect neurobehavioral or cardiovascular electrocardiogram (ECG) parameters (Studies 1660-027, 1660-028, 1660-045, and 1660-046). In addition, vatiquinone is not a potent inhibitor of hERG (human ether-à-go-go-related gene) channel current (Study 130416.FEK). Vatiquinone did not influence respiratory function in the rat (Study 1660-032).

Reproductive toxicity studies were conducted in rats and rabbits. A combined fertility study and embryo fetal development study in rat and embryofetal development study in rabbit demonstrated that vatiquinone did not induce reproductive or developmental toxicity at doses up to 100 mg/kg/day in rat and 1000 mg/kg/day in rabbit. There was no evidence of any teratogenic potential at the dose levels tested (Studies 1660-058 and 1660-061).

An in vitro phototoxicity study (Study PTC743-2020-003) conducted in BALB/c 3T3 mouse fibroblasts to assess phototoxic potential demonstrated that vatiquinone had no phototoxic potential.

1.5. Clinical Experience with Vatiquinone

Over 500 patients have been treated with vatiquinone in clinical trials at doses ranging from 50 mg daily to 400 mg tid. Subjects ranged in age from <1 year to 70 years old. The longest exposure has been over 10 years in a pediatric subject with Leigh syndrome (surfeit locus protein 1 [SURF1] variant). There have been seven serious adverse events (SAEs) in 5 subjects deemed possibly related to vatiquinone. One subject experienced three SAEs (pneumonia, tachycardia, and increased unresponsiveness), and SAEs of hypoglycemia, depression, pancreatitis, and neutropenia were experienced by one subject each. Except for the event of neutropenia, these events were all assessed as unlikely related to vatiquinone by the sponsor.

In a 24-month Phase 2b randomized, double-blind and placebo-controlled trial of vatiquinone in adults with FA, 63 participants were enrolled and randomized to receive vatiquinone at a dose of 400 mg tid (n=20), vatiquinone at a dose of 200 mg tid (n=22), or placebo (n=21). The study included a 6-month placebo-controlled phase followed by a 6-month open-label extension phase in which participants initially randomized to placebo were crossed over to vatiquinone treatment (either 200 mg or 400 mg), while participants originally taking the lower or higher dose of vatiquinone continued on those dosing levels. For the last 12 months of the study, all subjects received vatiquinone at a dose of 400 mg tid. There were no drug-related SAEs or dose-limiting toxicities reported. Increased triglycerides were noted in all 3 treatment groups and were assessed as related to the consumption of milk, which was ingested along with study medication to facilitate absorption. The most frequently reported AEs assessed as related to vatiquinone were dysgeusia, increased weight, and dyspepsia, which were reported in fewer than five participants in either treatment group for the entire 24-month study period (Zesiewicz 2018).

No indications of adverse changes in laboratory liver function, renal function, or coagulation tests have been recorded in clinical studies that have been deemed associated with vatiquinone.

1.6. Risk/Benefit Assessment

At the dose levels selected for this study it is not foreseen that subjects will endure any risks greater than minimal. In order to further minimize potential risks, subjects will be frequently monitored for changes in coagulation parameters and other clinical pathology assessments. Administration of study drug will be adjusted or completely stopped if coagulation parameters (prothrombin time, international normalized ratio [INR], partial thromboplastin time [PTT]) are found to be increased to more than 1.5×ULN.

There are no approved treatments available for patients with FA. In addition to improved neurological function, potential benefits may manifest in other specific aspects of disease morbidity such as functional ability.

Based on the available information in Section 1.5, the foreseeable risks and burdens are expected to be low and comparable to those risks and burdens encountered in routine clinical care of pediatric and adult patients with FA.

Subjects will be continually assessed at both in-person visits and by telephone. The frequency of visits and the type of procedures are considered no more burdensome than the standard of care for FA in the pediatric population.

To minimize and oversee risks, investigators are properly trained and experienced in studying the pediatric FA population, including the evaluation and management of potential pediatric adverse events. The investigators are familiar with the background and requirements of the study and with the characteristics and properties of the study drug as described in the Investigator's Brochure.

The principal investigator will ensure the privacy, health, and welfare of the subjects during and after the clinical study, and must ensure that trained personnel are immediately available in case of a medical emergency.

The investigator will conduct a complete physical examination, oversee, and assess the results of the laboratory and further examinations and hold regular conversations with the subject to assess the subject's condition and to collect information about any adverse events and relevant concomitant medication.

2. STUDY OBJECTIVE AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

The primary objective of the study is to evaluate the efficacy (using the modified Friedreich Ataxia Rating Scale [mFARS]) and safety of vatiquinone in subjects with FA.

2.1.2. Secondary Objectives

- Demonstrate the effects of vatiquinone on activities of daily living as assessed by the Friedreich Ataxia Rating Scale Activities of Daily Living (FARS-ADL) scale
- Demonstrate the effects of vatiquinone on ambulation as assessed by the 1-minute walk test (1MWT)
- Demonstrate the effects of vatiquinone on falls as assessed by a fall log

2.1.3. Exploratory Objectives

- Demonstrate the effects of vatiquinone on speech using Redenlab protocol
- Demonstrate the effects of vatiquinone on fatigue as assessed by the Modified Fatigue Impact Scale (MFIS)
- Demonstrate the effects of vatiquinone on health status using the EQ-5D-5L
- Demonstrate the effects of vatiquinone on the Upright Stability subscale of the mFARS

2.2. Endpoints

2.2.1. Primary Endpoint

The primary endpoint will be the change from baseline in the mFARS at Week 72.

2.2.2. Secondary Endpoints

Secondary endpoints will include change from baseline in the following assessments at Week 72.

- FARS-ADL scale (key secondary endpoint)
- 1MWT
- Fall log

2.2.3. Exploratory Endpoints

Exploratory endpoints will include change from baseline in the following assessments at Week 72.

- Speech using Redenlab protocol
- MFIS
- EQ-5D-5L
- Upright Stability subscale of the mFARS

3. STUDY DESIGN

3.1. Overall Design

This study will be a parallel-arm, double-blind, placebo-controlled trial during which subjects will be randomized 1:1 to receive either vatiquinone or placebo using an interactive response technology (IRT) (Figure 7). Subjects will be stratified by mFARS (<40 versus ≥40), age at disease onset (<14 years or ≥14 years), and age at Screening (≤21 years or >21 years). If randomized to vatiquinone, subjects will receive a dose of either 200 mg orally (PO) tid if <12 years of age and weighing <25 kg or 400 mg PO tid if ≥12 years of age and/or ≥25 kg. Weight will be assessed during every clinic visit, and the dose of study drug will be adjusted to 400 mg or down to 200 mg, as applicable, for any change in weight of ±5 kg from the 25 kg dosing determination threshold. The dose will also be adjusted if the subject's age changes from 11 to 12 years. If randomized to placebo, subjects will receive matching placebo tid PO. Following completion of the randomized placebo-controlled phase, subjects will enter into an open-label (24-week) extension phase during which they will receive open-label treatment with vatiquinone at the dose they received in the randomized phase of the study and then a safety follow-up. For subjects entering the extension phase who initially received vatiquinone, they will continue to receive the same dose of vatiquinone (unless there has been a change in weight or a change in age from 11 to 12 years [see Section 3.1.2 and Section 3.1.4]). For subjects entering the extension phase who initially received placebo, the dose of vatiquinone will be determined based on weight as described in Sections 3.1.2 and Section 3.1.4. Body weight will continue to be assessed at each visit during the extension phase and dose will be adjusted accordingly, as above. The maximum duration of subject treatment will be 96 weeks (including placebo-controlled phase and extension phase). The overall study duration will be a maximum of approximately 106 weeks per subject. See the Schedule of Events and Study Parameters in Section 7.1. Subjects who complete the study may have the option to enter an open-label expanded access program to continue receiving vatiquinone.

Figure 7: Study Design

3.1.1. Screening

Screening evaluations will be performed up to 42 days prior to the Baseline Visit. Concomitant use of interventional CoQ10, vitamin E, or any approved or non-approved medication for FA must be washed out for at least 30 days prior to the Screening Visit (see Appendix 1). These prohibited medications can be discontinued at the Screening Visit; if this is the case, the mFARS assessment must be repeated to confirm inclusion eligibility after a minimum of 30 days post discontinuation, and there must be no more than a 4-point difference in mFARS assessed from the Post-Discontinuation Visit to the Baseline Visit for eligibility. The time period between the screening (post-washout, if applicable) and baseline mFARS used for this inclusion criterion determination should occur at least 24 hours apart.

The investigator should inform each prospective subject of the nature of the study, explain the potential risks, and obtain written informed consent from (ICF) the subject or parent(s)/legal guardian(s) prior to performing any study-related screening procedures and prior to the administration of study drug. Subjects who are unable to adhere to the screening time window specified in the protocol due to unforeseen circumstances (eg, Coronavirus disease 2019 [COVID-19]) may repeat the Screening Visit upon Sponsor approval.

3.1.2. Randomization

After subjects complete the baseline procedures on Day 1 and are eligible to be randomized, site staff will utilize IRT to randomize each subject. Randomization will be 1:1 vatiquinone to placebo. Subjects will be stratified by mFARS (<40 versus ≥40), age at disease onset (<14 years or ≥14 years), and age at Screening (≤21 years or >21 years). If randomized to vatiquinone, subjects will receive a dose of either 200 mg PO tid if <12 years of age and weighing <25 kg, or 400 mg PO tid if ≥12 years of age and/or ≥25 kg. The database will be locked for a Week 72 analysis.

3.1.3. Placebo-controlled Phase

Subjects will be randomized to receive vatiquinone at a dose 200 mg or 400 mg tid or matching placebo administered tid for 72 weeks (stratified by mFARS [<40 versus ≥40], age at disease onset [<14 years or ≥14 years], and age at Screening [≤21 years or >21 years]).

During the Baseline Visit, study medication will be dispensed to the subject according to the randomization and age and weight as discussed in Section 3.1. The first dose of study drug will be taken with food with at least 25% fat the same day as the Baseline Visit after all baseline assessments are completed. During the placebo-controlled phase, clinic visits will occur at Weeks 12, 24, 36, 48, 60, and 72; procedures to be performed during these visits are shown in Section 7.1. Study site staff will perform telephone assessments for AEs/SAEs and concomitant medications on Weeks 4, 8, 16, 20, 28, 32, 40, 44, 52, 56, 64, and 68. All visits and telephone assessments during this phase will have a window of ±1 week.

3.1.4. Open-Label Extension Phase (Study Weeks 84 and 96 are in-Person Visits and Study Weeks 78 and 90 are Telephone Contacts ±2 weeks)

Following the 72-week placebo-controlled phase, subjects will enter into a 24-week open-label treatment phase with vatiquinone at a dose of 200 mg or 400 mg tid, the dose level they were assigned in the randomized phase. For subjects entering the extension phase who initially

received vatiquinone, they will continue to receive the same dose of vatiquinone (unless there has been a change in weight as described below). For subjects entering the extension phase who initially received placebo, the dose of vatiquinone will be determined based on weight as described in Section 3.1.2. Weight will be assessed during every clinic visit, and the dose of study drug will be adjusted to 400 mg or down to 200 mg, as applicable, for any change in weight of ±5 kg from the 25 kg dosing determination threshold; the dose will also be adjusted if the subject's age changes from 11 to 12 years. During this phase, subjects and investigators will remain blinded to the treatment received during the placebo-controlled phase.

In-person visits will occur every 12 weeks (±2 weeks), and there will be every 6 weeks (±2 weeks) telephone contact with the subject in between the in-person visits as measured from Baseline Visit date.

3.1.5. Follow-up Period

The follow-up contact will be by telephone and should be completed approximately 30 days (±5 days) post last study drug administration or termination visit, whichever is later. AEs deemed study drug-related and any SAE, whether or not deemed study drug-related, will be followed until normalized or resolved. At the investigator's discretion, an unscheduled office visit and additional tests may be conducted in order to ensure proper follow-up of an AE/SAE. If AEs that occurred during the study need to be followed up, blood samples should be taken per physician's orders.

3.1.6. Unscheduled Visits

If a subject returns to the clinic outside of the normal study visit windows, assessments will be made at the investigator's discretion. All study relevant unscheduled visit assessments will be recorded in the electronic case report form (eCRF) using the supplemental visit eCRF pages.

3.1.7. End of Treatment Visits

End of Treatment Visit takes place at Study Week 96 and includes the assessments listed in Section 7. Subjects who have an ongoing AE at the time of study completion will be followed for up to 30 days, until the event resolves, or until the sponsor and the investigator agree that further follow-up is not medically necessary.

3.1.8. Early Termination Study Visit

Subjects who terminate from the study after receiving first dose and prior to the completion of all scheduled visits should have the End of Treatment Visit assessments completed as soon as possible. The End of Treatment Visit will include the same assessments noted for the Week 96 Visit, as listed in Section 7.1. In the event of early termination from study drug, and unless consent is withdrawn, all visits and safety and efficacy assessments should be continued according to the Schedule of Events and Study Parameters (Section 7.1). Subjects who have an ongoing AE at the time of study completion will be followed for up to 30 days, until the event resolves, or until the sponsor and the investigator agree that further follow-up is not medically necessary.

3.2. Scientific Rationale for Study Design

Friedreich ataxia is a slowly progressive neurodegenerative disorder which affects multiple organ systems in addition to the central nervous system (CNS). Usual onset is during adolescence (mean 15.5 years, standard deviation 8 years) with a typical presenting symptom of unsteadiness of gait. Mean time to loss of independent gait is 8 years, with patients becoming wheelchair-bound after a mean disease duration of 11 to 15 years (Burk 2017). Currently, no medications are available to stop the relentless progression of this disease.

Despite its known slow progression, the progression rate is more rapid in patients with earlier onset and with longer GAA repeat length; of these factors, the age of onset is the stronger predictor (Patel 2016). Despite the mean age of onset of 15.5 years, one-fifth of patients are younger than 5 years at onset (Burk 2017). Given this, and the knowledge that in a progressive neurodegenerative disorder, function that is lost is seldom able to be regained, it is important to intervene early in pediatric patients. The present study will enroll 106 subjects with an age of 7 to 21, inclusive, and approximately 20 subjects over the age of 21 years. Subjects must be able to ambulate at least 10 feet in one minute with or without assistance (non-wheelchair), with an mFARS score of 20 to 70, inclusive. This mFARS range was chosen to avoid ceiling and floor effects, as the score on this scale is heavily determined by ambulatory factors.

Randomized, double-blind, parallel group, placebo-controlled trials are the gold standard for the evaluation of the clinical benefit of an investigational agent. Parallel group design allows recruitment of patients for all treatment arms in the same timeframe. In a disease state that does not have an approved treatment option, such as Friedreich ataxia, the inclusion of a placebo arm does not pose any ethical concerns. In this study, at randomization, subjects will be stratified by 3 factors, including baseline mFARS (<40 or ≥40), age at disease onset (<14 years or ≥14 years), and age at Screening (≤21 years or >21 years). The goal of stratifying by mFARS severity and age of disease onset is to achieve balance between disease severity and progression rate. Although the primary analysis is based on patient ages 7 to 21 years at screening in order to better assess efficacy (faster rate of progression in younger population), there is interest in understanding efficacy and safety of vatiquinone for the population older than 21 years. Therefore, approximately 20 subjects older than 21 years will be randomized. In order to maintain balance between number of subjects randomized to vatiquinone or placebo for both age groups, age at screening of ≤21 versus >21 years is also included as a stratification factor for randomization.

The primary clinical outcome endpoint of mFARS is extensively validated in the FA investigative community. The mFARS may prove superior in more complex studies because it provides a more detailed evaluation of overall patient status and a more complex yet valid construct, with improved psychometric properties when compared to FARS (Rummey 2019).

The present study includes secondary and exploratory clinical outcome endpoints to assess the effect of vatiquinone on subjects' quality of life. Loss of ambulation and dysarthria are key features of this disorder and have a notable impact on quality of life. The 1MWT and fall log directly relate to a subject's ability to ambulate during normal daily activities. The Redenlab speech assessment protocol is a sensitive measure of discrete components of speech ability.

Fatigue is another common finding in FA. Its impact is additive with any underlying neurological dysfunction, further limiting a patient's ability to perform their daily activities. The MFIS is a validated instrument that has been utilized in many neurological disorders, particularly in multiple sclerosis (Meca-Lallana 2019). FARS-ADL and EQ-5D-5L are measurements of activities of daily living and general health status. FARS-ADL, as part of FARS, was specifically designed taking into account the unique challenges of the FA patient. The EQ-5D-5L has been broadly applied to many different patient groups (Devlin 2018). The Upright Stability subscale of the mFARS includes 6 stance-related items (stance with feet apart, stance with feet apart and eyes closed, stance with feet together, stance with feet together and eyes closed, tandem stance, and stance on the dominant foot) as well as sitting posture, tandem walk, and gait. This subscale is thought to quantify disease progression in the early phase of FA (Rummey 2019).

The endpoints in this trial will be evaluated at 72 weeks. This treatment duration was chosen based upon the findings from other clinical trials, including the Phase 2b study of vatiquinone in subjects with FA (Zesiewicz 2018). In a slowly progressive neurodegenerative disorder such as FA, adequate time must be allowed to gauge any differences in progression between drug and placebo groups. Additionally, trials in FA with placebo arms have shown a considerable placebo effect which tends to peak at 12 weeks, and to diminish after approximately 6 months (Lynch 2010, Lynch 2019a). A 24-week open-label extension will follow the initial 72 weeks of treatment to evaluate the long-term safety and efficacy of vatiquinone in FA patients.

In conclusion, PTC Therapeutics (PTC) believes that the design of this trial will allow for safe and robust assessment of vatiquinone in the FA population.

3.3. Justification of Dose

In a study in FA adult patients treated with vatiquinone 200 mg and 400 mg tid (Study EPI-2010-006), the mean C_{max} and the area under the plasma concentration-time curve from time zero to 8 hours ($AUC_{0\text{-}8h}$) at 200 mg were 465.6 ng/mL and 1026.2 ng*h/mL, respectively, whereas the mean C_{max} and $AUC_{0\text{-}8h}$ at 400 mg tid were 1019.0 ng/mL and 2428.4 ng*h/mL, respectively. At steady state (Day 91), $AUC_{0\text{-}8h}$ was 70% to 90% higher than that at Day 1. Following the second daily dose of 200 mg, mean C_{max} reached 450 ng/mL and 471 ng/mL for Day 1 and 91, respectively. Following the second daily dose of 400 mg, the plasma concentration increased substantially higher compared to the first daily dose, both on Days 1 and 91. The mean C_{max} after the second daily dose of 400 mg was 1531 ng/mL and 2109 ng/mL on Days 1 and 91, respectively. The plasma concentration-time profile at the steady state (Day 91) with the lower dose group (200 mg tid) showed that vatiquinone plasma concentration was largely maintained above 100 ng/mL (227 nM) after the morning dose, which exceeded the half maximal effective concentration (EC_{50}) of cell-based assay of vatiquinone rescue of fibroblasts derived from patients with mitochondrial disorders and other disorders of oxidative stress including FA (EC_{50}=24 nM).

In the same clinical study, there were no drug-related SAEs during the course of the study. In addition, there were no drug-related laboratory abnormalities and no dose-limiting toxicities of vatiquinone. The frequency of subjects who experienced any AE was similar by treatment group: 100% (200-mg cohort), 81.8% (200 mg crossed-over cohort), 95.0% (400 mg cohort) and 90.0% (400-mg crossed-over cohort) and 90.5% (placebo). The most frequently reported events among subjects on active treatment were increased weight 32/63 (placebo 6/21), upper respiratory tract infection 23/63 (placebo 5/21), dysgeusia 13/63 (0 placebo), and headache 14/63 (placebo 3/21). Posthoc analysis of the long-term effects of vatiquinone on FA disease progression showed that treatment with vatiquinone was associated with an overall improvement in FARS scores of 1.8, whereas a matched natural history cohort had an overall worsening of 4.8 points over two years ($p<0.01$). These data suggest that long-term treatment with vatiquinone improved overall disease severity as well as slowed disease progression relative to disease natural history.

Collectively, both doses of 200 mg and 400 mg tid were demonstrated to be safe and effective in adults in a Phase 2 study of FA subjects. Clinical studies in other patient populations also showed acceptable safety profile. Therefore, in this Phase 2b/3 study, we propose a dose of 200 mg PO tid if <12 years of age and weighing <25 kg or 400 mg PO tid if ≥12 years of age and/or ≥25 kg.

3.4. End of Study Definition

The end of the study is defined as the last subject's last visit.

4. STUDY POPULATION

4.1. Overview

The study will be conducted at approximately 10 sites globally. Additional sites and investigators may be added as needed to complete the study. An estimated 126 subjects (106 subjects between ages 7 and 21 years and up to 20 subjects greater than 21 years) will be enrolled in the trial.

4.2. Inclusion Criteria

1. mFARS ≥20 to ≤70 at baseline
2. Minimum age 7 years at the time of Screening Visit
3. Must be able to ambulate at least 10 feet in one minute with or without assistance (non-wheelchair)
4. Friedreich ataxia diagnosis (homozygous for GAA repeat expansion in intron-1 of FXN gene), confirmed by clinical testing (Note: size of GAA repeat is not required for eligibility)
5. Consent to comply with study procedures. For subjects under the age of 18 (or age of consent), parent(s)/legal guardian(s) of the subject must agree to comply with the requirements of the study, including the need for frequent and prolonged follow-up; parent(s)/legal guardian(s) with custody of the subject must give their consent for subject to enroll in the study.
6. Difference in the mFARS between screening and baseline of no more than 4 points

7. Must be able to abstain from anticoagulants and any aspirin (including 81 mg) for 30 days prior to the Baseline Visit and for the duration of the study; any possible discontinuation of anticoagulants should be monitored and indicated by a specialist (eg, cardiologist, neurologist, or hematologist) and discontinuation will be noted by the prescribing physician (see Appendix 1).
8. Must be able to abstain from potent cytochrome P450 (CYP) 3A4 inducers/inhibitors (eg, ketoconazole, rifampin, St. John's wort, grapefruit juice or any grapefruit product) for at least 30 days prior to enrollment (see Appendix 1)
9. Must be able to swallow capsules
10. Males and females of childbearing potential must be willing to use an effective method of contraception as defined in protocol Section 7.5.10 from the time consent is signed until 30 days after the last dose of study drug or early termination visit. Male subjects must agree not to donate sperm during the study and for at least 30 days after the last dose of study drug or early termination visit.

4.3. Exclusion Criteria

1. Individuals with clinical diagnosis of FA who have point mutations or deletions or other non-GAA expansion mutations
2. Previous treatment with vatiquinone
3. Allergy to vatiquinone, sesame oil, gelatin (bovine and/or porcine), titanium dioxide, or red iron oxide
4. Ejection fraction <50%
5. Uncontrolled diabetes (HbA1c >7.0%) at the time of screening
6. Has current suicidal ideation based on Columbia-Suicide Severity Rating Scale (C-SSRS) within 3 months prior to screening or between screening and baseline at the Baseline Visit or suicidal behavior within the last year at the Screening Visit or between screening and baseline at the Baseline Visit
7. Pregnant or lactating subjects or those sexually active subjects who are unwilling to comply with proper birth control methods; females of childbearing potential must have a negative pregnancy test at Screening and during the Baseline Visit
8. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥2×ULN at time of screening
9. INR ≥1.5×ULN at time of screening or clinically significant (CS) bleeding, as determined by the investigator
10. Serum creatinine ≥1.5×ULN at time of screening
11. Comorbidities that may confound study results (eg, fat malabsorption syndrome, other mitochondrial disorder) in the opinion of the investigator
12. Participation in any other interventional clinical trial or received any investigational drug in any other clinical trial within 60 days prior to the Baseline Visit. Subjects may be rescreened after the exclusionary period of 60 days has passed.

13. Concomitant use of interventional CoQ10, vitamin E, or any approved or non-approved medication for FA within 30 days prior to the Screening Visit (Appendix 1). These prohibited medications can be discontinued at the Screening Visit; if this is the case, the mFARS assessment must be repeated to confirm inclusion eligibility after a minimum of 30 days post-discontinuation and there must be no more than a 4-point difference in mFARS assessed from the Post-Discontinuation Visit to the Baseline Visit.
14. Illicit drug use 30 days prior to screening and during the study is prohibited.

4.4. Screen Failures

Any subject that does not meet inclusion or exclusion criteria within the defined screening window prior to randomization, will be considered a screen failure.

5. STUDY INTERVENTION

5.1. Study Intervention(s) Administration

5.1.1. Study Intervention Description

Subjects meeting eligibility criteria will be randomized to receive either placebo or vatiquinone during the placebo-controlled phase of the study.

5.1.2. Dosing and Administration

Subjects will receive vatiquinone at a dose of 200 or 400 mg tid (at mealtimes [breakfast, lunch, and dinner]) with food with at least 25% fat. Vatiquinone (or placebo) dosing will occur according to the schedule described under Placebo-controlled and Open-label Extension Phase. A 25% fat meal is required for appropriate absorption of vatiquinone from the gastrointestinal tract. The study drug will be given orally and needs to be followed by eating yogurt, ice cream (no non-fat), or any other food with at least 25% calories from fat. Additional details on dosing can be found in the Pharmacy Manual.

5.1.3. Treatment of Missed Doses and Overdose

If a subject misses the breakfast or lunchtime dose of study drug, the dose may be “made up” up to 2 hours after scheduled. If more than 2 hours have elapsed from the time the missed dose was due, the subject will be required to skip that dose and wait until the next scheduled dose. If a subject misses the third dose (ie, the dinnertime dose), the dose may be made up anytime up until midnight and must be taken with a 25% fat meal requirement.

For this study, any dose of vatiquinone greater than the scheduled daily dose taken within a 24-hour time period (±1 hour) will be considered an overdose. PTC does not recommend specific treatment for an overdose of vatiquinone. The investigator will use clinical judgment to treat any overdose. Any overdose should be reported as an adverse event as described in Section 7.5.8.

5.2. Preparation/Handling/Storage/Accountability

5.2.1. Accountability

Adequate records of study drug receipt and disposition will be maintained by the (institution's) pharmacy records of receipts, investigational drug orders, dispensing records, and disposition forms. The study monitor will also assess drug accountability and will request to review the pharmacy records and investigator study file to assure the study medication is prescribed by the investigator or designee for the purpose of this study.

Subjects should return all used/unused study drug at each in person visit for proper study drug accountability. The Week 72 visit marks the end of the placebo-controlled period, and new study drug will be dispensed for the open-label phase at this visit. At study completion, all used/unused study drug should be returned to the drug depot or destroyed according to the study site's standard operating procedures after site/monitor verifies accountability.

Study medication will be reviewed to assess compliance on an ongoing basis. Subjects who take >80% of the prescribed doses and no more than 110% of the prescribed doses will be considered compliant. Subjects who fall outside of this threshold will be counseled and re-instructed on dosing procedures. Medication compliance will be recorded on the eCRF for each visit.

Vatiquinone will be stored at room temperature below 30ºC. The investigator will ensure that all study drugs are stored and dispensed in accordance with the Food and Drug Administration (FDA) and local regulations concerning the storage and administration of investigational drugs.

5.2.2. Formulation, Appearance, Packaging, and Labeling

Vatiquinone is manufactured as a 200 mg capsule (size 1 Swedish orange) unit dose for oral administration and is packaged in 97 count white high-density polyethylene (HDPE) bottles with a child resistant closure. Each bottle of 97 vatiquinone 200 mg capsules is enough for one month when dosing 200 mg tid or for approximately 2 weeks when dosing 400 mg tid. Therefore, subjects receiving 200 mg tid will receive 3 bottles at each clinic visit, and subjects receiving 400 mg tid will receive 6 bottles at each clinic visit.

The placebo for vatiquinone 200 mg capsules is sesame oil with a colorant that is filled into hard gelatin Swedish orange opaque size 1 capsule shell and sealed with a gelatin banding solution seal identical in appearance to the active drug product. The composition of the placebo capsule excludes the active vatiquinone and includes carotene as a 20% suspension in olive oil (Betatene® 20% OLV) to match the color of the fill solution. During the phase of the study where subjects are to receive placebo, the number of placebo capsules provided to each subject will match those of active received when assigned to vatiquinone treatment.

Each bottle is labeled with the following but not limited to the product name, product lot number, recommended storage conditions, expiration date, and a caution limiting it for Clinical Trial Use Only. Blister packs may be approved for use in the open-label extension phase later in the study.

5.2.3. Preparation

Not applicable

5.3. Measures to Minimize Bias: Randomization and Blinding

Subjects meeting the eligibility criteria for the study will be stratified by baseline mFARS (<40 versus ≥40), age at disease onset (<14 years or ≥14 years), and age at Screening (≤21 years or >21 years) and randomized 1:1 during the Baseline Visit (after completing the Baseline Visit procedures) to either vatiquinone treatment or placebo group associated with the assigned randomization number via IRT, according to a pre-generated randomization schedule that was prepared by an independent third party company. Based on subject's age at Screening and body weight, dose of vatiquinone or placebo will be determined as follows: Subjects <12 years of age and weighing <25 kg will receive vatiquinone 200 mg or matching placebo tid;
Subjects ≥12 years of age and/or ≥25 kg will receive vatiquinone 400 mg or matching placebo tid.

The investigators, study subjects, and sponsor will be blinded as follows: the sponsor will be blinded to the randomized treatment until the study is unblinded after all subjects complete the placebo-controlled phase; subjects and investigators remain blinded to the treatment received during both the placebo-controlled and open-label phases.

The appearance of vatiquinone and placebo are the same and the quantity of drug dispensed are the same as well to keep all parties blinded. Vatiquinone is manufactured as a 200 mg capsule (size 1 Swedish orange) unit dose for oral administration and is packaged in 97 count white HDPE bottles with a child resistant closure. For this study, placebo will consist of a size 1 Swedish orange capsule containing sesame oil NF and a colorant to match vatiquinone 200 mg capsule appearance of both the capsule exterior and contents. During the phase of the study where subjects are to receive placebo, the number of placebo capsules provided to each subject will match the number of capsules of vatiquinone provided to those assigned to vatiquinone treatment.

Under normal circumstances, the blind will not be broken. The appearance of vatiquinone and placebo are the same, as described in Section 5.2.2. The blind may be broken by the principal investigator if specific emergency treatment would be dictated by knowing the medication. In such cases, the Principal Investigator should contact the PTC medical monitor; however, in emergency the investigator may do so and notify the medical monitor.

5.3.1. Instructions for Unblinding

Investigators have the ability to unblind via the IRT. Additional details are provided in the IRT Site User Training presentation.

5.4. Study Intervention and Compliance

This study will be conducted in full accordance with all applicable Federal and local laws and regulations, including 45 Code of Federal Regulations (CFR) 46, 21 CFR Parts 50, 54, 56, 312, and 314 and the Good Clinical Practice: Consolidated Guideline approved by the International Council for Harmonisation (ICH). Any episode of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent and will report adverse events in accordance with site Institutional Review Board (IRB)/Institutional Ethics Committee (IEC) Policies and Procedures and all Federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

5.5. Concomitant Therapy

Any medication taken by a subject 60 days prior to Baseline Visit and during the course of the study and the reason for use of the medication will be recorded on the eCRF. During screening, each subject will be instructed to report the use of any medication to the investigator. Subjects will also be instructed about the importance of not taking any other medication throughout the study (including over-the-counter [OTC] medications) without consulting the investigator.

Subjects should abstain from anticoagulants (eg, enoxaparin, heparin, warfarin, any aspirin [including 81 mg]) for at least 30 days prior to the Baseline Visit and throughout study participation (see Appendix 1). Any possible discontinuation of anticoagulants should be monitored and indicated by a specialist (eg, cardiologist, neurologist, or hematologist), and discontinuation will be noted by the prescribing physician. Ongoing treatment with CYP inhibitors such as ketoconazole or CYP inducers such as rifampin, along with use of St. John's wort extract and/or grapefruit juice or any grapefruit product (see Appendix 1), must be completed at least 30 days prior to enrollment. Concomitant use of interventional CoQ10, vitamin E, or any approved or non-approved medication for FA within 30 days prior to Screening Visit will not be permitted (see Appendix 1). These prohibited medications can be discontinued at the Screening Visit; if this is the case, the mFARS must be repeated to confirm inclusion eligibility after a minimum of 30 days post-discontinuation, and there must be no more than a 4-point difference in mFARS assessed from the Post-Discontinuation Visit to the Baseline Visit. Participation in any other interventional clinical trial or use of any investigational drug in any other clinical trial within 60 days prior to the Baseline Visit will not be permitted. Subjects may repeat the Screening Visit once after the exclusionary period of 60 days has passed.

If considered necessary for the subject's well-being, drugs for concomitant medical conditions or for symptom management may be given at the discretion of the investigator. The decision to authorize the use of any other drug(s) should consider the subject's safety, the medical need, the potential for drug interactions, the possibility for masking symptoms of a more relevant underlying event, and whether use of a concomitant medication will compromise the outcome or integrity of the study. Illicit drug use 30 days prior to screening and during the study is prohibited.

Subjects and parents/caregivers or legal guardian should be instructed about the importance of the need to inform the clinic staff of the use of any drugs or remedies (whether prescribed, OTC, or illicit) before and during the course of the study.

The investigator is encouraged to consult the PTC medical monitor or designee with questions relating to specific drugs and their potential for interactions with PTC743.

5.6. Dose Modification and Stopping Rules

In the event that any subject develops any AE ≥Grade 3 per Common Terminology Criteria for Adverse Events (CTCAE) criteria version 5.0 in severity that is deemed related to treatment with study drug and not related to the underlying disease, the principal investigator should contact PTC's medical monitor to discuss dose modification options up to and including discontinuation of the administration of study drug.

In the event that any subject develops or is diagnosed with an allergy to vatiquinone sesame oil, gelatin (bovine and/or porcine), titanium dioxide, or red iron oxide after initiating treatment with study drug, administration of study drug will be discontinued.

In the event that any subject develops elevated INR ≥Grade 2 in severity (>1.5×ULN) per CTCAE criteria version 5.0 thought to be related to treatment with study drug, administration of study drug will be reduced according to Table 2. Should the INR toxicity not resolve to at least Grade 1 in severity within two weeks of the initial dose reduction, administration of study drug may either be further reduced or discontinued.

Once a subject's dose is reduced due to elevated INR thought to be related to study drug administration, their dose should not be re-escalated.

The investigator is responsible for decisions on dose holds, reductions, or interruptions for any CS AE. The Data Safety Monitoring Board (DSMB) is responsible for determining dose modification or stopping actions for any other safety event.

Table 2: Dose Modification and Stopping Rules for Vatiquinone

Qualifying Event	Example Guidelines for Management		
	Recommendation	**If Resolved To ≤ Grade 1**	**If Not Resolved To ≤Grade 2 After 14 Days**
INR ≥ Grade 2 or >1.5×ULN	If subject on 200 mg tid: Reduce dose by 1/3 from 200 mg tid to 200 mg bid. Re-evaluate 7 days after dose reduction.	Continue on study at 2/3 dose. *Once a subject is dose reduced, do not re-escalate for the duration of study participation.	Consider withdrawing the subject after consultation with the study medical monitor.
	If subject on 400 mg tid: Reduce dose by 1/2 to 200 mg tid. Re-evaluate 7 days after dose reduction.	Continue on study at ½ dose. *Once a subject is dose reduced, do not re-escalate for the duration of study participation.	

Abbreviations: bid, twice daily; INR, international normalized ratio; tid, three times daily; ULN, upper limit of normal

5.6.1. Procedure for Dose Modification

In order to determine that there is an INR (or other laboratory related AE) requiring dose modification, laboratory results classified by the investigator as clinically significant must be provided. In the case of other laboratory related AEs, the investigator will consult with the medical monitor since the protocol does not specify dosing parameters for this. Instructions on reducing the dose in IRT can be found in the IRT manual.

6. STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

6.1. Discontinuation of Study Intervention

Subjects will receive study treatment until protocol specified study completion or treatment discontinuation for one of the reasons listed below. However, subjects may discontinue study treatment or withdraw their consent to participate in the study at any time without prejudice. In the event that a subject discontinues from the study drug prematurely, and unless consent is withdrawn, all efforts must be made to collect efficacy and safety data by completing all study visits according to the Schedule of Events and Study Parameters (Section 7.1).

The following conditions require subject discontinuation from all study treatment:

- At their own request or at the request of their legally authorized representative
- If a subject experiences an AE that is deemed related to treatment with study drug and in the investigator's or the sponsor's medical judgment continuation of treatment would be detrimental to the subject
- At the specific request of a regulatory agency for termination of treatment of an individual subject or all subjects under the protocol
- Subject participation in another clinical study using an investigational agent or investigational medical device
- Refusal of sexually active fertile subjects (excluding subjects who have been sterilized) to use medically accepted methods of contraception
- If a subject becomes pregnant
- Significant noncompliance with the protocol in the opinion of the investigator or the sponsor

The date vatiquinone is discontinued and the reason for discontinuation will be recorded in the source documents and in the eCRF. The PTC medical monitor (and designee) should be informed via e-mail when a subject discontinues study drug.

When vatiquinone is discontinued, the investigator is expected to perform all of the evaluations according to the subject's original schedule and as required at the End of Study Visit and any additional evaluations that may be necessary to ensure that the subject is free of untoward effects.

6.2. Participant Discontinuation/Withdrawal from the Study

In all cases, the reason for withdrawal must be recorded in the eCRF and in the subject's medical records. If the reason is not known, the subject must be followed to establish whether the reason was due to an AE, and, if so, this must be reported in accordance with the procedures in the section entitled Adverse Event Reporting (Section 7.5.8).

Evaluations should be performed on all subjects who participate but do not complete the study according to protocol. Dropouts may be replaced at the request of the sponsor. Subjects who have an ongoing AE at the time of study completion will be followed until the event resolves, or until the sponsor and the investigator agree that further follow-up is not medically necessary.

6.3. Lost to Follow-up

A subject who repeatedly fails to return for scheduled visits and is unable to be contacted by the study site will be considered lost to follow-up.

The investigator will make every effort to contact subjects lost to follow-up.

The following actions should be taken if a subject fails to return to the clinic for a required study visit:

- Attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.

Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to contact the subject. These contact attempts should be documented in the subject's medical record. A minimum of 3 documented telephone contact attempts and 1 certified letter within 6 weeks of the most recent planned study visit must be sent in efforts to contact the subject/caregiver/legal guardian. After being considered lost to follow-up, a subject's status may be changed if the subject/caregiver/legal guardian makes contact at a later time provided the trial is ongoing.

7. STUDY ASSESSMENT AND PROCEDURES

7.1. Schedule of Events and Study Parameters

Study Period	**Screening[1] (Up to 42 days prior to Baseline)**	**Screening visit (for post-discontinuation mFARS)**	**Baseline (Day 1)**	**Placebo-controlled (All visits/contacts ± 1 week)**			**Open-label extension (All visits/contacts ± 2 weeks)**		**Follow-up (approximately 30 days [±5 days] after last dose or early termination visit)**
Study Week				**Weeks 4, 8, 16, 20, 28, 32, 40, 44, 52, 56, 64, & 68 Telephone calls**	**Weeks 12, 24, 36, 48, 60 In-person visits**	**Week 72 In-person visit**	**Weeks 78 and 90 Telephone calls**	**Weeks 84 and 96[2] In-person visits**	
Informed consent	X								
Eligibility assessment and Inclusion/ exclusion criteria	X		X						
Chart review-previous medical history[3] and demographics	X								
Genetic confirmation of Friedreich ataxia diagnosis[4]	X								
12-lead ECG	X		X		X	X		X	
Echocardiogram[5]	X				X	X		X	
Height, weight, oxygen saturation	X[6]		X		X	X		X	
Physical exam[7] and vital signs (Temp, HR, RR, BP)	X		X		X	X		X	
Pregnancy test[8]	X		X		X	X		X	X
Fasting hematology including CBC with differential and coagulation panel[9]	X		X		X	X		X	
Fasting serum chemistry[9, 10]	X		X		X	X		X	
HbA1c	X				X	X		X	
Urine drug screen (10 panel)	X								

Study Period	**Screening[1] (Up to 42 days prior to Baseline)**	**Screening visit (for post-discontinuation mFARS)**	**Baseline (Day 1)**	**Placebo-controlled (All visits/contacts ± 1 week)**			**Open-label extension (All visits/contacts ± 2 weeks)**		**Follow-up (approximately 30 days [±5 days] after last dose or early termination visit)**
Study Week				**Weeks 4, 8, 16, 20, 28, 32, 40, 44, 52, 56, 64, & 68 Telephone calls**	**Weeks 12, 24, 36, 48, 60 In-person visits**	**Week 72 In-person visit**	**Weeks 78 and 90 Telephone calls**	**Weeks 84 and 96[2] In-person visits**	
PK samples[11]			X		X	X		X	
AE/SAE assessment	SAEs only		X	X	X	X	X	X	X[12]
Concomitant medications	X		X	X	X	X	X	X	X
Randomization			X[13]						
Modified Friedreich Ataxia Rating Scale	X[14]	X[14]	X[14]		X	X		X	
One-minute walk test	X		X		X	X		X	
Modified Fatigue Impact Scale			X		X	X		X	
FARS-ADL			X		X	X		X	
EQ-5D-5L			X		X	X		X	
Fall log review					X	X		X	
Speech assessment	X		X		X	X		X	
C-SSRS[15]	X		X		X	X		X	
Train subject/caregiver on fall log completion			X[16, 17]						
Fall log entry[16. 17]			X———						
Vatiquinone (200 mg or 400 mg) or placebo dose PO tid with 25% fat meal			X[18] ———						
Dispense study drug			X[18]		X	X[19]		X	
Drug reconciliation					X	X		X	

Abbreviations: AE, adverse event; BP, blood pressure; CBC, complete blood count; COVID-19, Coronavirus disease 2019; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; FARS-ADL, Friedreich Ataxia Rating Scale Activities of Daily Living; GAA, guanine-adenine-adenine; GGT, gamma-glutamyl transferase; HR, heart rate; ICF, informed consent form; INR, international normalized ratio; LDH, lactate dehydrogenase; mFARS, modified Friedreich Ataxia Rating Scale; PK, pharmacokinetic; PO, by mouth; RR, respiratory rate; SAE, serious adverse event; Temp, temperature; tid, three times daily; wk, week

Note: Clinical lab samples should be collected with pre-dose PK samples to avoid multiple needle sticks. Dosing may occur prior to laboratory results being available.

[1] Screening will be conducted and completed up to 42 days prior to the Baseline Visit for those requiring a washout. Subjects who are unable to adhere to the screening time window specified in the protocol due to unforeseen circumstances (eg, COVID-19) may be rescreened upon Sponsor approval.
[2] The End of Treatment Visit will take place at Week 96.
[3] Fall history will be collected as part of the medical history. A fall log will be maintained as described in Footnote 17.
[4] If previous genetic testing is available, it does not have to be repeated. The size of GAA repeat is not required for eligibility (Section 4.2).
[5] Echocardiogram will take place after completion of all other assessments/procedures on the same day, as applicable, for primary and secondary endpoints. Echocardiogram will be performed at Screening and at the Week 36, Week 72, and Week 96 visits. Unscheduled echocardiograms may be performed at the investigator's discretion; any unscheduled echocardiogram is considered relevant at the investigator's discretion.
[6] Height will only be collected at the Screening Visit. All subsequent visits will collect weight and oxygen saturation.
[7] Physical examinations will include a neurologic assessment. Full physical examination will be performed at Screening, and a targeted examination (including neurologic assessment) may be performed at all subsequent visits.
[8] Female subjects of childbearing potential must have a negative serum pregnancy test at screening; urine pregnancy testing may be performed at all subsequent visits. At-home urine pregnancy test kits will be provided; subjects will be required to perform the test at home ~30 days post last dose of study drug and self-report the results via telephone.
[9] Since subjects may sign the ICF then have screening labs obtained immediately after, subjects may obtain screening hematology and serum chemistry laboratory samples under non-fasting conditions. All subsequent laboratory samples should be obtained under fasting conditions (ie, following an 8-hour fast). Screening laboratory samples will be used for inclusion/exclusion; baseline labs do not need to be resulted prior to the first dose of study drug. Local laboratories may be utilized sparingly for screening laboratory values or for INR follow-up for INR AE.
[10] Serum chemistry will include complete metabolic panel, magnesium, phosphorous, LDH, GGT, and lipid panel.
[11] Pharmacokinetic samples will be collected at each clinic visit starting at the Baseline Visit at 0 hour (immediately prior to the morning dose) and >1 hour following the dose for placebo-controlled visits only. Pre-dose PK samples will be collected at each visit during the open-label extension phase.
[12] The follow-up contact will be by telephone and should be completed approximately 30 days (±5 days) after last study drug administration or termination visit, whichever is later. Data to be followed will be limited to AEs that were deemed study drug-related or any SAE and will be followed until resolution or until they have normalized. At the investigator's discretion, an office visit and additional tests may be conducted in order to ensure proper follow-up of an AE/SAE.
[13] Randomization will occur on the same day as the Baseline Visit.
[14] The Screening and the Baseline mFARS must occur at least 24 hours apart. Subjects may have an additional Screening Visit for mFARS assessment after a minimum of 30-days post-discontinuation of interventional CoQ10, vitamin E, or any approved or non-approved medication for FA. If the subject has already been off of these medications for 30 days at the time of the Screening Visit, then an additional Screening Visit for mFARS will not be required.
[15] C-SSRS will be collected at Screening, Baseline, and during every in-person visit while on study treatment.
[16] During the Baseline Visit, the subject and/or caregiver will be trained on how to capture information in the fall log.
[17] The fall log will capture the date and time of each fall. Falls should be recorded daily by the patient or a live-in caregiver. The daily log should capture how often the patient falls during the day, whether the fall resulted in an injury, any other consequences from the fall (eg, went to the hospital, loss of consciousness), what the person was doing prior to the fall, and who reported the fall (ie, patient, caregiver, or another witness who reported it to the caregiver). Outcomes should assess both frequency of falls and fall severity (eg, falls leading to injury). All falls resulting in injury should be reported as an AE.
[18] First dose for the placebo-controlled phase of the study will be taken in the clinic on the same day as the Baseline Visit after all baseline assessments are completed. Study drug will be dispensed during the Baseline Visit and at each subsequent in-person visit (except for the Week 96 visit). Drug may be delivered via delivery service if needed.
[19] The Week 72 visit marks the end of the placebo-controlled phase; open-label study drug is dispensed at the Week 72 visit. Please remember that subjects are to bring back all used/unused study drug to each in person visit for accountability throughout the study.

7.2. Efficacy Assessments

Primary efficacy will be assessed by the change from baseline to 72 weeks in the mFARS score. Secondary endpoint assessments will include the FARS-ADL scale (key secondary endpoint), 1MWT, and fall log. Exploratory endpoints will include speech fluency, fatigue scale, EQ-5D-5L, and Upright Stability subscale of the mFARS.

The FARS is a disease-specific scale that measures progression of neurological effects of FA, specifically designed for this patient population and used as an outcome measure in several FA clinical trials. The FARS specially assesses FA disease progression when used at 1 and 2 years, following initial evaluation as seen in FA natural history studies (Zesiewicz 2018, Lynch 2019b). The mFARS is a validated and reliable 93-point scale with a Cronbach α=0.92; comprised of the neurologic component of the FARS, evaluating bulbar, upper limb, lower limb, and upright stability/gait function. For each item, responses categorize the corresponding neurological finding, and the findings are assigned a score ranging from 0 to 3, 4, or 5 with 0 being normal and higher numbers indicative of greater impairment. The FARS was converted to the mFARS by removing the peripheral nervous system component and 2 items of the bulbar subscore to improve overall construct and interrater reliability. As a result, subscale correlations and reliability of the mFARS score are improved and the items assessing functional ability are more psychometrically robust .

The FARS-ADL is a subsection of the FARS questionnaire that assesses activities of daily living, including speech, personal hygiene, feeding, and mobility. Subjects rank each category using a scale of 0 to 4, with lower scores indicative of "normal" function/activity.

The 1MWT is a timed performance test used to measure functional ability, walking endurance, balance, and muscle performance by measuring maximal walking speed in 1 minute. Patients are instructed to walk as quickly as possible for 1 minute without running. Maximal walking speed is measured upon completion of the walk and recorded. It has been validated for use in patients with cerebral palsy with similar functional limitations. It exhibits good test-retest reliability and may be a more useful measure of functional mobility, given its shorter length as compared to other tests, such as the 6-minute walk test, in this population (McDowell 2005).

Loss of ambulation is a key feature of FA and has a notable impact on quality of life. The 1MWT and fall log directly relate to a subject's ability to ambulate during normal daily activities. Thus, each subject will be required to maintain a fall log, which will include the date and time of each fall. Falls as defined by World Health Organization, "inadvertently coming to rest on the ground, floor or other lower level, excluding intentional change in position to rest in furniture, wall or other objects," will be reported (WHO 2007). Fall history will be assessed at baseline as part of the medical history and will be recorded daily during the study by the patient or a live-in caregiver. The daily log should capture how often the patient falls during the day, whether the fall resulted in an injury, any other consequences from the fall (eg, went to the hospital, loss of consciousness), what the person was doing prior to the fall, and who reported the fall (ie, patient, caregiver, or another witness who reported it to the caregiver). Outcomes should assess both frequency of falls and fall severity (eg, falls leading to injury). All falls that result in injury should be reported as AEs.

Speech measures may be sensitive to disease progression through the late stages of FA when arm and leg function have declined on the performance tests. Speech evaluations will be performed per the Redenlab protocol, which is described below.

- Speech Agility (syllable repetition): Measures speed and consistency of speech. Participants are required to rapidly and clearly produce repeating consonant-vowel syllabic strings. Testing commences with participants playing an example of the stimuli. On-screen instructions will ask: "Repeat the syllables /pataka/ as quickly and as clearly as possible for 10 seconds". The participant will produce the same task twice. A timer appears on-screen next to the voice meter confirming the recording process. The tester or participant must tap the record and stop button on the screen before and after the task. This test takes approximately 45 seconds for both iterations.
- Prosody Tests (reading, days of the week): Measures vocal control and timing. Tasks vary in linguistic complexity allowing for differentiation of motor/cognitive contribution to speech timing. Participants are asked to complete two speech tasks, including saying the days of the week and reading a standardized passage. All tasks are elicited via on-screen instructions. The days of the week task is repeated twice. This test takes approximately 3 minutes to complete.
- Voice Performance (long vowel): Measures voice quality and phonatory-respiratory support. A picture appears on-screen prior to the task prompting participants to sit up straight, thereby standardizing posture. Participants are prompted to produce two tasks. The first requires participants to complete a maximum phonation task. On-screen instructions ask: "Take a deep breath and say /ah/ for as long as you can". Participants then repeat the task. On-screen instructions then ask: "Say 'ah' for 5 seconds using your best and clearest voice". A timer appears on-screen next to the voice meter confirming the recording process. This test takes approximately 1 minute to complete for all iterations.
- Articulation and timing (picture description, monologue): Measures language performance, speech clarity and timing. Participants are asked to complete one speech task: 1. Unprepared monologue (describing happy story, memory, friends, family etc.). All tasks are elicited via on-screen instructions. The task is elicited once. This test takes approximately 1 to 2 minutes to complete.

Fatigue is another common finding in FA. Its impact is additive with any underlying neurological dysfunction, further limiting a patient's ability to perform their daily activities. The MFIS is a 21-item, reliable, validated instrument that has been utilized in many neurological disorders. It is a modified form of the Fatigue Impact Scale, a component of the Multiple Sclerosis Quality of Life Inventory, with a Cronbach's α=0.90. It assesses fatigue in three Modules as it relates to physical, cognitive, and psychosocial functioning. Higher scores indicate greater impact of fatigue on participant function (Meca-Lallana 2019).

The EQ-5D-5L is a standardized measure of health status. It is comprised of 2 parts. The descriptive portion examines mobility, self-care, usual activities, pain/discomfort, and anxiety/depression and asks the subject to rank each category on a scale of 1, indicating no problem, to 5, indicating extreme problems, with higher values indicating greater problems. The second part of the EQ-5D-5L includes a visual analogue scale, which records the subject's self-rated health on a vertical visual analogue scale with response options including "The best health you can imagine" (score of 100) and "the worst health you can imagine" (score of 0) (Herdman 2011, Devlin 2018). The EQ-5D-5L is the most appropriate utility instrument for FA patients in children aged 7 and above.

The Upright Stability subscale of the mFARS demonstrates a Cronbach α of 0.87 and includes 6 stance-related items (stance with feet apart, stance with feet apart and eyes closed, stance with feet together, stance with feet together and eyes closed, tandem stance, and stance on the dominant foot) as well as sitting posture, tandem walk, and gait. This subscale is thought to quantify disease progression in the early phase of FA (Rummey 2019).

7.3. Pharmacokinetic and/or Other Assessments

Pharmacokinetic (PK) samples will be collected in the placebo-controlled phase at each clinic visit starting at the Baseline Visit at 0 hour (trough; just prior to the morning dose) and >1 hour following the dose. During the open-label extension phase of the study, pre-dose PK samples will be collected at each visit. Subjects will be instructed to refrain from taking their morning dose on clinic visit days; the dose on these days will be taken immediately following pre-dose PK and clinical laboratory collection. The time of dose administration at the night before and in the morning will be recorded (none will be recorded at the Baseline Visit since the first dose of study drug will be taken at this visit). Each dose will be taken with a 25% fat meal requirement.

7.4. Safety Assessments

Safety will be evaluated by physical examinations, vital signs assessments, echocardiograms, 12-lead ECGs, routine clinical laboratory tests (including blood chemistry, hematology, coagulation as described below), and AE assessments from baseline through study completion. SAEs will be collected from the time of obtaining informed consent through the end of the extension phase. Suicide risk assessment will be performed throughout the study using the C-SSRS. The C-SSRS is a semi-structured clinician-rated interview to assess severity of suicidal behavior and ideation in the pediatric, adolescent population in community, clinical, and research settings . The C-SSRS can be administered by any research personnel regardless of degree, as long as they view the C-SSRS training and are issued a training certificate. Sites will follow their internal processes for referrals, if a patient is found to have suicidal ideation based on the results of the C-SSRS throughout the study. There is no indication that the investigational product leads to increased suicidality; however, per FDA guidelines, suicidality should be assessed in studies of drugs with CNS activity (FDA 2012).

If at any time during the treatment phase of the study, in the opinion of the investigator, a finding of an AE precludes continuation of treatment with study drug at the dose level at which the AE was observed, the dose and/or dose regimen for the study drug may be reduced or terminated altogether at the discretion of the investigator. The investigator will consult with sponsor prior to discontinuation of treatment with vatiquinone and the DSMB will be notified of all AEs and SAEs.

7.4.1. Physical Examination, Height, Weight, and Vital Signs

A complete physical examination will be conducted (excluding genital/rectal exam) at the Screening Visit. The physical examination will consist of an examination of the following: neurological assessment and assessments of general appearance, skin, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest, heart, abdomen, and extremities. Targeted physical examinations, including a neurological assessment, will be conducted at all subsequent visits.

Medical history and demographics including age, gender, and race, will be collected at the Screening Visit. Weight (kg) will be measured in ordinary indoor clothing (ie, street clothes, scrubs, etc.) with shoes off. Height will be recorded in centimeters (cm).

If clinically significant findings, as determined by the investigator, are recorded for a particular symptom, sign, or abnormal measurement, that measurement will be repeated at medically appropriate intervals until the value returns to an acceptable range, a specific diagnosis is established, or the condition is otherwise explained.

Vital sign measurements (temperature, pulse rate, blood pressure, and respiration rate) will be obtained in the sitting position (after the subject has been sitting for 5 minutes if the subject is capable of sitting for 5 minutes). Oxygen saturation will be obtained along with all vital sign assessments.

7.4.2. Laboratory Evaluations

Subjects will have approximately 169 mL of blood drawn over the course of the study. This blood volume estimate is based on draw values of approximately 2 mL each for hematology and HbA1c, about 4 mL for chemistries, about 2.7 mL for coagulation panels, and about 4 mL for drug concentrations per sampling; there are 10 scheduled samplings for hematology, coagulation, and chemistry; 9 scheduled samplings for HbA1c; and 16 samplings for PK. The variables discussed below will be collected at various times (according to the Schedule of Events and Study Parameters) to assess safety.

7.4.2.1. Hematology and Coagulation

The following hematology and coagulation values will be collected according to the Schedule of Events and Study Parameters shown in Section 7.1.

- Erythrocytes: red blood cell (RBC) count, hematocrit, hemoglobin, mean corpuscular volume (MCV)
- Leukocytes: white blood cell count and differential (basophils, eosinophils, lymphocytes, monocytes, and neutrophils)
- Platelets: platelet count
- Coagulation: prothrombin time with INR, and PTT

7.4.2.2. Serum Chemistry

The following chemistry values will be collected according to the Schedule of Events and Study Parameters shown in Section 7.1.

- Liver: alkaline phosphatase (ALP), ALT (serum glutamic-pyruvic transaminase [SGPT]), AST (serum glutamic-oxaloacetic transaminase [SGOT]), bilirubin (total, direct), gamma-glutamyl transferase (GGT), and lactic dehydrogenase (LDH)
- Renal: blood urea nitrogen (BUN), and creatinine
- Electrolytes: sodium, potassium, chloride, and carbon dioxide (CO_2), calcium, magnesium, phosphorous
- General: total protein, albumin, glucose
- Lipids: cholesterol (total) and triglycerides
- HbA1c

7.4.2.3. Urine Drug Screen

A 10-panel urine drug test will be collected at the Screening Visit (see the Schedule of Events and Study Parameters shown in Section 7.1).

7.4.3. Urine or Serum Pregnancy Test

Both men and women should be counseled to abstain from sexual activity or use an acceptable method of birth control while participating in this clinical research study and for approximately 30 days after the last dose. Subjects will be required to use effective method of contraception (hormonal or double-barrier method). Female subjects who become pregnant should be immediately discontinued from the study if they have not yet received study drug. If a subject is found to be pregnant after she has received study drug, she should discontinue dosing, complete all end of study procedures, and be followed to determine the outcome of the pregnancy. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. See Section 7.5.11 for rules regarding reporting pregnancies.

Human chorionic gonadotropin (HCG) beta will be measured on all female subjects of childbearing potential at Screening (serum), Baseline (urine), every 12 weeks (urine) throughout the study, and 30 days after the last administration of study drug (urine).

7.4.4. Abnormal Laboratory Findings

Laboratory values will be collected throughout the study to assess for safety. The investigator must review and assess all laboratory results in a timely manner, and determine whether the abnormal laboratory values, if any, are CS or not clinically significant (NCS), and whether there are associated signs and symptoms. Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they are associated with an already reported clinical event will be recorded as AEs.

An abnormal laboratory finding in absence of any other signs or symptoms is not necessarily an AE. If the abnormal laboratory finding is accompanied by signs or symptoms, report the signs and symptoms as the AE in lieu of the abnormal laboratory value. If a diagnosis is available, report the diagnosis. Clinically significant laboratory abnormalities after taking study medication that reflect a meaningful change from the screening value(s) and that require active management are to be considered by the investigator as AEs (eg, abnormalities that require study treatment dose modification, discontinuation, more frequent follow-up assessments, etc.).

Laboratory tests that result in significantly abnormal values should be repeated for verification. Additional tests and other evaluations required to establish the significance or etiology of an abnormal result, or to monitor the course of an AE, should be obtained when clinically indicated. In particular, if a CS abnormal result is observed that is not resolved by the final study visit, repeat tests should be performed to document resolution or stability of the abnormality.

Diagnoses associated with any National Institutes of Health Common Terminology Criteria (CTC) v5.0 Grade 3 or 4 laboratory abnormalities will be recorded as AEs on the eCRF. Repeated and verified laboratory tests that meet at least Grade 3 AE requirements will be reported to the IRB/IEC per institutional requirements. The recorded AEs should indicate the underlying abnormality or diagnosis (eg, renal insufficiency) if known, as opposed to the observed deviation in laboratory results (eg, elevated creatinine). Any additional relevant laboratory results obtained by the investigator during the study will be supplied to the sponsor.

7.5. Adverse Events and Serious Adverse Events

7.5.1. Definition of Adverse Events

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not it is considered related to the drug. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease in a study subject who is administered study drug in this study.

For this protocol, untoward medical occurrences that should be reported as AEs include the following:

- All AEs during the course of treatment with study drug administration
- All AEs resulting from medication misuse, abuse, withdrawal, or overdose, of study drug
- All AEs resulting from medication errors such as dispensing or administration error outside of what is described in the protocol
- Apparently unrelated illnesses, including worsening of a preexisting illness
- Injury or accidents. Note that if a medical condition is known to have caused the injury or accident (a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) should be reported as 2 separate AEs. The outcome of the accident (hip fracture secondary to the fall) should be recorded in source documents.
- Abnormalities in physiological testing or physical examination findings that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test)
- Laboratory or ECG abnormalities that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they are associated with an already reported clinical event. Laboratory abnormalities associated with a clinical event should be captured in the source documents. Laboratory abnormalities not requiring clinical intervention or further investigation will be captured as part of overall laboratory monitoring, and should not be reported as AEs.

- A preexisting condition (eg, allergic rhinitis) must be noted on the appropriate eCRF for Visit 1, but should not be reported as an AE unless the condition worsens, or episodes increase in frequency during the AE reporting period. Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that occurs during the treatment with study drug should be reported as the AE and the resulting appendectomy should be recorded in the source documents and eCRF. If a surgical procedure was planned prior to entry into the study, and the surgery is not performed because of a worsening of a baseline condition, this should not be reported as an AE. Note that, as described in Section 7.5.2 any hospitalization occurring as the consequence of an AE during the study period should be reported as an SAE.

Each AE is to be classified as serious or non-serious by the investigator using medical and scientific judgment.

7.5.2. Definition of Serious Adverse Events

An SAE is an untoward medical occurrence or effect associated with the use of a study drug at any dose, regardless of whether it is considered to be related to the study drug, which results in one of the following:

- Results in death. This includes all deaths on treatment or within 30 days after last study drug administration, including deaths due to disease progression. Any death occurring later than 30 days following the last dose need not be reported as an SAE unless it is a result of an event that started within the period covered by the on-study definition. The reported AE should be the event that caused the death. In addition, any AE resulting in death that occurs subsequent to the AE reporting period and that the investigator assesses as possibly related to the study drug should also be reported as serious.
- Is life-threatening. This refers to an event in which the subject was at risk of death at the time of the event. It does not include an event that, had it occurred in a more severe form, hypothetically might have caused death.
- Requires hospitalization or prolongation of existing hospitalization (excluding hospitalizations for administration of the study drug, procedures required by the study protocol, or treatment-related diagnostic procedures; other planned hospitalizations; or hospitalizations related only to progression of disease). Treatments in the emergency room for procedures such as hydration that do not require admitting the subject to the hospital and observational durations in the emergency room for less than 24 hours do not fall into this category but the event may be serious due to another seriousness criterion.
- Results in persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions.

- Any other medically important event that the investigator or the sponsor judges to be serious or which is defined as serious by the regulatory agency in the local country. These are AEs that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Medical judgment should be exercised in deciding whether an AE is serious based on above definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- A pregnancy resulting in spontaneous abortion, stillbirth, neonatal death, or congenital anomaly (including that in an aborted fetus).

An event need not be reported as an SAE if it exclusively represents an expected change or progression of the disease under study.

Note that any SAEs occurring from the time of informed consent through 30 days following the last dose of study drug should be reported to the sponsor if the investigator becomes aware of them.

7.5.3. Unexpected Adverse Events

The Investigator Brochure contains the Reference Safety Information (RSI) which will be used for assessing expectedness. If an event is not listed in the RSI, it should be considered unexpected or if the AE occurs at a greater severity, specificity, or frequency, it should be considered unexpected.

7.5.4. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject/parent(s)/legal guardian/legally acceptable representative. In addition, each study subject/parent(s)/legal guardian/legally acceptable representative will be questioned about AEs at each scheduled clinic visit after study drug administration or during any telephone contact with the subject/parent(s)/legal guardian/legally acceptable representative. The type of question asked should be open-ended, for example, "*How have you been feeling*?" or a similar type of query.

7.5.5. Recording Non-serious AEs and SAEs

All AEs (both serious and non-serious) that occur in subjects during the AE reporting period must be recorded, whether or not the event is considered drug -related. In addition, any known untoward event that occurs subsequent to the AE reporting period that the investigator assesses as possibly related to the investigational drug/product should also be recorded as an AE.

All AEs are to be recorded in the source documents and on the eCRF using concise medical terminology; whenever possible, terms contained in the Medical Dictionary for Regulatory Activities (MedDRA) should be employed. In addition, the following information should be recorded:

- Indication of whether the event is serious or non-serious (see Section 7.5.2)
- Relationship to study drug (see Section 7.5.6)

- Severity of the event (see Section 7.5.7)
- Onset date
- Resolution date, or date of death
- Action taken
- Outcome of the event

Classification of the event as serious or non-serious determines the reporting procedures to be followed.

7.5.6. Describing Adverse Event Relationship to Study Drug

The investigator should provide an assessment of the relationship of the AE to the study drug, ie, whether there is a reasonable possibility that the study drug caused the AE, using the considerations outlined in Table 3.

Table 3: Relationship of Study Drug to Adverse Event Relationship

Relationship	Description
Probable	A clinical event in which a relationship to the study drug seems probable because of such factors as consistency with known effects of the drug; a clear temporal association with the use of the drug; improvement upon withdrawal of the drug; recurrence upon rechallenge with the drug; lack of alternative explanations for the event.
Possible	A clinical event occurring coincident with administration of the study drug and which may or may not be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal or rechallenge may be lacking.
Unlikely	A clinical event with a temporal relationship to the study drug exposure that does not preclude causality but for which there is a clear alternate cause that is more likely to have caused the adverse event than study drug. Such alternatives include a concomitantly administered drug, the subject's disease state, other medical conditions, or environmental factors.
Unrelated	A clinical event, for which a relationship to the study drug seems improbable because of factors such as inconsistency with known effects of the study drug, lack of a temporal association with study drug administration, lack of association of the event with study drug withdrawal or rechallenge, and/or presence of alternative explanations for the event. Alternative explanations might include a known relationship of the adverse event to a concomitant drug, medical history of a similar event, the subject's disease state, other medical conditions, or environmental factors.

7.5.7. Grading of Severity of Adverse Event

The severity of AE will be graded using the CTCAE Version 5.0 (refer to the Study Manual). For each episode, the highest severity grade attained should be reported.

If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the AE. For purposes of consistency with the CTCAE, these intensity grades are defined in Table 4.

Table 4: Grading of Adverse Event Severity Grade

Grade	Adjective	Description
Grade 1	Mild	Sign or symptom is present, but it is easily tolerated, is not expected to have a clinically significant effect on the subject's overall health and well-being, does not interfere with the subject's usual function, and is not likely to require medical attention
Grade 2	Moderate	Sign or symptom causes interference with usual activity or affects clinical status, and may require medical intervention
Grade 3	Severe	Sign or symptom is incapacitating or significantly affects clinical status and likely requires medical intervention and/or close follow-up
Grade 4	Life-threatening	Sign or symptom results in a potential threat to life
Grade 5	Fatal	Sign or symptom results in death

7.5.8. Adverse Event Reporting

Investigator site reporting requirements for AEs are summarized in Table 5.

Table 5: Investigator Site Requirements for Reporting Adverse Events

Event	Recorded on the eCRF	Reported on the SAE or Pregnancy Report (as applicable) Form to PTC Pharmacovigilance Within 24 Hours of Awareness
Serious AE	All	All
Non-Serious AE	All	None
Exposure to the study drug during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), except occupational exposure	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

Abbreviations: AE, adverse event; eCRF, electronic case report form; SAE, serious adverse event

All AEs should be followed up by the investigator until they are resolved, or the investigator assesses them as chronic or stable. The investigator should consider protocol guidelines and use his/her discretion in ordering additional tests as necessary to monitor the resolution of such events. In the event of additional investigations, the PTC Pharmacovigilance Department or designee should be informed via e-mail or fax. A subject withdrawn from the study because of an AE must be followed by the investigator until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized. Follow-up may need to continue after the subject has discontinued from the study, and additional investigations may be requested by the PTC medical monitoring team.

The first day of AE reporting will coincide with the date of signing of informed consent and including a minimum of 30 calendar days after the last administration of study drug.

7.5.9. Serious Adverse Event Reporting

All SAEs occurring from the time of informed consent through 30 days following the last dose of study drug should be reported via the SAE report form to PTC within 24 hours of becoming aware of the event(s). In addition, the AE portion of the eCRF must also be completed.

The SAE report form should be signed by the investigator; however, if the investigator is unable to sign at the time of the event or within 24 hours, the form should be signed by the clinical staff member reporting the SAE (eg, the study coordinator). The SAE report form must be faxed or e-mailed to the PTC Pharmacovigilance Department or designee and to the site IRB/IEC (if required by local regulations) within 24 hours.

Follow-up information to the SAE should be clearly documented as "follow-up" in the SAE report form and must also be faxed or e-mailed to the same party. All follow-up SAE report forms for the event must be signed by the investigator. Any source documents (eg, progress notes, nurses' notes, laboratory and diagnostic test results, discharge summaries) provided to the sponsor should be redacted so that the subject's name, address, and other personal identity information are obscured. Only the subject's study number and initials are to be provided (in regions where the provision of such information is permitted). The information in the AE portion of the eCRF and the SAE report form(s) must match or be reconciled. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (for example, if a subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and to document his/her first awareness of the AE.

The PTC Pharmacovigilance Department contact information for reporting SAEs is provided below. This information is also provided in the Study Manual and in the SAE report form.

PTC Therapeutics Safety Department
Attention: Pharmacovigilance
E-mail: Pharmacovigilance@ptcbio.com
Facsimile: 1 (908) 325-0355

7.5.10. Contraception

Women of childbearing potential (WOCBP) includes any female who has experienced menarche and who has not undergone successful surgical sterilization (eg, hysterectomy, bilateral tubal ligation, bilateral oophorectomy) or is not postmenopausal. Postmenopausal is defined as ≥12 months with no menses without an alternative medical cause. Women who are using an active method of birth control, are practicing abstinence or where the partner is sterile (eg, vasectomy), are considered to be WOCBP.

WOCBP must use 2 forms of effective contraception simultaneously for the duration of study participation and through approximately 30 days after the last dose or early termination in a manner such that risk of failure is minimized. Periodic and/or temporary abstinence such as declaration of abstinence during study participation or fertility awareness-based methods to prevent pregnancy (including but not limited to symptothermal and ovulation estimation by either calendar day or salivary/cervical secretions) are not considered effective methods of birth control; however, true (absolute) sexual abstinence (ie, in line with the preferred and usual lifestyle of the subject) may be permitted. Effective methods of birth control approved for use in this study are:

- Implants (eg, Norplant® system)
- Injectable (eg, Depo-Provera®)
- Transdermal patch
- Combined oral contraceptives
- Barrier methods (condoms and diaphragm with spermicide) - note: double-barrier method is required if no other methods of birth control are in use.
- Intrauterine devices (eg, ParaGard®, Mirena®)

Prior to trial enrollment, WOCBP must be advised of the importance of avoiding pregnancy during trial participation and through approximately 30 days after the last dose or early termination. During the trial, all WOCBP will be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual period).

Male subjects must agree not to donate sperm during the study and for at least 30 days after treatment discontinuation or early termination.

7.5.11. Reporting Pregnancy

PTC should be notified in the event that a female subject in the study, or a female partner of a male subject in the study, becomes pregnant on-study or within 30 days of the last administration of study drug must be reported on a Pregnancy Notification Form (see the Study Manual for details).

This must be done whether or not an AE has occurred and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of birth or pregnancy termination.

Written consent is required prior to collecting and reporting any information on a female partner of a male subject in the study.

If possible, the investigator should follow the subject, or the pregnant female partner of a male subject, until completion of the pregnancy and notify the PTC medical monitor of the outcome within 5 days or as specified below. The investigator will provide this information as a follow-up to the initial Pregnancy Notification Form via the Pregnancy Outcome Form (see the Study Manual for details).

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the investigator should follow the procedures for reporting SAEs, ie, report the event to the PTC Safety Department or designee and follow-up by submission of appropriate AE eCRFs (see Section 7.5.9).

7.5.12. PTC Therapeutics Adverse Event Reporting Requirement

As the sponsor of the study, PTC is responsible for reporting certain safety information, such as suspected unexpected serious adverse reactions (SUSARs) and other significant safety findings, per local reporting requirements, to each investigator in an expedited manner. If notification of a SUSAR requiring expedited reporting to investigators is received, PTC or its designated representative will contact each investigational site participating in this study by e-mail, fax, and/or overnight mail such that the investigator can promptly notify the site IRB/IEC per their local requirements. The initial expedited safety report will be provided as required according to local regulations (eg, within 15 days) after the earliest date PTC or an agent of PTC (eg, a site monitor) becomes aware of the event. This awareness date is the date the regulatory reporting clock begins and the date is considered Day 0.

8. STATISTICAL CONSIDERATIONS

The primary objective of this study is to evaluate the efficacy (using the mFARS) and safety of vatiquinone on subjects with Friedreich ataxia.

After the last subject completes the double-blind Week 72 visit or follow-up visit (in case of subject withdrawal), database will be cleaned, locked, and unblinded. Statistical analysis of double-blind portion of the study will be conducted while subjects continue to participate in the open-label extension portion of the study. Open-label extension portion of the data will be cleaned and locked after the last subject has completed the follow-up procedures.

8.1. Statistical Hypotheses

The primary efficacy hypotheses are:

H0: $\mu v = \mu P$ vs H1: $\mu v > \mu P$, where μv is the treatment effect of vatiquinone in change from baseline in mFARS score and μP is the treatment effect of placebo in change from baseline in mFARS score at Week 72. A larger numerical decrease from baseline in mFARS represents a larger treatment effect.

8.2. Sample Size Determination

Based on Phase 2 Study EPI-2010-006 data, vatiquinone 400 mg tid dose demonstrated a change from baseline in mFARS score for 400 mg dose of -1.31 after 18 months of treatment, and natural history showed an estimated increase of 3.26 after 18 months of disease progression (Patel 2016). Assuming a common standard deviation of 6.76, with 1-sided type I error of 2.5% and 90% power, 47 subjects per group is required to detect a treatment difference of -4.57 in mFARS score. Assuming a dropout rate of 10%, a total of 106 subjects between 7 and 21 years of age will be randomized. The primary efficacy analysis will be based on change from baseline in mFARS score of subjects between 7 and 21 years old.

In order to explore the treatment efficacy and safety, approximately 20 subjects >21 years of age will be randomized for a total of approximately 126 subjects.

8.3. Population for Analyses

8.3.1. Randomized Analysis Set

The Randomized Analysis Set will include all subjects who are randomized for the study.

8.3.2. Intent-to-Treat Set

The intent-to-treat (ITT) set will include all subjects who are randomized, have received at least one dose of study drug (vatiquinone or placebo), and have baseline and at least one post-baseline measurement of the primary endpoint.

Analysis in mFARS change from baseline to Week 72 based on the ITT set will be considered as secondary analysis.

8.3.3. Modified Intent-to-Treat Set

The modified intent-to-treat (mITT) set will include all subjects who are randomized, between age of 7 and 21 years, inclusive, at Screening, have received at least one dose of study drug (vatiquinone or placebo), have baseline and at least one post-baseline measurement of the primary endpoint.

Analysis in mFARS change from baseline to Week 72 performed based on the mITT set will be considered as primary efficacy analysis.

8.3.4. Safety Analysis Set

The safety analysis set will include all subjects who receive at least one dose of study drug. This will be the primary analysis set for summarizing safety data. Subjects will be summarized by the treatment they received.

8.3.5. Pharmacokinetic Analysis Set

The PK analysis set will include all subjects who have any evaluable plasma concentration.

8.4. Statistical Analyses

8.4.1. General Approach

Descriptive statistics will be provided for demographic, safety, and efficacy. Descriptive statistics on continuous data will include number of subjects, mean, median, standard deviation, minimum, and maximum while categorical data will be summarized using frequency counts and percentages.

Subjects randomized to vatiquinone will be treated as one group regardless of the dose (200 mg tid or 400 mg tid).

Assessments of change from baseline to posttreatment or the ratio of posttreatment to baseline will include only those subjects with both baseline and posttreatment measurements. The last non-missing value of a variable taken before the first dose of study drug will be used as the study baseline value, unless otherwise specified. In general, missing or dropout data will not be imputed for the purpose of data analysis, unless otherwise specified.

Efficacy variables will be summarized and analyzed for the double-blind phase based on treatment assigned at randomization. Analyses and summaries will be performed for both the mITT set and the ITT set unless specified otherwise. Analysis results based on the mITT set will be considered primary support of efficacy and those based on ITT set will be considered secondary.

Safety summaries will be presented by treatment received and will be performed based on the safety analysis set.

All statistical summaries and analyses will be performed using SAS® software (SAS Institute, Cary, North Carolina, USA).

A detailed Statistical Analysis Plan (SAP) describing the methodology to be used in the final analysis will be prepared and finalized before the study is unblinded after all subjects complete the placebo-controlled phase.

8.4.2. Analysis of Primary Efficacy Endpoints

The primary estimand is the treatment difference between vatiquinone and placebo in change from baseline to Week 72 in mFARS score attributable to the initially randomized treatment for randomized subjects who received at least 1 dose of study medication and between 7 and 21 years of age at screening. Missing mFARS score will be imputed as described below to form a complete set for analysis.

Intermittent missing mFARS scores will be imputed using Monte Carlo Markov Chain (MCMC) method with adjustment for covariates (for example, but not limited to, treatment group, age, region, gender) to produce 5 monotone missing pattern datasets first. Missing data after dropout will be imputed assuming missing not at random using pattern mixture complete case missing value pattern. Approximately 1000 complete data sets will be produced. The change from baseline at each visit will be calculated using the completed data sets for analysis. The primary efficacy analysis will be performed for subjects between 7 and 21 years of age at screening, and will compare change from baseline in mFARS neurological score to Week 72 between vatiquinone- and placebo-treated subjects using mixed model repeated measure (MMRM) stratified by baseline mFARS score (<40 and ≥ 40) and age of onset (<14 and ≥ 14 years) with treatment and region as the main effects and baseline mFARS and age as covariates using an unstructured variance-covariance matrix structure. If the model failed to converge, other variance-covariance structure will be explored. The test will be performed using one-sided type I error of 2.5%. The results of MMRM analysis from each complete imputed dataset will be combined using Rubin's rule (Little 2002). Detail of the imputation will be specified in the SAP.

A completer analysis will be performed for all subjects who took medication till the end of double-blind period as specified by the protocol and have mFARS score at Week 72 visit.

The overall Neurological section score (sum of the Bulbar [except for tongue and facial atrophy], Upper Limb Coordination, Lower Limb Coordination and Upright Stability), total score from each subsection, and Stance from Upright Stability will be summarized at baseline and each time point along with the change from baseline by treatment. For the subsections containing the measurements from the left and the right, the sum of the two scores will be used in the calculation for the total section score. For Upright Stability subsections (2a, 2b, 3a, 3b, 4, and 5), the average score from the 3 trials will be used in the calculation for the total section score. Higher score reflects greater Friedreich ataxia disease severity thus, a negative change from

baseline suggests an improvement. Summaries will present observed values and no imputation will be performed for missing values.

Open-label Extension Period

After all subjects complete long-term follow-up, subjects' mFARS score from double-blind and long-term follow-up will be summarized in the following way:

- For subjects randomized to vatiquinone, the change from study baseline (also their vatiquinone treatment baseline) will be presented for each visit from Week 12 to the end of the follow-up to show long-term treatment effect of vatiquinone.
- For subjects randomized to placebo, their last mFARS score will be used as vatiquinone treatment baseline. Change from vatiquinone treatment baseline to each long-term follow-up visit will be calculated. In this fashion, change to Week 84 shows change from treatment baseline after 12 weeks of vatiquinone treatment, and Week 96 shows changes after 24 weeks of treatment.
- The above two sets of summary statistics for changes from treatment baseline will be presented in one table to show the treatment effect of vatiquinone by treatment group, and overall (combine the 12, 24, 36, 48, 60, and 72 weeks vatiquinone-treated change from baseline for the placebo group with originally vatiquinone-treated group's week 12 and 24 weeks change from baseline) to show the overall change from vatiquinone treatment baseline.

Listings will be provided to show the observed efficacy variables by visit.

8.4.3. Analysis of Secondary and Exploratory Efficacy Endpoints

Secondary efficacy variables include the following:

- Change from baseline in FARS-ADL scale to Week 72
- Change from baseline in 1MWT to Week 72
- Number of falls through Week 72

Exploratory efficacy variables include the following:

- Change from baseline in Speech evaluation to Week 72
- Change from baseline in MFIS to Week 72
- Change from baseline in EQ-5D-5L score to Week 72
- Change from baseline in Upright Stability subscale of mFARS score to Week 72

Comparisons between treatment groups for change from baseline in FARS-ADL scale, one minute timed walk, MFIS score, EQ-5D-5L, and Upright Stability subscale of the mFARS to Week 72 will be analyzed using the same model as the primary efficacy variable by using its respective baseline and age as covariates. Summary statistics will be provided for total score at each visit as well as change from baseline at each visit.

A summary of the number of falls will be presented, and the number of falls over time will be compared between the two treatment groups.

Handling and comparison between treatment groups for change from baseline in speech will be provided by Redenlab and will be described in a separate document.

Long-term Follow-Up Extension

For long-term follow-up data, the change from vatiquinone treatment baseline will be presented in the same fashion as mFARS described above for FARS-ADL, 1MWT, MFIS, EQ-5D-5L, and Upright Stability scale of the mFARS. The observed number of falls will be presented in similar fashion.

8.4.4. Safety Analyses

Safety data (including AEs, vital signs, physical examinations, laboratory data, C-SSRS, echocardiogram, and ECG data) will be listed and summarized by treatment group for subjects in the safety analysis set. All safety data collected on or after the date of the first dose of study drug through completion of the study will be summarized by treatment. The last measurements taken prior to first dose will be used as study baseline. The last measurements taken during double-blind period for subjects originally treated with placebo will be the vatiquinone treatment baseline. For subjects originally treated with vatiquinone, their study baseline is also their vatiquinone treatment baseline. This definition will be used for all the numerical safety variables.

Exposure to study drug and study drug compliance will be summarized for both the double-blind and open-label extension periods.

8.4.4.1. Adverse Events

Adverse events will be coded using MedDRA. Treatment-emergent AE (TEAE) is defined as AE first occurred on or after the first dose date and up to 30 days after the last dose or with onset prior to the first dose but worsened in severity.

An overall AE summary will be provided to show number and percentage of subjects with TEAE, SAE, treatment-emergent SAE (TESAE), study-drug related TEAE, discontinuation due to AE, and death. Treatment-emergent AE will be summarized by System Organ Class (SOC) and Preferred Term (PT) for treatment subjects received.

Double-blind Period

Summary TEAE tables for each treatment will be presented for the following for each treatment group:

- All TEAEs
- All TEAEs by relationship to study drug
- All TEAEs by severity
- All TESAEs
- All TEAEs leading to discontinuation of study drug

Multiple events by PT and SOC will be counted once only per subject for each treatment.
For summaries by severity, the most severe event with the same PT will be selected for that PT.
For summaries by relationship, the most related event with the same PT will be selected for that PT.

Long-term Follow-up

Subjects randomized to placebo will have AE summary presented side-by-side for the period they received placebo and the period they received vatiquinone.

Subjects randomized to vatiquinone will have all their AEs occurred during double-blind and follow-up portion combined and presented as one table. In addition, summary of new AEs occurred during double-blind and during long-term follow-up will be presented side-by-side.

All AEs occurring during vatiquinone treatment (combining original vatiquinone-treated subject data and follow-up data of originally placebo-treated subjects' data) will also be presented for all TEAEs and all TESAEs in the same fashion as in the double-blind period.

Listings of all AEs and SAEs reported will be presented as well.

8.4.4.2. Clinical Laboratory Evaluations

Double-blind Period

Laboratory data will be summarized at baseline and at each time point by treatment. Change from baseline will also be summarized. A shift table, presenting 2-way frequency tabulation for baseline and the worst posttreatment value, will be provided.

Long-term Follow-up

Laboratory data and change from treatment baseline will be presented for subjects originally treated with vatiquinone as well as for subjects originally treated with placebo.

Only values obtained at scheduled assessment times will be included in the summary.

8.4.4.3. Vital Signs, Weight, and Oxygen Saturation

Double-blind Period

Descriptive statistics will be provided by treatment group for the vital sign, body weight, and oxygen saturation measurements and changes from baseline by scheduled time of evaluation and the maximum and minimum posttreatment values for double-blind.

Long-term Follow-up

Descriptive statistics will be provided for change from treatment baseline to each visit. Treatment baseline is defined as the last observed values during double-blind period for original placebo-treated subjects. All vital sign data will also be listed.

8.4.4.4. Electrocardiogram and Echocardiogram

Double-blind Period

Descriptive statistics and listings will be provided by treatment group for ECG parameters and changes from baseline by scheduled time of evaluation.

The number and percentage of subjects with investigator findings of normal, abnormal (NCS) and abnormal (CS) as well as shift from baseline to each visit will be provided for ECG and for echocardiogram.

Long-term Follow-up

Descriptive statistics for change from vatiquinone treatment baseline will be presented for subjects originally treated with vatiquinone as well as for subjects originally treated with placebo to each visit in the same fashion as described for double-blind period.

8.4.4.5. Physical Examination

Physical examination findings will be listed for both double-blind period and open-label period.

8.4.4.6. Columbia-Suicide Severity Rating Scale

Double-blind Period

Number and percentage of subjects' response for each question will be provided at each visit for each treatment group for both double-blind period and open-label long-term follow-up period. Shift table presenting responses to each question at baseline versus each visit for each treatment group will be provided.

Listing of the response will also be provided for each subject.

Long-term Follow-up Period

Number and percentage of subjects' response for each question will be provided at each visit for open-label portion of the data. Shift table presenting responses to each question at treatment baseline versus each visit for each originally randomized group will be presented.

8.4.4.7. Concomitant Medication

Concomitant medications will be coded using the World Health Organization (WHO) drug dictionary (most recent version). Number and percentage of subjects taking concomitant medications will be summarized for both double-blind and long-term follow-up periods. Concomitant medications will also be listed.

8.4.5. Baseline Descriptive Statistics

8.4.5.1. Disposition of Subjects

The summary of disposition of subjects will provide the number of subjects screened, number and percentage (by randomized treatment and overall) for randomized subjects, in the full analysis set (FAS), safety analysis set, PK set, completing treatment in the double-blind portion of the study, discontinued from the double-blind portion of the study, enrolled in long-term follow-up, discontinued from the long-term follow-up portion of the study.

Number and percentage will also be provided for reason of discontinuing treatment in the double-blind and long-term follow-up by treatment group and overall.

8.4.5.2. Demographic and Baseline Characteristics

Summary of demographic information, genetic confirmation of FA diagnosis and baseline mFARS, FARS-ADL, 1MWT, MFIS, and EQ-5D-5L will be summarized by treatment group for subjects randomized to the double-blind portion of the study.

Demographic information will also be summarized for subjects who rollover to the long-term follow-up by the original randomized treatment and overall.

Number of subjects, mean, median, standard deviation, minimum, and maximum will be provided for continuous variables and number and percentage will be provided for categorical variables.

Listing will be provided for demographic, genetic confirmation of Friedreich ataxia, and medical history.

8.4.6. Pharmacokinetic Analyses

Due to sampling schedule, no PK parameters will be calculated for this study. Modeling and simulation using the blood concentration will be described and reported in a separate report.

8.4.7. Planned Interim Analyses

There is no planned interim analysis.

8.4.8. Subgroup Analyses

Subgroup summaries will be provided for age of disease onset in change from treatment baseline to each visit for mFARS, FARS-ADL, one-minute walk test, MFIS score, Upright Stability subscale of the mFARS, and for observed number of falls in between visits.

For double-blind treatment period, this will be performed for each treatment group.

Once all subjects completed long-term follow-up, this subgroup summary will be presented as described for long-term follow-up in Section 8.4.2.

8.4.9. Sensitivity Analysis

Sensitivity analysis will be performed for the primary efficacy variable by using placebo multiple imputation to test the robustness of the results. The placebo multiple imputation method will be performed following the creation of a monotone data structure using methods as described for the primary analysis. The missing mFARS score is then imputed adjusting for covariates (age, region) based on information from the placebo arm only. Values of shift parameters used in the pattern mixture model for the primary analysis will be perturbed to further test the robustness of the primary results. Analysis of the imputed data will follow the same approach as the primary analysis.

9. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

9.1. Regulatory, Ethical, and Study Oversight Considerations

9.1.1. Informed Consent Process

By signing the protocol, the investigator assures that informed consent/assent will be obtained from each subject prior to study entry and that the informed consent/assent will be obtained in accordance with current regulations.

The investigator or subinvestigator will give each subject full and adequate verbal and written information regarding the objectives and procedures of the study and the possible risks involved. An informed consent/assent document will be provided to each subject in a language in which the subject is fluent. This information must be provided to the subject prior to undertaking any study-related procedure. Adequate time should be provided for the subject to read the informed consent, to understand the risks and benefits of participating in the study, and to ask any questions that the subject may have about the study. The subject should be able to ask additional questions as and when needed during the conduct of the study. The subject's signature on the ICF should be obtained at the investigator site in the presence of the investigator or a qualified representative (eg, subinvestigator). Where applicable, the subject will sign an age-appropriate assent form. If a subject reaches adulthood while on study, he or she will be reconsented as an adult.

Each subject will be given a copy of the signed consent/assent form. The original signed ICFs will be retained by the investigator with the study records.

The written subject information must not be changed without prior approval by PTC and the IRB/IEC.

9.1.2. Study Discontinuation and Closure

PTC reserves the right to discontinue the study prior to inclusion of the intended number of subjects. The investigator, after consultation with the PTC medical monitor, reserves the right to discontinue the study at the investigator site for safety reasons at any time.

After a decision to terminate the study, investigators must contact all subjects who are continuing their participation in the study and must do so within a time period set by PTC. As directed by PTC, all study materials must be collected and all electronic data entry forms completed to the greatest extent possible.

9.1.3. Confidentiality and Privacy

Research records will be collected and stored in a manner that protects the confidentiality of subject information. The names and identities of all research subjects will be kept in strict confidence and will not appear on eCRFs or other records provided to or retained by PTC (or its authorized designee). The names and identities of the subjects need not be divulged; however, the records must nevertheless be inspected. This will be accomplished by blanking out the subject's name and replacing the name with the subject's study identification number on any record provided to or retained by PTC. The ICF must include appropriate statements explaining these requirements.

By signing this protocol, the investigator affirms to PTC that the investigator will maintain, in confidence, information furnished by PTC and will divulge such information to the IRB/IEC under an appropriate understanding of confidentiality with such board.

9.1.4. Future Use of Stored Specimens and Data

As part of the current study, serum and plasma blood samples are being collected.

Sample processing will be performed by a laboratory under the direction of the sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol. Laboratories contracted to perform the analysis on behalf of the sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The sponsor will not sell the samples to a third party.

Samples will be stored until the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a health authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, the samples will be stored until the questions have been adequately addressed.

No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with any of the biologic samples. All samples will be single coded. The sponsor will take steps to ensure that data are protected accordingly, and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The sponsor and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this research. These include:

- Contract research organizations (CROs) retained by the sponsor
- IECs or IRBs that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report which can include part or all of the coded data, in listing or summary format. Other publication (eg, in peer-reviewed scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the data analysis, it will not be possible to return individual data to subjects. The results that may be generated are not currently anticipated to have clinical relevance to the patients or their family members. Therefore, these results will not be disclosed to the patients or their physicians.

9.1.5. Safety Oversight

External oversight for this trial will be provided by a DSMB. The DSMB consists of 3 members, including an unblinded statistician with experience in the indication and will meet approximately quarterly or more frequently if there are safety concerns. The primary responsibility of the DSMB is to protect the safety and welfare of subjects participating in this clinical trial and to ensure the integrity of the clinical trial.

Specifically, for this study, the DSMB will be responsible for:

- Examining accumulated safety data and compliance data in order to make recommendations concerning continuation, termination, or modification of the trial based on the safety of the interventions under study

- Reviewing major study design modifications proposed by PTC or the investigators prior to implementation of those modifications
- Reviewing the general progress of the study as in regard to accrual, protocol deviations, and study conduct

The DSMB may review the safety data at any time as warranted by emerging results. Based on review of the safety data, the DSMB can recommend continuation of the study unchanged, study interruption, study termination, modification of the trial, or alteration in the DSMB monitoring plan. Further information regarding the DSMB review process is provided in the DSMB charter (see the Study Manual).

9.1.6. Clinical Monitoring

In accordance with 21 CFR Part 312.56 and/or relevant ICH guidelines, PTC or a designee will periodically inspect all eCRFs, study documents, research facilities, and clinical laboratory facilities associated with this study at mutually convenient times, before, during, and after completion of the study. As required by applicable regulations (Responsibilities of Sponsors and Investigators), the monitoring visits provide PTC with the opportunity to evaluate the progress of the study; verify the accuracy and completeness of data in the eCRFs; ensure that all protocol requirements, relevant regulations, and investigator's obligations are being fulfilled; and resolve any inconsistencies in the study records. This includes inspection of all documents and records required to be maintained by the investigator, including but not limited to medical records (office, clinic, or hospital) for the subjects in this study. The names and identities of all research subjects will be kept in strict confidence and will not appear on eCRFs or other records provided to or retained by PTC. The investigator/institution guarantees direct access to source documents by PTC and appropriate regulatory authorities.

It is important that the investigator and relevant institutional personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

9.1.7. Quality Assurance and Quality Control

To ensure compliance with Good Clinical Practice (GCP) and all applicable regulatory requirements, PTC, PTC's representatives, a regulatory authority, or/and IRB may conduct a quality assurance audit. Reasons for quality assurance audit may include but are not limited to random selection, geographic proximity, suspected GCP violation, high enrolling site, recurring protocol deviations, etc. The purpose of a sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. The investigator should contact the sponsor immediately if contacted by a regulatory agency about an inspection.

9.1.8. Data Handling and Record Keeping

To enable evaluations and/or audits from regulatory authorities or PTC, the investigator agrees to keep accurate and complete records, including the identity of all participating subjects (sufficient information to link eCRFs and clinic records/source documents), all original signed ICFs, electronic copies (ie, CD-ROM, USB, etc.) or paper copies of the data that have been captured in the electronic data capture for each subject (eCRFs), and detailed records of study drug disposition. All records and documents pertaining to the study will be maintained by the investigator until notification is received from PTC that the records no longer need to be retained.

The investigator must obtain written permission from PTC before disposing of any records. The investigator will promptly notify PTC in the event of accidental loss or destruction of any study records. If the investigator relocates, retires, or for any reason withdraws from the study, the study records may be transferred to an acceptable designee, such as another investigator, another institution, or to PTC as applicable.

9.1.9. Protocol Deviations

A protocol deviation is defined as any intentional or unintentional change to, or noncompliance with, the approved protocol procedures or requirements. Deviations may result from the action or inaction of the subject, investigator, or site staff. Examples of deviations include, but are not limited to:

- Failure to adhere to study exclusion and inclusion criteria
- Failure to comply with dispensing or dosing requirements
- Use of medications that are specifically prohibited in the protocol
- Missed or out-of-window visits
- Drug dosing not administered within the time frame specified in the protocol
- Failure to adhere to test requirements, including vital signs, laboratory tests, physical examinations, PK blood draws, medical history, etc. - either tests not done, incorrect tests done, or not done within the time frame specified in the protocol
- Procedural deviations such as incorrect storage of study drug, failure to update the ICF when new risks become known, or failure to obtain IRB/IEC approvals for the protocol and ICF revisions

Major deviations are any deviations that impact subject eligibility (ie, protocol inclusion/exclusion violations), subject safety or a subject's ability to continue in the clinical trial.

At the outset of the study, a process for defining and handling protocol deviations will be established with the CRO. This will include determining which deviations will be designated as major; thus, requiring immediate notification to the PTC medical monitor and the sponsor.

Prospective deviations (eg, protocol waivers) are prohibited per PTC policy.

The investigator is responsible for seeing that any known protocol deviations are recorded as agreed.

9.1.10. Publication and Data Sharing Policy

The information developed during the conduct of this clinical study is considered confidential by PTC. This information may be disclosed as deemed necessary by PTC.

PTC intends that the data from this study will be presented and published. The PTC staff under the direction of the PTC Chief Medical Officer or designee in collaboration with the investigator will be responsible for writing presentations and manuscripts for publication. investigators will not be allowed to publish or present the data from this study without prior agreement with PTC.

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the Clinical Study Site Agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

Data from all sites participating in the study will be pooled and analyzed by the sponsor or the sponsor's designee. The first publication of the study results shall be made in conjunction with the results from other study sites as a multicenter publication. If a multicenter publication is not forthcoming within 24 months of completion of the study at all sites, the investigator may publish or present the results generated at his or her site.

The investigator will provide the sponsor with a copy of any proposed publication or presentation for review and comment at least 60 days prior to such presentation or submission for publication. The sponsor shall inform the investigator in writing of any changes or deletions in such presentation or publication required to protect the sponsor's confidential and proprietary technical information and to address inaccurate data or inappropriate interpretations in the context of any pooled multicenter results. At the expiration of such 60-day period, the investigator may proceed with the presentation or submission for publication unless the sponsor has notified the institution or the investigator in writing that such proposed publication or presentation discloses the sponsor's confidential and proprietary technical information. Further, upon the request of the sponsor, the investigator will delay the publication or presentation for an additional 90 days to permit the sponsor to take necessary actions to protect its intellectual property interests.

9.2. Protocol Amendment History

Version 1.0: 15 April 2020

Amendment 1: 31 July 2020 (Version 2.0)

Amendment 2: 28 August 2020 (Version 3.0)

Amendment 3: 03 March 2021 (Version 3.1)

Amendment 4: 15 April 2021 (Version 4.0)

Amendment 5: 21 May 2021 (Version 5.0)

9.2.1. Amendment 2: 28 August 2020 (Version 3.0)

The overall reasons for Version 3.0 of the protocol was to revise the length of the placebo-controlled portion of the trial from 48 weeks to 72 weeks and the open-label portion from 48 weeks to 24 weeks and to add Upright Stability subscale as an exploratory endpoint.

Item No.	Protocol Section	Version 3/Update	Reason/ Rationale
1	Protocol	The version number and date were updated throughout. Editorial revisions (eg, typographical errors, punctuation, tenses, abbreviations) were incorporated to provide clarity. The synopsis was updated to be consistent with changes in the protocol.	Update
2	Section 2.1.1	Clarification added that the efficacy in the primary objective will be assessed using the mFARS	Clarification
3	Section 2.1.3	Upright Stability subscale was added to the exploratory objectives.	Update
4	Section 2.2.3	Upright stability subscale was added to the exploratory endpoints.	Update
5	Section 3.1	Clarification that dose will also be adjusted if the subject's age changes from 11 to 12 years Sentence added to indicate that subjects who complete the study may have the option to enter into an open-label expanded access study to continue receiving vatiquinone.	Update and Clarification
6	Section 3.1 and Section 3.1.1	Screening period revised from 35 days (±5 days) to up to 42 days	Update
7	Section 3.1.2	Revisions to reflect the change in length of the placebo-controlled phase from 48 to 72 weeks along with the applicable revisions to the timing of the in-person and telephone visits	Update
8	Section 3.1.4	Revisions to reflect the change in length of the open-label extension phase from 48 to 24 weeks along with the applicable revisions to the timing of the in-person and telephone visits Clarification that dose will also be adjusted if the subject's age changes from 11 to 12 years	Update and Clarification
9	Section 3.1.8	Revision to state that the end of treatment visits will include the same assessments noted for the Week 96 visit	Clarification
10	Section 3.2	Explanation of the Upright Stability subscale score added Revision of endpoint evaluation from 48 to 72 weeks and revision to 72 and 24 weeks of the placebo-controlled and open-label extension phases, respectively	Update

Item No.	Protocol Section	Version 3/Update	Reason/ Rationale
11	Section 4.2	Addition of a sub-bullet noting that if a subject is taking a prohibited concomitant medication at Screening, the difference in mFARS is to be assessed between a Post-Discontinuation Visit and Baseline Visit	Update
12	Section 4.3	Reversed numbering of exclusion criteria 10 and 11 Revision to criterion 11 (previously criterion 10) to exclude use of any investigational drug in any other clinical trial within 60 days prior to the Baseline Visit and addition of statement that subjects may be rescreened after the exclusionary period of 60 days have passed. Revision to criterion 12 to exclude CoQ10, vitamin E, idebenone, or any other non-approved medication within 30 days prior to the Screening Visit. Clarification added that these medications may be discontinued at the Screening Visit, and if this is the case, Screening mFARS must be repeated following a 30-day washout.	Update
13	Section 5.5	Revisions to concomitant medications for consistency with updates in exclusion criteria 11 and 12	Update
14	Section 6.1	Clarification added that any sites should make every effort to complete the Termination Visit and final Follow-up Visit for subjects who discontinue from the study prematurely	Clarification
15	Section 7.1	"Post-Discontinuation" Screening Visit added for mFARS assessment, consistent with revisions to exclusion criterion 12 Revision of screening period from 35±5 days to up to 42 days Revisions to visit schedule to reflect change in lengths of placebo-controlled and open-label phases of the study Addition of baseline fall assessment to be collected with medical history Revision to include an extra Screening mFARS assessment (if needed) and revision to the applicable footnote (14)	Updates
16	Section 7.2	Revision from 48 to 72 weeks for efficacy assessments Addition of baseline fall history to be collected with medical history Addition of explanation of Upright Stability	Updates
17	Section 8 Section 8.1 Section 8.3.2 and Section 8.3.3	Revision from "Week 48" to "Week 72" to reflect revised timing of efficacy analyses	Update
18	Section 8.2	Sample size determination language revised to reflect 18-month data due to change in randomized portion of the study from 48 to 72 weeks	Update
19	Section 8.4.2	Revision from 48 to 72 weeks for analysis of primary efficacy endpoints and related revisions in "change from baseline" measurements	Update
20	Section 8.4.3	Revision from 48 to 72 weeks for all efficacy endpoints Addition of the Upright Stability subscale as an exploratory endpoint Revision of assessment approach for the secondary endpoint of falls	Updates
21	Section 8.4.9	Clarification of analysis of primary mFARS results	Clarification

Abbreviations: DSUR, Development Safety Update Report; FA, Friedreich ataxia; FARS-ADL, Friedreich Ataxia Rating Scale Activities of Daily Living; ITT, intent-to-treat; mFARS, modified Friedreich Ataxia Rating Scale; mITT, modified intent-to-treat; No., number; SAEs, serious adverse events; SOPs, standard operating procedures

9.2.2. Amendment 3: 03 March 2021 (Version 3.1)

The overall reasons for Version 3.1 of the protocol was to clarify unblinding procedures, clarify disease worsening as a reason for discontinuation from study treatment, add a table (Appendix 1) of prohibited medications, add an echocardiogram at Week 36, and add text clarifying the volume of blood that will be drawn during the study.

Item No.	Protocol Section	Version 3.1/Update	Reason/ Rationale
1	Protocol	The version number and date were updated throughout. Editorial revisions (eg, typographical errors, punctuation, tenses, abbreviations) were incorporated to provide clarity. The synopsis was updated to be consistent with changes in the protocol.	Update
2	Section 5.3.1	Addition of this section to indicate details on unblinding	Clarification
3	Section 6.1	Revision of text in the second point has been revised to replace “vatiquinone” with “study drug”	Clarification
4	Section 7.1	Revision of the Schedule of Events and Study Parameters to add an echocardiogram at Week 36 and to indicate that unscheduled echocardiograms may be performed at the investigator’s discretion	Update
5	Section 7.4.2	Revision of approximate total of blood volume to be drawn over the course of the study and addition of draw volumes of chemistry, hematology, pregnancy, and PK samples	Update and clarification
6	Section 9.1.5	Update of Safety Oversight to remove PK data assessment by the DSMB	Update
7	Appendix 1	Addition of Appendix 1	Update

Abbreviations: AE, adverse event; DSMB, Data Safety Monitoring Board; PK, pharmacokinetic

9.2.3. Amendment 4: 15 April 2021 (Version 4.0)

The overall reasons for Version 4.0 of the protocol was to add risk/benefit language with regard to the pediatric population, revise the timing of the follow up visit from 10 to 30 days to approximately 30 days, and add details regarding maintaining the blind.

Protocol Section	Amendment/Update	Reason/ Rationale
Protocol	The version number and date were updated throughout. Editorial revisions (eg, typographical errors, punctuation, tenses, abbreviations) were incorporated to provide clarity. The synopsis was updated to be consistent with changes in the protocol. Update of Biostatistician to [redacted]	Update
Section 1.4	Addition of in vitro phototoxicity study summary result	Update
Section 1.5	Date of review period removed Update of vatiquinone exposure from “over 9 years” to “over 10 years”	Update
Section 1.6	Risk/benefit language with regard to pediatric population added	Update
Section 3.1 Section 3.1.5 Section 7.1	Timing of follow-up visit revised from 10 to 30 days to approximately 30 days (±5 days) after last dose or termination visit to align with follow-up pregnancy test	Update
Section 3.1.8	Addition of statement indicating all safety and efficacy assessments should be continued according to the Schedule of Events and Study Parameters in the event of early termination	Clarification
Section 4.2	Note added to Inclusion Criterion #4 that the size of GAA repeat is not required for eligibility	Clarification

Protocol Section	Amendment/Update	Reason/ Rationale
Section 4.2 Section 5.5	Revision of 4 weeks to 30 days for exclusion of potent CYP 3A4 inducers/inhibitors (eg, ketoconazole, rifampin, St. John's wort, grapefruit juice) Addition of "any grapefruit product" along with grapefruit juice Addition of text regarding discontinuation of anticoagulants	Updates
Section 4.2 Section 7.5.10	Addition of statement indicating that male subjects must agree not to donate sperm during the study and for at least 30 days after treatment discontinuation	Clarification
Section 4.3	Separation of previous exclusion criterion #2 (Previous treatment with vatiquinone or allergy to vatiquinone, sesame oil, gelatin [bovine and/or porcine], titanium dioxide, or red iron oxide) into 2 separate criteria (ie, #2 [Previous treatment with vatiquinone] and #3 [Allergy to vatiquinone, sesame oil, gelatin (bovine and/or porcine), titanium dioxide, or red iron oxide]) Clarify that subjects cannot have had suicidal ideation or behavior based on C-SSRS within 3 months prior to screening or at baseline since the last visit	Clarification
Section 4.3 Section 5.5 Section 7.1	Idebenone removed as a prohibited concomitant medication and revision of statement to reflect "any approved or non-approved" medication for FA	Update
Section 5.1.2 Section 5.2.1 Section 7.1	Removed dosing diary language for consistency with administrative letter dated 29 October 2020	Update
Section 5.2.1	Revision of compliance range from 80% to 100% to 80% to 110%	Update
Section 5.2.1 Section 7.1	Clarification added that all used/unused study drug from the placebo-controlled phase of the study should be returned at the Week 72 visit and new study drug will be dispensed for the open-label phase at this visit. Footnote 19 added in Section 7.1 for consistency with this revision in Section 5.2.1	Clarification
Section 5.2.2	Revised description of placebo to include more detail	Clarification
Section 5.3	Section revised to further detail how the blind will be maintained	Clarification
Section 5.6.1	New section (Procedure for Dose Modification) added	Update
Section 6.1	Clarification that all study visits should be completed for subjects who discontinued study drug prematurely (unless consent is withdrawn)	Clarification
Section 7.1	Footnote 4 updated to clarify the size of GAA repeat is not required for eligibility Footnote 9 updated to reflect an 8 hour fast for laboratory draws and to note that local laboratories may be used at screening and sparingly for coagulation values	Clarification and update
Section 7.4	Addition of text to specify who can administer the C-SSRS and that sites will follow their internal processes for referrals, if indicated	Clarification
Section 7.4.1	Addition of temperature to vital signs	Clarification
Section 7.4.2	Addition of details on blood volume to be drawn during the study	Update
Section 7.5.2	Clarification added to indicate that events leading to treatment in the emergency room or hospitalization <24 hours may be serious due to another seriousness criterion	Clarification
Section 7.5.9	Revision to indicate that SAEs occurring from the time of informed consent through 30 days following the last dose of study drug should be reported	Clarification
Section 8.2	Revision of statistical difference in mFARS of -4.87 to -4.57 to correct typographical error	Clarification

Abbreviations: AE, adverse event; C-SSRS, Colombia Columbia-Suicide Severity Rating Scale; CYP, cytochrome P450; FA, Friedreich ataxia

9.2.4. Amendment 5: 21 May 2021 (Version 5.0)

The overall reason for Version 5.0 of the protocol was clarify concomitant medication use and add exclusion of illicit drug use.

Protocol Section	Amendment/Update	Reason/ Rationale
Protocol	The version number and date were updated throughout. Editorial revisions (eg, typographical errors, punctuation, tenses, abbreviations) were incorporated to provide clarity. The synopsis was updated for consistency with changes in the protocol.	Update
Section 3.1.1	Clarification of medications that need to be washed out for at least 30 days prior to the Screening Visit. Expansion of explanation of timing of mFARS assessments with regard to washout period	Clarification
Section 3.1.8	Clarification that "early termination" refers to early termination from study drug Clarification that all visits should be continued in the event of early termination from study drug unless consent is withdrawn	Clarification
Section 4.2	Removal of bullet point regarding post-discontinuation mFARS in inclusion criterion #6 Clarification that contraception must be used until 30 days after the last dose of study drug or early termination visit (revised from "treatment discontinuation")	Clarification
Section 4.3	Clarification that suicidal behavior in the past year at the time of screening or between screening and baseline is exclusionary (criterion #6) Clarification in exclusion criterion #13 of "interventional" use of CoQ10, vitamin E, or any approved or non-approved medication for FA is excluded Addition of illicit drug use 30 days prior to screening and during the study as an exclusion criterion (#14)	Update
Section 5.2.1	Clarification that subjects should return all used/unused study drug at each in person visit and that Week 72 marks the end of the placebo-controlled period	Clarification
Section 5.2.2	Addition of statement that blister packs may be approved for use in the open-label extension phase later in the study	Update
Section 5.5	Clarification in exclusion criterion #13 of "interventional" use of CoQ10, vitamin E, or any approved or non-approved medication for FA is excluded Addition of illicit drug use 30 days prior to screening and during the study as an exclusion criterion (#14)	Clarification
Section 7.1	Addition of 10 panel urine drug screen at screening Clarification in footnote 1 that screening may be up to 42 days for subjects requiring a washout Clarification in footnote 9 that local laboratories may also be used sparingly for follow-up INR AE Clarification in footnote 19 that subjects should return all used/unused study drug at each in person visit and that Week 72 marks the end of the placebo-controlled period	Update and clarification

Protocol Section	Amendment/Update	Reason/ Rationale
Section 7.2	Addition of statement indicating that all falls resulting in injury should be reported as AEs	Clarification
Section 7.4.2.3	Addition of section for 10-panel urine drug screen	Update
Section 7.5.10	Clarification added that contraception should be used and pregnancy should be avoided through ~30 days after the last dose or early termination	Clarification
Appendix 1	Appendix revised to indicate exclusion of investigational medications as in a clinical study and movement of CoQ10 and vitamin E into the Interventional medications and supplements for FA category	Clarification

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APPENDIX 1. PTC743-NEU-003-FA PROHIBITED MEDICATION LIST

Table 6: PTC743-NEU-003-FA Prohibited Medication List

Prohibited Medications	Examples
Anticoagulants	• heparin • warfarin • aspirin • clopidogrel/Plavix • apixaban/Eliquis • dabigatran/Pradax • edoxaban/Savaysa • enoxaparin/Lovenox • rivaroxaban/Xarelto
CYP3A4 Strong Inducers	• apalutamide • carbamazepine • enzalutamide • mitotane • phenytoin • rifampin • St. John's wort
CYP3A4 Strong Inhibitors	• boceprevir • cobicistat • danoprevir and ritonavir • elvitegravir and ritonavir • grapefruit juice (any grapefruit product) • indinavir and ritonavir • itraconazole • ketoconazole • lopinavir and ritonavir • paritaprevir and ritonavir and (ombitasvir and/or dasabuvir) • posaconazole • ritonavir • saquinavir and ritonavir • telaprevir • tipranavir and ritonavir • telithromycin • troleandomycin • voriconazole • clarithromycin • idelalisib • nefazodone • nelfinavir
Investigational Medications	• as in a clinical study
Interventional Medications/Supplements for FA[a]	• Idebenone • CoQ10 • vitamin E • etravirine • resveratrol • vitamin B3/nicotinamide • vitamin D3/calcitriol

Abbreviations: CoQ10, coenzyme Q10; CYP3A4, cytochrome p450 3A4; FA, Friedreich ataxia
Note: This list is neither comprehensive, nor final. Please contact the medical monitor with any questions regarding prohibited medications.

[a] Low doses of Vitamin E and/or CoQ10, for general health/as part of a multivitamin and Vitamin D3 for deficiency or for bone health are allowable if the dose remains stable throughout the study.

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