# CLINICAL PROTOCOL

# VATIQUINONE (PTC743, FORMERLY KNOWN AS EPI-743)

# AN OPEN-LABEL, SAFETY STUDY FOR PREVIOUSLY TREATED VATIQUINONE (PTC743) SUBJECTS WITH INHERITED MITOCHONDRIAL DISEASE

**PTC743-CNS-005-LSEP**

**25 JANUARY 2023**

**VERSION 3.0**

**PTC THERAPEUTICS, INC.**
**100 CORPORATE COURT**
**SOUTH PLAINFIELD, NJ 07080 USA**

## PROTOCOL IDENTIFIERS AND STUDY PERSONNEL

| | |
|---|---|
| **Project Code** | PTC743-CNS |
| **International Nonproprietary Name** | Vatiquinone |
| **Therapeutic Area** | Neurology |
| **PTC Therapeutics Substance Identifier** | PTC743 (formerly EPI-743) |
| **IND Number** | 107401; 140755 |
| **EudraCT** | 2020-002100-39 |
| **Protocol Number** | PTC743-CNS-005-LSEP |
| **Protocol Version** | 3.0 |
| **Protocol Version Date** | 25 January 2023 |
| **Protocol Phase** | 3 |
| **Protocol Title** | An Open-label, Safety Study for Previously Treated Vatiquinone (PTC743) Subjects With Inherited Mitochondrial Disease |
| **PTC Clinical Lead** | PPD |
| **PTC Medical Monitor** | PPD |
| **PTC Biostatistician** | PPD |
| **PTC Study Manager** | PPD |

## SIGNATURE PAGE

### Sponsor's Approval

The protocol has been approved by PTC Therapeutics.

### Sponsor's Authorized Officers:

PPD
PTC Therapeutics, Inc.

**Date**

PPD
PTC Therapeutics, Inc.

**Date**

PPD
PTC Therapeutics, Inc.

**Date**

The eSignature Page is located on the last page.

## INVESTIGATOR'S AGREEMENT

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

_____

Printed Name of Investigator
<<Institution Name>>
<<Address>>
<<Telephone Number>>
<<Fax Number>>

_____

Signature of Investigator

_____

Date

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# LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation or Specialized Term | Explanation |
|---|---|
| 15-LO | 15-lipoxygenase |
| AE | adverse event |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| CBC | complete blood count |
| CFR | Code of Federal Regulations |
| CRF | case report form |
| CTCAE | Common Terminology Criteria for Adverse Event |
| CYP | cytochrome P450 |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EOT | End-of-Treatment |
| ET | Early Termination |
| G-tube | gastrostomy tube |
| GCP | Good Clinical Practice |
| Gpx4 | glutathione peroxidase 4 |
| IB | Investigator's Brochure |
| ICF | informed consent form |
| ICH | International Council for Harmonisation |
| IEC | Independent Ethics Committee |
| INR | international normalized ratio |
| IRB | Institutional Review Board |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MELAS | mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes |
| MERRF | myoclonic epilepsy with ragged-red fibers |
| NOAEL | no-observed-adverse-effect level |
| NPMDS | Newcastle Pediatric Mitochondrial Disease Scale |
| PCH6 | pontocerebellar hypoplasia type 6 |
| PedsQL | Pediatric Quality of Life Inventory™ |
| PT | prothrombin time |
| PTT | partial thromboplastin time |
| RSI | Reference Safety Information |
| SAE | serious adverse event |
| Study MIT-E | Study PTC743-MIT-001-EP |
| SURF1 | surfeit locus protein 1 |
| SUSAR | suspected unexpected serious adverse reaction |
| TID | three times a day |
| ULN | upper limit of normal |
| WOCBP | women of childbearing potential |

# 1. SYNOPSIS

| | | |
|---|---|---|
| **Name of Sponsor/Company:** PTC Therapeutics, Inc. | | |
| **Name of Investigational Product:** Vatiquinone (PTC743, formerly known as EPI-743) | | |
| **Name of Active Ingredient:** Alpha-tocotrienol quinone | | |
| **Protocol Number:** PTC743-CNS-005-LSEP | **Phase:** 3 | **Country:** Global |
| **Title of Study:**<br>An Open-label, Safety Study for Previously Treated Vatiquinone (PTC743) Subjects With Inherited Mitochondrial Disease | | |
| **Studied period (years):**<br>June 2021 until approximately March 2025. All subjects will receive a minimum of 12 months of treatment. | | |
| **Objectives:**<br>**Primary:** To assess the safety of vatiquinone in subjects with inherited mitochondrial disease who participated in a previous vatiquinone clinical study or treatment plan.<br>**Exploratory:**<br>• To explore the effects of vatiquinone in motor seizure count in subjects previously enrolled in Study PTC743-MIT-001-EP (Study MIT-E).<br>• To explore the effects of vatiquinone based on the Newcastle Pediatric Mitochondrial Disease Scale (NPMDS) in subjects previously enrolled in Study MIT-E.<br>• To demonstrate the effects of vatiquinone on health-related quality of life in subjects previously enrolled in Study MIT-E.<br>**Study Design:** This is an open-label, Phase 3, safety study of vatiquinone in subjects with inherited mitochondrial disease who participated in a previous clinical study or treatment plan (parent study). A target of approximately 200 previously treated vatiquinone subjects will be enrolled at up to approximately 40 investigational sites worldwide. Subjects will receive vatiquinone oral solution (100 mg/mL), up to 400 mg, administered orally or via feeding tube three times a day (TID). Subjects will continue the dosing regimen from their parent study. The study will include a Screening/Baseline Visit, a Treatment Period, and an End-of-Treatment Visit. For subjects that will discontinue early, an Early Termination Visit will be performed 6 weeks after discontinuation.<br>Safety assessments for subjects will be performed at Screening/Baseline and every 6 months. Safety assessments will also be collected for all subjects at the End-of-Treatment Visit. | | |
| **Sample Size Justification:**<br>The sample size for this study is based on the number of subjects in previous vatiquinone studies and is not based upon any formal statistical hypothesis. | | |
| **Number of patients (planned):**<br>Up to 200 subjects | | |
| **Diagnosis and main criteria for inclusion:**<br>**Inclusion criteria**:<br>Participants are eligible to be included in the study only if all of the following criteria apply:<br>1. Subjects with inherited mitochondrial disease including Leigh syndrome, Alpers syndrome, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), myoclonic epilepsy with ragged-red fibers (MERRF), pontocerebellar hypoplasia type 6 (PCH6), or other mitochondrial disease who participated in a previous vatiquinone clinical study or treatment plan. | | |

2. Women of childbearing potential (as defined in (CTFG 2020)) must have a negative pregnancy test at Screening/Baseline and agree to abstinence or the use of at least one of the following highly effective forms of contraception (with a failure rate of <1% per year when used consistently and correctly). Highly effective contraception or abstinence must be continued for the duration of the study and for up to 50 days after the last dose of study drug:
   - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
     - oral
     - intravaginal
     - transdermal
   - progestogen-only hormonal contraception associated with inhibition of ovulation:
     - oral
     - injectable
     - implantable
   - intrauterine device
   - intrauterine hormone-releasing system
   - vasectomized partner with confirmed azoospermia

   All females will be considered of childbearing potential unless they are postmenopausal (at least 12 months consecutive amenorrhea in the appropriate age group without other known or suspected cause) or have been sterilized surgically (eg, bilateral tubal ligation, hysterectomy, bilateral oophorectomy).
3. Fertile men, as defined in (CTFG 2020), who are sexually active with women of childbearing potential and who have not had a vasectomy, must agree to use a barrier method of birth control during the study and for up to 50 days after the last dose of study drug.

**Exclusion criteria**:

Participants are excluded from the study if any of the following criteria apply:

1. Current participation in any other interventional study
2. Pregnancy or breastfeeding

**Investigational product, dosage, and mode of administration:**

Vatiquinone oral solution (100 mg/mL), up to 400 mg, administered orally or via feeding tube, TID. Subjects will continue the dosing regimen from their parent study.

**Duration of treatment:**

The duration of vatiquinone treatment will be subject to the following conditions:

- The subject has the right to withdraw consent and discontinue vatiquinone at any time.
- The relevant regulatory authority and/or PTC Therapeutics (PTC) may discontinue the study at any time.
- If the subject's condition substantially worsens after initiating vatiquinone treatment in this study, the subject will be carefully evaluated by the investigator in consultation with the PTC medical monitor. The subject will be withdrawn from treatment if continuing would place the subject at risk.
- The investigator may withdraw the subject from vatiquinone treatment if, in the investigator's clinical judgment, it is not in the subject's best interest to continue.

- If the subject is unable to tolerate vatiquinone, the subject will be withdrawn from treatment.

**Reference therapy, dosage, and mode of administration:**
None

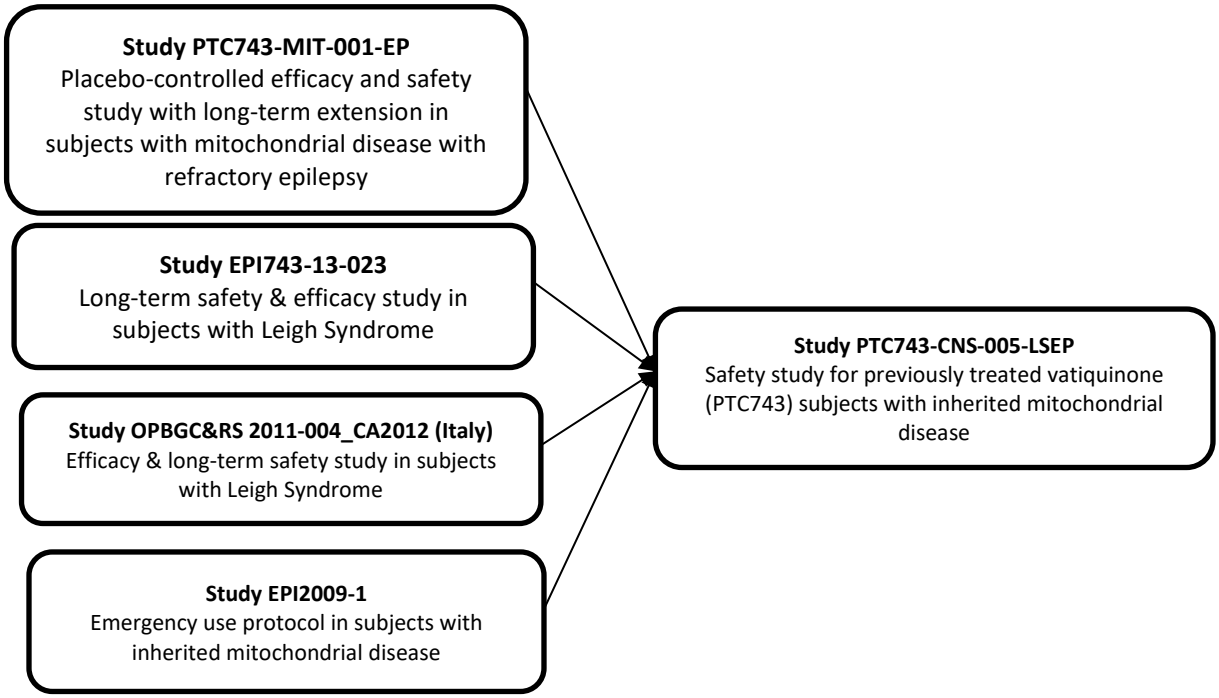
**Criteria for evaluation:**
**Efficacy:**
Efficacy assessments will include number of motor seizures recorded in the seizure diary for rollover subjects previously enrolled in Study MIT-E only. The NPMDS and health-related quality of life as measured by the CarerQoL-7D and the Pediatric Quality of Life Inventory™ (PedsQL) questionnaires will be assessed for rollover subjects previously enrolled in Study MIT-E only.
**Safety:**
Subjects will be monitored for adverse events (AEs)/serious adverse events (SAEs), laboratory abnormalities, vital signs, and electrocardiograms (ECGs).

**Statistical methods:**
All subjects who receive ≥1 dose of vatiquinone will be included in the analyses of safety.
All statistical methods will be descriptive in nature. For continuous variables, median, mean, standard deviation, minimum, maximum, and number of subjects with non-missing data will be presented. For categorical variables, the number (percent) of subjects in each category will be provided.
Frequencies of AEs will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class, Preferred Term, severity, relationship to study drug, and seriousness.
The change in the NPMDS score (sum of Sections 1 to 3) and the health-related quality of life, as measured by the CarerQoL-7D and PedsQL, will be summarized descriptively based on the safety population in subjects previously enrolled in Study MIT-E.
Vital signs, laboratory data, and ECG will be summarized by visit. Changes from baseline will be summarized by visit, where appropriate.

## 1.1. Clinical Study Participation History

Clinical study participation history of subjects who were previously treated with vatiquinone is shown in Figure 1.

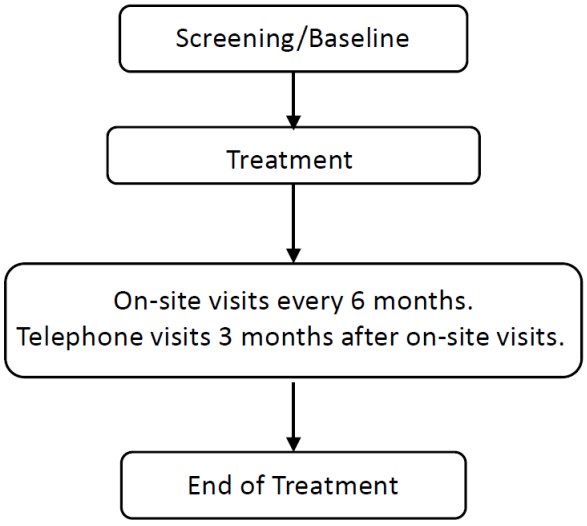
**Figure 1: Clinical Study Participation History of Subjects in Study PTC743-CNS-005-LSEP**




## 1.2. Schema

The study schema is shown in Figure 2.

**Figure 2: Study Schema**



## 1.3. Schedule of Assessments

**Table 1: Schedule of Assessments**

| **Study Period** | **Screening/Baseline**[a] | **Treatment** | | **EOT Visit** | **ET (6 Weeks After D/C)**[b] |
|---|---|---|---|---|---|
| **Study Month** | **Day 1** | **Telephone Visits 3 Months (84±7 Days) After On-Site Visits** | **Every 6 Months (168±7 Days)** | | |
| Informed consent | X[c] | | | | |
| Demographics | X | | | | |
| Medical history | X | | | | |
| Vital signs | X | | X | X | X |
| Height | X | | | | |
| Weight | X | X[d] | X | X | X |
| Physical examination | X | | X | X | X |
| 12-Lead ECG | X | | X | X | X |
| Urine pregnancy test (WOCBP)[l] | X | | X | X[e] | X |
| Hematology (CBC w/ differential) | X[m] | | X[m] | X[m] | X[m] |
| Serum chemistry | X[m] | | X[m] | X[m] | X[m] |
| Coagulation panel | X[m] | | X[m] | X[m] | X[m] |
| Urinalysis[f] | X | | X | X | X |
| NPMDS[g] | X | | X | X | X |
| CarerQoL-7D[g] | X[h] | | X | X | X |
| PedsQL[g] | X[h] | | X | X | X |
| Drug dispensed[i] | X | X | X | | |
| Pre-/post-shipment contact[j] | | X | | | |
| Drug compliance[k] | | | X | X | X |
| AE/SAE assessment | X | X[d] | X | X | X |
| Prior/concomitant medication | X | X[d] | X | X | X |

**Abbreviations**: AE, adverse event; CBC, complete blood count; D/C, discontinuation; ECG, electrocardiogram; EOT, End-of-Treatment; ET, Early Termination; NPMDS, Newcastle Pediatric Mitochondrial Disease Scale; PedsQL, Pediatric Quality of Life Inventory™; SAE, serious adverse event; Study MIT-E, Study PTC743-MIT-001-EP; WOCBP, women of childbearing potential

[a] On-site visit applicable to all subjects rolling over to this study. For subjects rolling over from Study MIT-E, the Screening/Baseline Visit in this study will also be the Week 72 visit in Study MIT-E.

[b] Subjects who discontinue vatiquinone prematurely should complete an ET Visit.

[c] Informed consent will be signed before any study procedures. In case the subject/caregivers cannot attend the Screening/Baseline Visit in the clinic, remote consenting can be obtained.

[d] Clinical site staff will contact subject or parent(s)/legal guardian(s) every 3 months (by telephone if there is no clinic visit) to assess AEs, weight, and concomitant medications.

[e] At-home urine pregnancy test kits will be provided; subjects will be required to perform the test at home 30 days after the last dose of study drug and self-report the results via telephone.
[f] Urinalysis by dipstick collection or serum test.
[g] To be performed only for subjects previously enrolled in Study MIT-E.
[h] These assessments will be performed at Week 72 of Study MIT-E and will be used as the Baseline assessment for this study.
[i] Drug will be dispensed to the subject every 3 months.
[j] Clinical site staff will contact the subject or parent(s)/legal guardian(s) to confirm details and timing of the upcoming study drug shipment. Post-shipment contact will confirm receipt of and condition of study drug.
[k] Subjects or parent(s)/caregiver(s) or legal guardian(s) should return all used and unused bottles of vatiquinone as instructed in order to assess study drug compliance.
[l] A pregnancy test will be administered every 6 months throughout the study. If urine pregnancy test is not possible, subjects can have a serum pregnancy test done.
[m] Approximately 7.7 mL of blood will be drawn per visit
Note: If a site visit is not possible, a telephone visit and local laboratory may be performed and reviewed by the investigator to assess safety and concomitant medications.

# 2. INTRODUCTION

Vatiquinone (PTC743, EPI-743, alpha-tocotrienol quinone) is a novel small molecule therapeutic in development for the treatment of mitochondrial diseases and associated disorders of oxidative stress and inflammation. Vatiquinone inhibits 15-lipoxygenase [15-LO], an oxidoreductase enzyme involved in response to oxidative stress and can promote inflammation and cell death. Vatiquinone is the quinone oxidation product of alpha-tocotrienol and is a member of the para-benzoquinone class of drugs. Vatiquinone is administered orally, crosses the blood-brain barrier, and works by targeting oxidoreductases that are critical to energy metabolism, oxidative stress, and inflammation.

For the most comprehensive nonclinical and clinical information regarding vatiquinone refer to the latest version of the Investigator's Brochure (IB) for vatiquinone.

## 2.1. Study Rationale

This open-label study will serve as a continued access study for subjects that have previously participated in a vatiquinone study. The purpose of this study is to ensure continued safety of vatiquinone dosing in previously treated subjects. To date, vatiquinone has been evaluated in a number of clinical studies for the treatment of mitochondrial diseases and has demonstrated a reduction of seizure- and disease-related morbidity in clinical studies of patients with mitochondrial disease and associated refractory epilepsy and has been shown to prevent cell death in cellular models for diseases of mitochondrial dysfunction.

This study explores the safety and efficacy of long-term treatment with vatiquinone.

## 2.2. Background

### 2.2.1. Nonclinical Safety Assessment 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 (Study 1660-045) and 9-month (Study 1660-046) 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 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 values of 48786 (rat) and 107426 ng.h/mL (dog). The dose-limiting adverse effect in both rat and dog studies was anticoagulation as demonstrated by prolonged prothrombin time (PT) and activated partial thromboplastin time (PTT) that most likely results from weak vitamin K antagonism exhibited by this class of compounds.

Vatiquinone was negative in the Good Laboratory Practice 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 rats (Studies AD75SX.503.BTL, AD75SX.348ICH.BTL, and AD75SX.125012ICH.BTL).

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 human ether-à-go-go-related gene channel current (Study 130416.FEK). Vatiquinone did not influence respiratory function in rat (Study 1660-032).

An in vitro phototoxicity study conducted in BALB/c 3T3 mouse fibroblasts to assess phototoxic potential, demonstrated that vatiquinone had no phototoxic potential when administered to the fibroblasts at concentrations up to 17.8 µg/mL (approximately 2 times the $C_{max}$ NOAEL of 8.828 µg/mL in rats).

### 2.2.2. Clinical Safety Studies

To date, over 500 patients have been treated with vatiquinone, ranging in age at enrollment from <1 year to 70 years old. Total drug exposure to date is more than 523000 patient days, with the longest exposure being over 10 years in a pediatric subject with Leigh syndrome (surfeit locus protein 1 [SURF1] variant). There have been 7 serious adverse events (SAEs) deemed possibly related to vatiquinone:

- One subject experienced 3 SAEs (pneumonia, tachycardia, and increased unresponsiveness) assessed as possibly related to vatiquinone by the investigator
- One subject experienced hypoglycemia assessed as possibly related to vatiquinone by the investigator
- One subject experienced depression assessed as possibly related to vatiquinone by the investigator
- One subject developed pancreatitis assessed as possibly related to vatiquinone by the investigator
- One subject developed neutropenia assessed as possibly related by the Investigator and the Sponsor

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.

## 2.3. Benefit/Risk Assessment

### 2.3.1. Risk Assessment

At the dose levels selected for this study it is not foreseen that subjects will endure any risks greater than minimal. However, as the dose-limiting adverse effect in nonclinical toxicology studies was anticoagulation, 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 (PT, PTT) are found to be increased to more than 1.5× upper limit of normal (ULN).

### 2.3.2. Benefit Assessment

There are no effective and/or approved treatments available for seizures in the majority of patients with mitochondrial disease. In order to participate in this study, subjects must have frequent seizure episodes despite treatment with existing antiepileptic therapies. In addition to improved seizure control, potential benefits may manifest in a variety of ways, such as in disease-related parameters, functioning, and quality of life.

### 2.3.3. Overall Benefit/Risk Conclusion

The Screening criteria for this study include that subjects must have seizures that are refractory to antiepileptic therapies. Therefore, the potential benefit to subjects is better control of their seizure activity. In order to further minimize risks, subjects will be closely monitored with a variety of safety measures.

# 3. OBJECTIVES AND ENDPOINTS

| Objectives | Endpoints |
|---|---|
| Primary | |
| • To assess the safety of vatiquinone in subjects with inherited mitochondrial disease who participated in a previous vatiquinone clinical study or treatment plan | • Adverse events (AEs)/SAEs, ECGs, vital signs, and laboratory data (hematology, biochemistry, and urine data) |
| Exploratory | |
| • To explore the effects of vatiquinone in motor seizure count in subjects previously enrolled in Study PTC743-MIT-001-EP (Study MIT-E) | • Total frequency of motor seizures per 28 days |
| • To explore the effects of vatiquinone based on the Newcastle Pediatric Mitochondrial Disease Scale (NPMDS) in subjects previously enrolled in Study MIT-E | • Change in the total score for NPMDS Sections 1 to 3 |
| • To demonstrate the effects of vatiquinone on health-related quality of life in subjects previously enrolled in Study MIT-E | • Measured by the CarerQoL-7D and Pediatric Quality of Life Inventory™ [PedsQL] questionnaires |

# 4. STUDY DESIGN

## 4.1. Overall Design

This is an open-label, Phase 3, safety study of vatiquinone in subjects with inherited mitochondrial disease who vatiquinone clinical study or treatment plan (parent study).

A target of approximately 200 previously treated vatiquinone subjects will be enrolled at up to approximately 40 investigational sites worldwide. Subjects will receive vatiquinone oral solution (100 mg/mL), up to 400 mg, administered orally or via feeding tube, three times a day (TID). Subjects will continue the dosing regimen from their parent study (Figure 1).

The study will include a Screening/Baseline Visit, a Treatment Period, and an End-of-Treatment Visit. For subjects that discontinue early, an Early Termination Visit will be performed 6 weeks after discontinuation.

The duration of vatiquinone treatment will be subject to the following conditions:

- The subject has the right to withdraw consent and discontinue vatiquinone at any time.
- The relevant regulatory authority and/or PTC Therapeutics (PTC) may discontinue the study at any time.
- If the subject's condition substantially worsens after initiating vatiquinone treatment in this study, the subject will be carefully evaluated by the investigator in consultation with the PTC medical monitor. The subject will be withdrawn from treatment if continuing would place the subject at risk.
- The investigator may withdraw the subject from vatiquinone treatment if, in the investigator's clinical judgment, it is not in the subject's best interest to continue.
- If the subject is unable to tolerate vatiquinone, the subject will be withdrawn from treatment.

Safety assessments for subjects will be performed at Screening/Baseline and every 6 months. Safety assessments will also be collected for all subjects at the End-of-Treatment Visit.

A diagram of the study design is provided in Section 1.2.

## 4.2. Scientific Rationale for Study Design

Seizures are a common symptom of mitochondrial disease and occur in up to 60% of patients with inherited mitochondrial disease. Over 90% of patients with mitochondrial disease-associated epilepsy have seizures that are refractory to traditional antiepileptic therapies (Saneto 2017). The refractory nature of seizures that occur in patients with inherited mitochondrial disease may be related to the fact that traditional antiepileptic therapies do not target the energetic pathways that underpin seizure pathology in these patients (Verrotti 2020). Furthermore, traditional antiepileptic therapies have been reported to increase oxidative stress which could have the potential to exacerbate mitochondrial disease pathology (Hamed 2004, Aycicek 2007). There is increasing evidence that seizure pathology is associated with ferroptosis (a form of programmed cell death that is regulated by the enzymes 15-LO and glutathione peroxidase 4 [Gpx4]). Vatiquinone, a novel small molecule therapeutic in development for

inherited mitochondrial disease, inactivates 15-LO and downregulates the production of oxidized lipid signaling molecules key to the mechanism of ferroptosis. In preclinical studies, vatiquinone has been demonstrated to rescue cells from patients with mitochondrial disease and associated epilepsy by inhibiting 15-LO. In previous clinical studies, vatiquinone therapy has been associated with a decrease in seizure frequency and seizure-related morbidity in patients with refractory epilepsy and mitochondrial disease.

### 4.3. Justification for Dose

Subjects will continue the dosing regimen from their parent study and the dose will be adjusted based on the subject's body weight, if applicable (Table 2).

**Table 2: Weight-Based Dosing in mL of the 100-mg/mL Solution**

| Subject Weight (kg) | Dose (mg/kg) TID | Dose Volume (mL) |
|---|---|---|
| 4 | 15 | 0.6 |
| 5 | 15 | 0.8 |
| 6 | 15 | 0.9 |
| 7 | 15 | 1.1 |
| 8 | 15 | 1.2 |
| 9 | 15 | 1.4 |
| 10 | 15 | 1.5 |
| 11 | 15 | 1.7 |
| 12 | 15 | 1.8 |
| 13 | 15 | 2.0 |
| Above 13 kg | 200 mg per dose | 2.0 |

**Subjects enrolled from Study MIT-E**

Vatiquinone oral solution is manufactured at 100 mg/mL for oral administration. The dose of 15 mg/kg if body weight <13 kg, and 200 mg if body weight ≥13 kg, TID (Table 2) was selected on the basis of clinical experience with vatiquinone and plasma concentration data in pediatric patients treated with doses of 100 to 200 mg TID. This dose range was well tolerated in all patients, showed biochemical evidence of target engagement, and was associated with clinical improvements in pediatric patients with mitochondrial disease. Using body weight-based dosing is standard of care for pediatric patients and eliminates the potential for overdose in low body weight patents, and also allows adequate plasma concentrations to be achieved in the face of significant variability in bioavailability.

Weight-based dose adjustment exposed above is only applicable to subjects transitioning from Study MIT-E. Subjects transitioning from Studies EPI743-13-023, OPBGC&RS 2011-004_CA2012(Italy), and EPI2009-1 will continue the vatiquinone dosing regimen from their parent study.

### 4.4. End of Study Definition

The end of the study per subject disposition will be the date of the last study visit for the last subject in the study.

# 5. STUDY POPULATION

The study population consists of male and female subjects who have genetically determined mitochondrial disease and associated refractory epilepsy (defined as those who were unsatisfactorily treated with at least 2 antiepileptic drugs).

## 5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Subjects with inherited mitochondrial disease including Leigh syndrome, Alpers syndrome, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), myoclonic epilepsy with ragged-red fibers (MERRF), pontocerebellar hypoplasia type 6 (PCH6), or other mitochondrial disease who participated in a previous vatiquinone clinical study or treatment plan.
2. Women of childbearing potential, as defined in (CTFG 2020), must have a negative pregnancy test at Screening/Baseline and agree to abstinence or the use of at least one of the following highly effective forms of contraception (with a failure rate of <1% per year when used consistently and correctly). Highly effective contraception or abstinence must be continued for the duration of the study, and for up to 50 days after the last dose of study drug:
   - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
     - oral
     - intravaginal
     - transdermal
   - progestogen-only hormonal contraception associated with inhibition of ovulation:
     - oral
     - injectable
     - implantable
   - intrauterine device
   - intrauterine hormone-releasing system
   - vasectomized partner with confirmed azoospermia

   All females will be considered of childbearing potential unless they are postmenopausal (at least 12 months consecutive amenorrhea in the appropriate age group without other known or suspected cause) or have been sterilized surgically (eg, bilateral tubal ligation, hysterectomy, bilateral oophorectomy).
3. Fertile men, as defined in (CTFG 2020), who are sexually active with women of childbearing potential and who have not had a vasectomy, must agree to use a barrier method of birth control during the study and for up to 50 days after the last dose of study drug.

## 5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Current participation in any other interventional study.
2. Pregnancy or breast feeding.

## 5.3. Lifestyle Considerations

Potential subjects must be willing and able to adhere to the following lifestyle restrictions during the study to be eligible for participation:

1. Refer to Section 6.8 for details regarding prohibited and restricted therapy during the study.
2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

## 5.4. Screen Failures

Any subject that does not meet inclusion or exclusion criteria at Screening/Baseline prior to enrollment, will be considered a screen failure. Screen failures can be rescreened after consultation with the medical monitor.

# 6. STUDY INTERVENTION AND CONCOMITANT THERAPY

Study intervention is defined as any investigational product(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

## 6.1. Study Intervention Administered

Details for the investigational product are shown in Table 3.

**Table 3: Investigational Product**

| | **Investigational Product** | |
|---|---|---|
| **Product Name** | Vatiquinone | |
| **Product Description** | Oral solution (100 mg/mL) is a solution of vatiquinone drug substance in super refined, preservative free sesame oil | |
| **Type** | Drug | |
| **Dose Formulation** | Oral solution | |
| **Unit Dose Strength(s)** | 100 mg/mL | |
| **Dose Level(s)** | Parent study: Study MIT-E<br>Vatiquinone at a dose of 15 mg/kg if body weight <13 kg, and 200 mg if body weight ≥13 kg TID | Parent Study: Studies other than Study MIT-E<br>Subjects will continue the vatiquinone dosing regimen from their parent study |
| **Route of Administration** | Oral or via gastric or nasogastric feeding tube | |
| **Use** | Experimental | |
| **Investigational Medicinal Product** | Yes | |
| **Sourcing** | Centrally by sponsor or locally by the study site, subsidiary, or designee | |
| **Packaging and Labeling** | Oral Solution Bottles (Booklet Labels) | |
| **Current/Former Names** | PTC743/EPI-743 | |

**Abbreviations**: Study MIT-E, Study PTC743-MIT-001-EP

Food is required for appropriate absorption of vatiquinone from the gastrointestinal tract. For subjects who have a gastrostomy tube (G-tube) installed, the study drug will be instilled into the G-tube using an oral dispenser. For subjects who are receiving continuous feed with liquid nutritional preparation such as PediaSure, the feed is interrupted to allow instillation of the drug solution into the G-tube using an oral dispenser, followed by resumption of the continuous feed to flush the drug into the stomach. For subjects who received G-tube feeding as bolus, the study drug is instilled into the G-tube using an oral dispenser, followed by the feed bolus to flush the drug into the stomach. The same procedures are to be followed in case the subject has a nasogastric tube installed. Additional detail on vatiquinone can be found in the Pharmacy Manual.

For subjects who do not have a G-tube installed and who can swallow, the study drug is given orally using an oral dispenser along with a meal that includes foods such as cream cheese, peanut butter, or other fatty components. The dose of study drug needs to be followed by eating yogurt, ice cream (no non-fat), or any other food with at least 25% calories from fat.

## 6.2. Preparation, Handling, Storage, and Accountability

### Preparation/Handling/Storage

No preparation is required; vatiquinone is provided as a ready to use oral solution.

At room temperature, vatiquinone is a yellow to orange clear liquid. Fifty-four mL of the solution is filled into a 60 mL amber glass bottle and closed with child resistant cap suitable for multiple dose administration.

Each bottle will be labeled with the following but not limited to: Product name, concentration, batch number, expiration date, storage conditions, and a caution limiting it for Clinical Trial Use Only.

### 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 assess drug accountability and will request to review the Pharmacy Records and investigator study file to assure the study drug is prescribed by the investigator or designee for the purpose of this study.

At study completion, all drug supplies including partially used and empty containers must be either returned to the Sponsor or designee or destroyed per your institution's guidelines for destruction of investigational product after drug accountability has been performed by the study monitor.

## 6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study. Subjects will continue the dosing regimen from their parent study.

## 6.4. Study Intervention Compliance

Study drug will be reviewed to assess compliance on an ongoing basis. Subjects who take >80% of the prescribed doses and no more than 120% of the prescribed doses will be considered compliant. Subjects who fall outside of this threshold will be counseled and instructed on dosing procedures. Medication compliance will be recorded in the diary.

## 6.5. Dose Modification

This protocol allows some alteration from the currently outlined dosing schedule as described in Section 4.3.

## 6.6. Continued Access to Study Intervention After the End of the Study

There is no planned continued access after the end of the study.

## 6.7. Treatment of Overdose

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 AE as described in the applicable clinical study protocol.

## 6.8. Concomitant Therapy

Any medication taken by a subject 30 days prior to the Screening/Baseline Visit and during the course of the study and the reason for use of the medication will be recorded on the electronic case report form (eCRF)/paper case report form (CRF). During the Screening/Baseline Visit, 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 medication throughout the study (including over-the-counter medications) without consulting the investigator.

All immunizations will be considered as concomitant medications and will be recorded in the eCRF/CRF. Subjects will be instructed to consult the investigator before immunization. The final decision on any immunization should be made by the treating physician in consultation with the patient and/or caregiver.

### 6.8.1. Rescue Medicine

Use of rescue medications for epilepsy will be collected. The following standardized criteria should be used for use of rescue medications:

- Seizure lasting longer than 4 minutes
- Occurrence of status epilepticus
- Cluster of 15 or more seizures

### 6.8.2. Prohibited Medications

Subjects will be required to maintain a stable regimen of mitochondrial disease supplements from Screening throughout the study.

Anticoagulants such as vitamin K antagonists, Factor Xa inhibitors are not permitted during the course of the study because of the potential interaction with vatiquinone on vitamin K associated coagulation factor synthesis.

Cytochrome P450 (CYP) inhibitors such as itraconazole have been demonstrated to significantly increase the plasma concentrations of vatiquinone (up to 2-fold). CYP inducers such as rifampin significantly reduce the plasma concentrations of vatiquinone (up to 50% less). Therefore, strong CYP inducers and inhibitors, including grapefruit/grapefruit juice and St John's wort extract, should be avoided during the course of the study.

In case treatment with a CYP inhibitor is required during the course of the study, coagulation parameters should be monitored and vatiquinone dose should be reduced by 33% in case international normalized ratio (INR) increases over 1.5×ULN or Common Terminology Criteria for Adverse Event (CTCAE) Grade 2.

In the event that a CYP inducer is used, no adjustment of the study drug dose will be required because there are no safety concerns with CYP inducers.

# 7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1. Discontinuation of Study Intervention

Subjects receive study drug until treatment discontinuation for one of the reasons listed below. However, subjects may discontinue study drug or withdraw their consent to participate in the study at any time without prejudice.

The following conditions require subject discontinuation from all study drug:

- 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 vatiquinone and, in the investigator's or the Sponsor's medical judgment, continuation of treatment would be detrimental to the subject
- Spontaneous bleeding in a 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 (Section 5.1)
- If a subject becomes pregnant
- Significant noncompliance with the protocol in the opinion of the Investigator or the Sponsor
- Use of prohibited concomitant medication

## 7.2. Participant Discontinuation/Withdrawal From the Study

In all cases of subject withdrawal or discontinuation, the reason for withdrawal must be recorded in the eCRF/CRF 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 Section 8.3.

Evaluations should be performed on all subjects who participate but do not complete the study according to protocol. The investigator will make every effort to contact subjects lost to follow-up. 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.

## 7.3. Lost to Follow-up

Subjects are considered lost to follow-up if the subject does not return to the clinic and attempts to contact the subject are unsuccessful. Efforts must be made on the part of the site to avoid any subject being lost to follow-up during the study. Before subjects are considered lost to follow-up, a minimum of 2 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. After being considered lost to follow-up, a subject's status may be changed if the subject makes contact at a later time provided the study is ongoing.

# 8. STUDY ASSESSMENTS AND PROCEDURES

The Schedule of Assessments (Table 1) summarizes the frequency and timing of safety measurement applicable to the study. Every effort should be made to keep participants on the planned study schedule.

## 8.1. Efficacy Assessments

### 8.1.1. Seizure Assessment – Subjects Previously Enrolled in Study MIT-E Only

Efficacy assessments will include numbers of motor seizures recorded in the seizure diary.

### 8.1.2. Newcastle Pediatric Mitochondrial Disease Scale – Subjects Previously Enrolled in Study MIT-E Only

The NPMDS assessment that corresponds to the subject's age at the time of informed consent will be used. According to the NPMDS manual, NPMDS Sections 1 to 3 will be assessed by the investigator or subinvestigator (by the same physician during the entire study period, whenever possible), and NPMDS Section 4 will be assessed by the subject's guardian (by the same guardian during the entire study period, whenever possible) and the subject (if he or she is 7 years of age or older and is able to complete the assessment). The investigator or subinvestigator are to record the dates and results of assessments in the CRF.

Cognitive function in NPMDS Section 3 is not planned to be measured.

### 8.1.3. Quality of Life – Subjects Previously Enrolled in Study MIT-E Only

The health-related quality of life, as measured by the CarerQoL-7D and the PedsQL questionnaires, will be captured in the electronic diary or recorded on the appropriate page of the CRF.

## 8.2. Safety Assessments

AEs will be reported and followed by the investigator as specified in Section 8.3.

The study will include the following evaluations of safety and tolerability according to the time points provided in the Schedule of Assessments (Table 1).

### 8.2.1. Demographic/Medical History

Medical history and demographics including age, gender, and race, will be collected at the Screening/Baseline Visit. The investigator should review the study candidate's clinical history, including details relating to inherited mitochondrial disease and any other medical conditions. Information regarding current medications must be captured on the concomitant medication eCRF/CRF.

### 8.2.2. Physical Examination, Height, Weight, and Vital Signs

Complete physical exams will be conducted (excluding genital/rectal exam) at protocol specified study visits. The physical examination will consist of an examination of the following: general appearance, skin, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest, heart, abdomen, and extremities (Table 1).

Standing height (in cm) will be measured at Screening/Baseline Visit. Weight (kg) will be measured at Screening/Baseline Visit, every 3 months, End-of-Treatment Visit, and at the Early Termination Visit (6 weeks after discontinuation of study drug), if applicable. As noted in Table 1, when not at the clinical site, weight will be collected by telephone. Weight will be measured in ordinary indoor clothing (ie, street clothes, scrubs) with shoes off.

Vital signs measurements (including systolic and diastolic blood pressure, pulse rate, 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). Vital signs will be monitored at the Screening/Baseline Visit, every on-site treatment visit, End-of-Treatment Visit, and at the Early Termination Visit (6 weeks after discontinuation of study drug), if applicable (Table 1).

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.

### 8.2.3. 12-Lead Electrocardiograms

12-Lead ECG will be measured at Screening/Baseline Visit, every on-site treatment visit, and End-of-Treatment Visit as noted in Table 1.

### 8.2.4. Clinical Safety Laboratory Assessments

Hematology, serum chemistry, and urinalysis will be collected as noted in Table 1 to assess safety. Subjects will have approximately 15 mL of blood drawn per visit over the course of the study. The total amount of blood drawn will vary per subject depending on the duration of study participation.

#### *8.2.4.1. Hematology*

- Erythrocytes: red blood cell count, hematocrit, hemoglobin, mean corpuscular volume
- Leukocytes: white blood cell count and differential (basophils, eosinophils, lymphocytes, monocytes, and neutrophils)
- Platelets: platelet count

#### *8.2.4.2. Coagulation*

- PT with INR and PTT

#### *8.2.4.3. Serum Chemistry*

- Liver: Alkaline phosphatase, alanine aminotransferase (ALT), serum glutamic-pyruvic transaminase), aspartate aminotransferase (AST), serum glutamic-oxaloacetic transaminase), bilirubin (total, direct), gamma-glutamyl transferase, and lactic dehydrogenase
- Renal: blood urea nitrogen and creatinine
- Electrolytes: sodium, potassium, chloride, carbon dioxide, calcium, magnesium, phosphate

- General: total protein, albumin, glucose
- Lipids: cholesterol (total) and triglycerides

#### *8.2.4.4. Urinalysis (Dipstick or Serum)*

- pH
- Protein
- Glucose
- Ketones
- Blood
- Bilirubin

### 8.2.5. Pregnancy Testing

Urine or serum pregnancy test will be measured on all female subjects of childbearing potential as noted in Table 1. At-home urine pregnancy test kits will be provided; subjects will be required to perform the test at home 30 days after the last dose of study drug and self-report the results via telephone.

## 8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

### 8.3.1. 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, 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 8.3.2 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 nonserious by the investigator using medical and scientific judgment.

### 8.3.2. 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
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization*
- Results in persistent or significant disability or incapacity
- 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).

*Excluding hospitalizations for administration of vatiquinone, procedures required by the study protocol, or treatment-related diagnostic procedures, other planned hospitalizations, or hospitalizations related only to progression of disease. Emergency room visits that do not require admission to the hospital do not fall into this category, but the event may be serious due to another seriousness criterion.

Serious adverse events will be assessed from the time of the Screening Visit through 30 days after the end of the subject's participation in the study (last dose) and should be reported to the sponsor if the investigator becomes aware of them.

### 8.3.3. Unexpected Adverse Events

The IB 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.

### 8.3.4. 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.

### 8.3.5. Recording Nonserious Adverse Events and Serious Adverse Events

All AEs (both serious and nonserious) 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 nonserious (Section 8.3.2)
- Relationship to study drug (Section 8.3.6)
- Severity of the event (Section 8.3.7)
- Onset date
- Resolution date, or date of death
- Action taken
- Outcome of the event

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

### 8.3.6. 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 4.

**Table 4: Relationship of Study Drug to Adverse Event 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 AE 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 AE to a concomitant drug, medical history of a similar event, the subject's disease state, other medical conditions, or environmental factors. |

**Abbreviations**: AE, adverse event

### 8.3.7. Grading of Severity of Adverse Event

The severity of AE will be graded using 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 5.

**Table 5: Grading of Adverse Event Severity 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 |

### 8.3.8. Adverse Event Reporting

Investigator site reporting requirements for AEs are summarized in Table 6.

**Table 6:** Investigator Site Requirements for Reporting Adverse Events

| Event | Recorded on the eCRF | Reported on the SAE/Pregnancy Report Form to PTC Pharmacovigilance Within 24 Hours of Awareness |
|---|---|---|
| SAE | All | All |
| Non-SAE | 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.

### 8.3.9. Reporting Serious Adverse Events

All SAEs occurring from the Screening Visit 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 Institutional Review Board (IRB) or Independent Ethics Committee (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**

PTC is responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify the IRB or IEC of all SAEs that occur at his or her site. Investigators will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical study. Each site is responsible for notifying its IRB or IEC of these additional SAEs.

### 8.3.10. 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 and must be reported on a Pregnancy Notification Form (see 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/CRFs (Section 8.3.9).

### 8.3.11. PTC Safety Reporting Requirement

As the sponsor of the study, PTC is responsible for reporting certain safety information, particularly suspected unexpected serious adverse reaction (SUSAR) and other significant findings as required, to each investigator in an expedited manner. If notification of an 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 a SAE. This awareness date is the date the regulatory reporting clock begins, and the date is considered Day 0.

## 8.4. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

## 8.5. Genetics

Genetics are not evaluated in this study.

## 8.6. Biomarkers

Biomarkers are not evaluated in this study.

# 9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods used to analyze the safety data is outlined below. Specific details will be provided in the statistical analysis plan.

## 9.1. Statistical Hypotheses

No hypotheses are planned to be tested.

## 9.2. Analysis Sets

**Safety population**: All subjects who receive at least 1 dose of vatiquinone in the study. Safety population will be used for all summaries in this study.

## 9.3. Statistical Analyses

### 9.3.1. General Considerations

The statistical analysis plan will be finalized prior to database lock and it will include a more detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses.

All statistical methods will be descriptive in nature. For continuous variables, median, mean, standard deviation, minimum, maximum, and number of subjects with non-missing data will be presented. For categorical variables, the number (percent) of subjects in each category will be provided.

By-subject listings will be created for each eCRF/CRF module.

### 9.3.2. Subject Disposition and Baseline Characteristics

The number of subjects who completed or discontinued from the study and the reasons of discontinuation will be summarized based on the safety population.

Demographics and Baseline characteristics will also be summarized.

### 9.3.3. Analysis of Efficacy

Total frequency of motor seizures per 28 days is an exploratory efficacy endpoint in subjects previously enrolled in Study MIT-E.

Seizure frequency will be based on the number of seizures per 28 days, calculated as the number of seizures over the time interval, divided by the number of the days in the interval, and multiplied by 28.

Motor seizure frequency in 28 days will be summarized by visit based on the safety population.

The change in the NPMDS score (sum of Sections 1 to 3) will be summarized by visit based on the safety population in subjects previously enrolled in Study MIT-E.

Health-related quality of life, as measured by the CarerQoL-7D and PedsQL, will be summarized descriptively based on the safety population in subjects previously enrolled in Study MIT-E.

### 9.3.4. Analysis of Safety

Frequencies of AEs will be tabulated by MedDRA System Organ Class, Preferred Term, severity, relationship to study drug, and seriousness.

Vital signs, laboratory data, and ECG will be summarized by visit. Changes from Baseline will be summarized by visit, where appropriate.

## 9.4. Interim Analysis

No interim analysis is planned.

## 9.5. Sample Size Determination

The sample size for this study is based on the number of subjects in previous vatiquinone studies and is not based upon any formal statistical hypothesis.

# 10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## 10.1. Regulatory, Ethical, and Study Oversight Consideration

### 10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations

The protocol, protocol amendments, informed consent form (ICF), IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

### 10.1.2. Informed Consent Process

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or their legally authorized representative. Adequate time should be provided for the participant to read the ICF, 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. This information must be provided to the participant prior to undertaking any study-related procedure.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy, and data protection requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants or their legally authorized representative must be reconsented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant or their legally authorized representative in a language in which the participant is fluent.

### 10.1.3. 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, CRFs, 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.

### 10.1.4. Clinical Monitoring

In accordance with 21 CFR Part 312.56 and/or relevant International Committee on Harmonisation guidelines, PTC or a designee will periodically inspect all eCRFs/CRFs, 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/CRFs; 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/CRFs 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.

### 10.1.5. Data Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, PTC, PTC's representatives, a regulatory authority and/or 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.

### 10.1.6. 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/CRFs and clinic records/source documents), all original signed ICFs, electronic copies (ie, CD-ROM, USB) 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.

### 10.1.7. Study and Site Start and Closure

**First Act of Recruitment**

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first site open is considered the first act of recruitment and it will be the study start date.

**Study Termination**

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

### 10.1.8. 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.

# 11. PROTOCOL AMENDMENT HISTORY

## 11.1. Amendment 2 (Version 3.0): 25 January 2023

Overall reason for Amendment 2 (Version 3.0): The overall reason for this amendment of the protocol was to add 2 new exploratory objectives and endpoints for subjects who were previously enrolled in Study MIT-E.

All changes to the protocol are listed below in the table. Minor editorial changes (typographical errors, punctuation. abbreviations, etc.) have been made to the protocol but are not listed below. All changes in the body of the protocol were made to the corresponding sections of the synopsis.

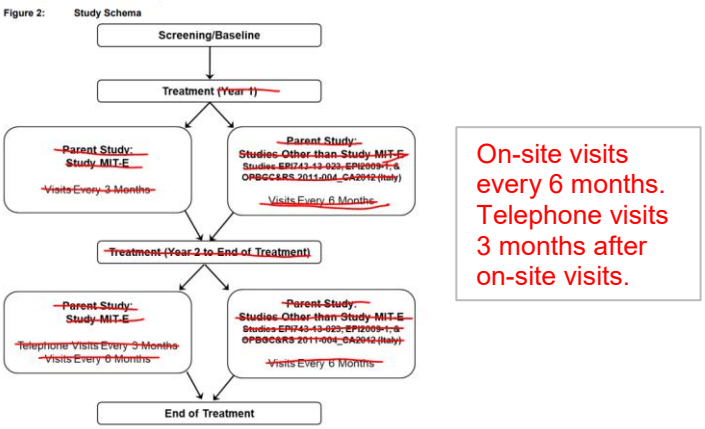
| Protocol Section | Amendment/Update | Reason/ Rationale |
|---|---|---|
| Table 1 | Revision of Table of Assessments to include the efficacy assessments for subjects in Study MIT-E, to clarify the visit windows, to clarify serum test could be performed for urinalysis tests, and to clarify all subjects who discontinue treatment prematurely were to have an ET visit. | Update |
| Section 2 | The description of vatiquinone has been updated. | Update |
| Section 2.1 | The study rationale was revised. | Update |
| Section 3 | Previous objectives were edited for clarity, and 2 new exploratory objectives and endpoints were added. | Update |
| Section 4.1 | The description of the study design was revised, the duration of treatment in this study was updated, and the description of when safety assessments were performed was clarified. | Update |
| Section 6.6 | The description of the potential for subjects to have access to vatiquinone after the study was updated. | Update |
| Section 8.1 | Previous endpoint was edited for clarity, and a description of the new efficacy assessments was added. | Update |
| Section 8.2.4.4 | Serum test for urinalysis was added. | Update |
| Section 9.3.3 | Previous endpoint was edited for clarity, and a description of the statistical plans for the new efficacy assessments was added. | Update |

**Abbreviations**: Study MIT-E, Study PTC743-MIT-001-EP

## 11.2. Amendment 1 (Version 2.0): 11 April 2022

Overall reason for Amendment 1: All subjects rolling over to this study will follow the same visit scheme from Screening/Baseline Visit. The protocol was updated and redundancies removed.

| Protocol Section | Amendment/Update | Reason/ Rationale |
|---|---|---|
| Table 1 | The current Table 1: Schedule of Assessments for Subjects from Studies Other than Study MIT-E:<br>- Drug dispensed: An "X" was marked for "telephone visits 3 months after on-site visits."<br>- Pre-/Post-shipment contact: An "X" was marked for "telephone visits" and removed for "every 6 months" visits.<br>- Physical examination, ECG, and drug compliance were added for ET visit.<br>- Header written "Telephone visit every 3 months" must was replaced by "Telephone Visits 3 Months After On-site Visits." | Update |
| Table 1, Table 2 | Revision of Table of Assessments to accommodate all subjects following the same scheme from Screening/Baseline<br>- Table 1 and all abbreviations related to Table 1 were removed.<br>- Table 2 stated: Table 1: Schedule of Assessments for Subjects From Studies Other Than Study MIT-E and also included the change mentioned in Item 6 above.<br>- Table footnote 'a' stated: ~~Subjects from studies other than Study MIT-E; includes subjects from Studies EPI743-13-023, EPI2009-1, and OPBGC&RS 2011-004_CA2012~~. On-site visit applicable to all subjects rolling over to this study. For subjects rolling over from Study MIT-E, the Screening/Baseline Visit in this study will also be the Week 72 in Study MIT-E. | Update |
| Table 1 | Added text below to the end of table footnote 'c'<br>In case the subject/caregiver cannot attend Screening/Baseline Visit in the clinic, remote consenting can be obtained. | Update to consent procedure |
| Table 1 | Added new footnote 'j' to "Urine pregnancy test (WOCBP)"<br>- 'j' A pregnancy test will be administered every 6 months throughout the study. If urine pregnancy test is not possible, subjects can have a serum pregnancy test done. | Update to pregnancy procedure |
| Section 1 | The following change was applied to accommodate all subjects following the same study scheme from Screening/Baseline.<br>~~Safety assessments and seizure data for subjects previously enrolled in vatiquinone Study MIT-E will be performed at screening/baseline, every 3 months for the first year after enrollment, and then every 6 months until vatiquinone becomes commercially available or the program is terminated.~~ Safety assessments for subjects ~~previously enrolled in vatiquinone studies other than Study MIT-E~~ will be performed at screening/baseline and every 6 months until vatiquinone becomes commercially available or the program is terminated. Safety assessments will also be collected for all subjects at the End-of-Treatment Visit. | Update to study procedures |

| Protocol Section | Amendment/Update | Reason/ Rationale |
|---|---|---|
| Figure 2 | Revision of study scheme to reflect all subjects following the same study scheme from Screening/Baseline.<br>  <br> | Update |
| Section 4.1 | The following change was applied to accommodate all subjects following the same study scheme from screening/baseline.<br>~~Safety assessments and seizure data for subjects previously enrolled in vatiquinone Study MIT-E will be performed at screening/baseline, every 3 months for the first year after enrollment, and then every 6 months until vatiquinone becomes commercially available or the program is terminated.~~ Safety assessments for subjects ~~previously enrolled in vatiquinone studies other than Study MIT-E~~ will be performed at screening/baseline and every 6 months until vatiquinone becomes commercially available or the program is terminated. Safety assessments will also be collected for all subjects at the End-of-Treatment Visit. | Update to study procedures |
| Section 4.3 | Added the following text:<br>Weight-based dose adjustment exposed above is only applicable for subjects transitioning from Study MIT-E. Subjects transitioning from Studies EPI743-13-023, OPBGC&RS 2011-004_CA2012(Italy), and EPI2009-1 will continue the vatiquinone dosing regimen from their parent study. | Clarification of dose |
| Section 6.5 | Change to text:<br>This protocol allows some alterations from the currently outlined dosing schedule~~, but the maximum daily dose will no exceed 200 mg TID,~~ as described in Section 4.3. | Update |
| Section 8 | The Schedule of Assessments (Table 1~~ and Table 2~~) summarizes the frequency and timing of safety measurement applicable to the study. Every effort should be made to keep participants on the planned study schedule. | Update |
| Section 8.2 | The study will include the following evaluations of safety and tolerability according to the time points provided in the Schedule of Assessments (Table 1~~ and Table 2~~). | Update |

| Protocol Section | Amendment/Update | Reason/ Rationale |
|---|---|---|
| Section 8.2.2 | Complete physical exams will be conducted (excluding genital/rectal exam) at protocol specified study visits. The physical examination will consist of an examination of the following: general appearance, skin, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest, heart, abdomen, and extremities (Table 1 ~~and Table 2~~).<br>Standing height (in cm) will be measured at Screening/Baseline Visit.<br>Weight (kg) will be measured at Screening/Baseline Visit, every 3 months, End-of-Treatment Visit, and at the Early Termination Visit (6 weeks after discontinuation of study drug), if applicable. As noted in Table 1 ~~and Table 2~~, when not at the clinical site, weight will be collected by telephone. Weight will be measured in ordinary indoor clothing (ie, street clothes, scrubs) with shoes off.<br>Vital signs measurements (including systolic and diastolic blood pressure, pulse rate, 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). Vital signs will be monitored at the Screening/Baseline Visit, every on-site treatment visit, End-of-Treatment Visit, and at the Early Termination Visit (6 weeks after discontinuation of study drug), if applicable (Table 1 ~~and Table 2~~). | Update |
| Section 8.2.3 | 12-lead ECG will be measured at Screening/Baseline Visit, every on-site treatment visit, and End-of-Treatment Visit as noted in Table 1 ~~and Table 2.~~ | Update |
| Section 8.2.4 | Hematology, serum chemistry, and urinalysis will be collected as noted in Table 1 ~~and Table 2~~ to assess safety. Subjects will have approximately 15 mL of blood drawn per visit over the course of the study. The total amount of blood drawn will vary per subject depending on the duration of study participation. | Update |
| Section 8.2.5 | Urine or serum pregnancy test will be measured on all female subjects of childbearing potential as noted in Table 1 ~~and Table 2~~. At-home urine pregnancy test kits will be provided; subjects will be required to perform the test at home 30 days after the last dose of study drug and self-report the results via telephone. | Update |

**Abbreviations**: ECG, electrocardiogram; ET, early termination; WOCBP, woman of childbearing potential

## 12. REFERENCES

Aycicek, A and Iscan, A. The effects of carbamazepine, valproic acid and phenobarbital on the oxidative and antioxidative balance in epileptic children. Eur Neurol 2007;57(2):65-69.

CTFG. (2020). "Clinical Trial Facilitation Group: Recommendations related to contraception and pregnancy testing in clinical trials." Retrieved 08 March 2021, from https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2020_09_HMA_CTFG_Contraception_guidance_Version_1.1_updated.pdf.

Hamed, SA, Abdellah, MM and El-Melegy, N. Blood levels of trace elements, electrolytes, and oxidative stress/antioxidant systems in epileptic patients. J Pharmacol Sci 2004;96(4):465-473.

Saneto, RP. Epilepsy and Mitochondrial Dysfunction: A Single Center's Experience. Journal of Inborn Errors of Metabolism and Screening 2017;5.

Verrotti, A, Lattanzi, S, Brigo, F and Zaccara, G. Pharmacodynamic interactions of antiepileptic drugs: From bench to clinical practice. Epilepsy Behav 2020;104(Pt A):106939.

Signature Page for PTC743-CNS-005-LSEP Clinical Protocol V3.0 - 25JAN2023 v3.0

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| Clinical Approval | PPD<br>Clinical Approval<br>I approve the document(s)<br>25-Jan-2023 21:01:11 GMT+0000 |

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| Statistics Approval | PPD<br>Statistics Approval<br>I approve the document(s)<br>25-Jan-2023 22:28:45 GMT+0000 |

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| Clinical Approval | PPD<br>Clinical Approval<br>I approve the document(s)<br>26-Jan-2023 13:26:59 GMT+0000 |

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