STATISTICAL ANALYSIS PLAN

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

PTC743-CNS-005-LSEP

04 APRIL 2025

VERSION 1.0

PTC THERAPEUTICS, INC.
500 WARREN CORPORATE CENTER DRIVE
WARREN, NJ 07059 USA

APPROVAL SIGNATURES

PPD

PTC Therapeutics, Inc.

Date

PPD

PTC Therapeutics, Inc.

Date

PPD

PTC Therapeutics, Inc.

Date

The eSignature page is located on the last page.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Term
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CarerQoL-7D	Care-Related Quality of Life-7 Dimensions
CRF	Case Report Form
ECG	Electrocardiogram
FDA	United States Food and Drug Administration
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
MedDRA	Medical Dictionary for Regulatory Activities
NPMDS	Newcastle Pediatric Mitochondrial Disease Scale
PedsQL	Pediatric Quality of Life Inventory™
PT	Preferred Term
PTT	Partial Thromboplastin Time
QTc	corrected QT interval
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SoA	Schedule of Assessments
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TFL	Table, Figure, and Listing
TID	ter in die (Three times a day)
WHO	World Health Organization

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze data and report results for PTC743-CNS-005-LSEP (Protocol version 3.0 dated on 25 January 2023. De novo subjects are introduced in Protocol version 2.1 specific for France and Italy). Table, figure, and listing (TFL) specifications are contained in a separate document.

This SAP will be approved prior to the database lock.

1.1. Study Design

This is an open-label, Phase 3, safety study of vatiquinone in subjects with inherited mitochondrial disease who either participated in a previous clinical study or treatment plan (rollover subjects) or failed to meet study entry criteria in a prior vatiquinone clinical study (de novo subjects). A target of approximately 200 previously treated vatiquinone subjects and approximately 4 de novo subjects will be enrolled at up to approximately 40 investigational sites worldwide. De novo subjects will receive vatiquinone oral solution (100 mg/mL), up to 200 mg, administered orally or via feeding tube three times a day (TID). Rollover 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 de novo subjects, the study visits will include Screening, Run-in, Baseline, Treatment Period and End-of-Treatment Visit. For subjects that will 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 rollover subjects will be performed at Screening/Baseline and every 6 months. Safety assessments for de novo subjects will be performed at screening, baseline, months 1, 3, 6, and 12, and every 6 months thereafter. Safety assessments will also be collected for all subjects at the End-of-Treatment Visit. Detailed schedule of activities are described in Table 2, Table 3, and Table 4. Diagrams of the study design are provided in Figure 1, Figure 2, and Figure 3.

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

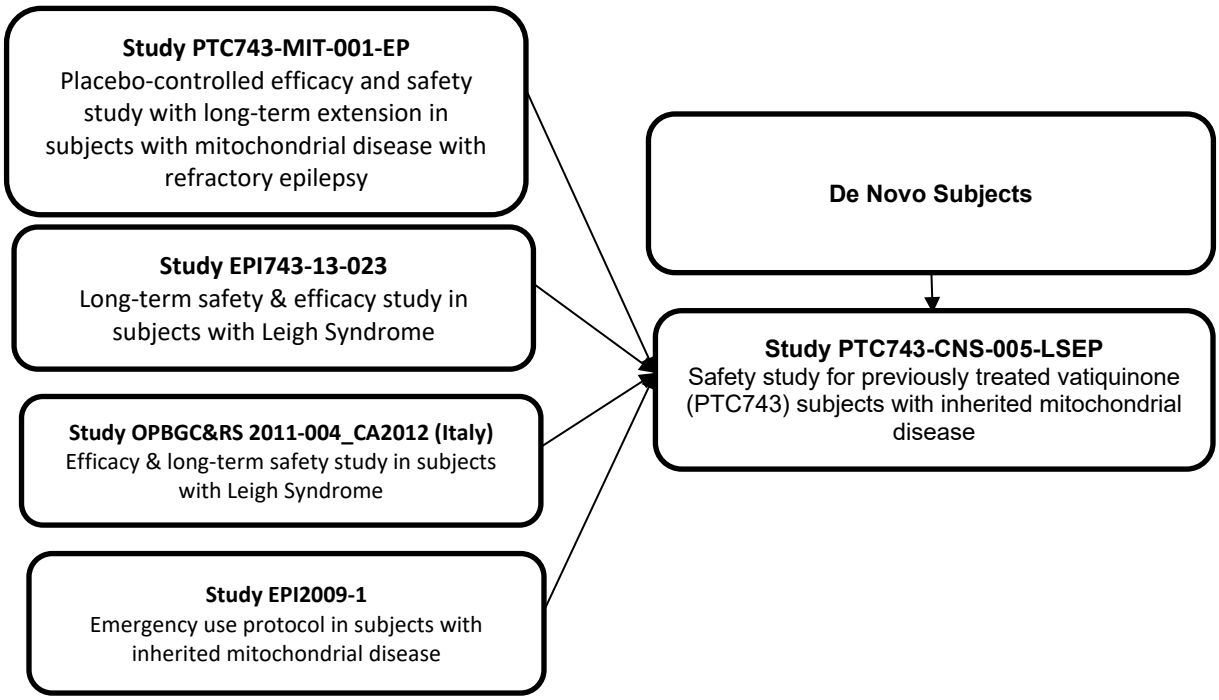


Figure 2: Study Schema (Rollover Subjects)

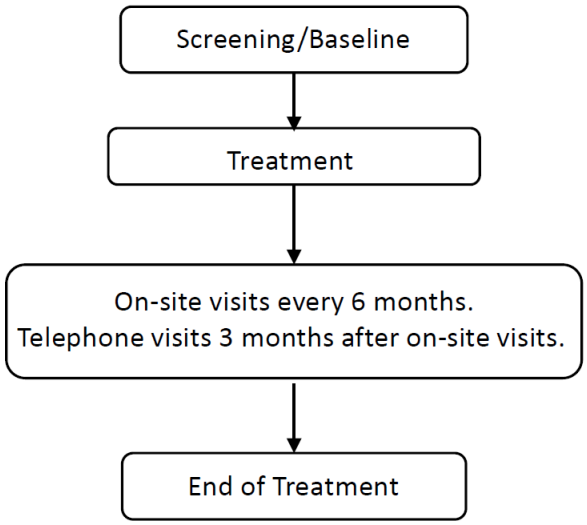
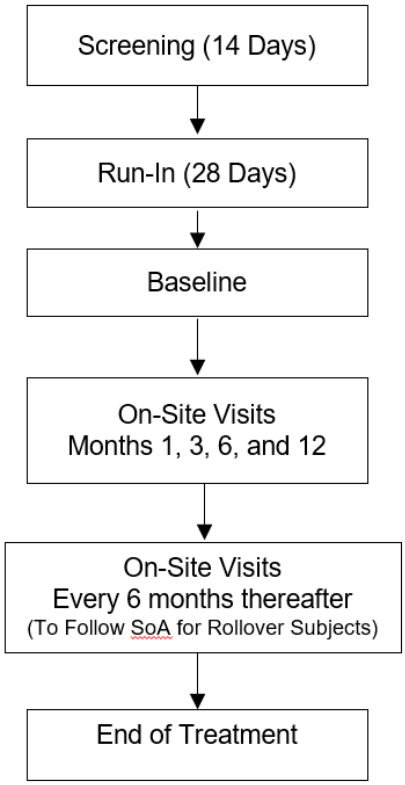


Figure 3: Study Schema – De Novo Subjects (France/Italy)



1.2. Study Objectives

1.2.1. Primary Objective

The primary objective of the study is to assess the safety of vatiquinone in subjects with inherited mitochondrial disease who participated in a previous vatiquinone clinical study or treatment plan, and de novo subjects who failed to meet study criteria in a prior vatiquinone clinical study.

1.2.2. Exploratory Objectives

Exploratory objectives of the study are:

- To explore the effects of vatiquinone in motor seizure count in subjects previously enrolled in Study PTC743-MIT-001-EP (referred to Study MIT-E hereafter) and in all de novo subjects.
- To explore the effects of vatiquinone based on the Newcastle Pediatric Mitochondrial Disease Scale (NPMDS) in subjects previously enrolled in Study MIT-E, and in all de novo subjects.
- To demonstrate the effects of vatiquinone on health-related quality of life in subjects previously enrolled in Study MIT-E, and in all de novo subjects.

1.3. Endpoints

1.3.1. Primary Endpoints

The primary endpoints of the study are adverse events (AEs), serious AEs (SAEs), electrocardiogram (ECGs), vital signs, and laboratory data (hematology, biochemistry, and urine data).

1.3.2. Exploratory Endpoints

Exploratory endpoints of the study are as follows:

- Total frequency of motor seizures per 28 days.
- Change in the total score for NPMDS Sections 1 to 3.
- Measured by the CarerQoL-7D and Pediatric Quality of Life Inventory™ [PedsQL] questionnaires.

1.4. 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.

2. STUDY POPULATIONS

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

3. GENERAL CONSIDERATIONS

For continuous variables, mean, standard deviation, median, minimum, maximum, and number of subjects with non-missing data will be provided. For categorical variables, the number and percentage of subjects in each category will be provided.

Day 1 is defined as the first dose date. Study days after day 1 are calculated as: assessment date - first dose date + 1. Study days prior to day 1 are calculated as assessment date - first dose day.

Measurements collected from unscheduled visits, or repeated assessments will be included in the listings only, unless otherwise specified.

The descriptive summaries will be presented by total subjects for safety endpoints. Exploratory and efficacy endpoints will be presented in listings only. All summaries will be based on nominal visits.

3.1. Baseline

For safety and efficacy endpoints, baseline will be defined as the last measurement prior to or on the date of first dose date in PTC743-CNS-005-LSEP.

3.2. Missing Data Handling

All analyses will be based on observed data only, and no missing values will be imputed unless otherwise indicated.

3.3. Changes of Analysis from Protocol

Although summaries for exploratory endpoints were included in the protocol, these endpoints will only be listed.

4. SUBJECT DATA

4.1. Participant Dispositions

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

4.2. Protocol Deviation

All major protocol deviations will be summarized for the safety population. A listing of protocol deviations will be presented for the safety population.

All major protocol deviations will be identified and documented by PTC team prior to database lock.

4.3. Demographic and Baseline Characteristics

Demographics and baseline characteristics including age, sex, race, ethnicity, region, country, height, weight, and body mass index (BMI) will be summarized for safety population.

4.4. Medical History

Medical history will be coded with the Medical Dictionary for Regulatory Activities (MedDRA, version 26.0). Medical history records will be summarized for the safety population.

A by-subject data listing of medical history will be provided.

4.5. Concomitant Medications

All investigator terms for medications recorded on the case report form (CRF) will be coded using the World Health Organization (WHO) Drug Dictionary (Version B3 Mar 2025).

Prior medications will be defined as medications started prior to the first dose of study drug. Concomitant medications will be defined as medications (other than the study drug) that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug.

Any medication with partial or missing end date in which the concomitant medication status cannot be determined will be considered as a concomitant medication.

Prior and concomitant medication will be summarized as following for the safety population:

- Number and percentage of subjects with at least one concomitant medications.
- By Anatomical Therapeutic Chemical (ATC) level 2 and preferred term (PT).

A by-subject data listing of all concomitant medications will be generated.

4.6. Duration of Treatment with Study Drug

Duration of treatment with study drug will be calculated as number of days from the date of the first dose in PTC743-CNS-005-LSEP to the date of the last dose, inclusive.

Duration of treatment will be summarized for safety population and will also be summarized by the following categories.

- <6 months
- ≥6 to <12 months
- ≥12 to <18 months
- ≥18 to <24 months
- ≥24 to <30 months
- ≥30 months

4.7. Study Drug Accountability

A by-subject data listing of study drug accountability, dose modification and medication error details will be provided.

5. PRIMARY ANALYSES

All primary analysis will be based on the safety population. Descriptive summaries will be based on nominal visits.

5.1. Adverse Events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into medical terminology using the MedDRA. AEs will be coded by System Organ Class (SOC) and Preferred Term (PT) using MedDRA, Version 26.0.

Only treatment-emergent AEs (TEAEs) will be included in summary tables. All AEs will be presented in subject data listings.

5.1.1. Treatment Emergent Adverse Event

A TEAE is defined as an AE that had an onset date on or after the first dose of study drug but prior to 30 days after last dose or it occurs prior to first dose of study drug and worsens in severity after first dose of study drug.

AEs with missing or partial onset date and cannot be determined if it occurred prior to the first dose of study treatment will be counted as TEAEs.

An overview TEAE table, including number and percentage of subjects with TEAEs, TEAEs by maximum CTCAE grade, treatment related TEAE, treatment related TEAE by maximum CTCAE grade, treatment-emergent SAEs (TESAEs), treatment related TESAEs, and TEAEs leading to study discontinuation will be provided.

Summary information (the number and percentage of subjects) will be tabulated for:

- Incidence of TEAEs by SOC and PT
- Incidence of TEAEs by PT in descending order
- Incidence of treatment-related TEAEs by SOC and PT
- Incidence of TEAEs by SOC, PT, and maximum CTCAE grade
- Incidence of TEAEs by SOC, PT, and relationship to study drug

TEAE tables will be sorted by SOC and then PT in decreasing frequency of the number and percentage of subjects in total column.

A by-subject data listing will be provided for all AEs.

5.1.2. Deaths, serious AE, and AE leading to discontinuation

The following summaries will be presented:

- Incidence of TESAEs by SOC and PT
- Incidence of treatment-related, treatment-emergent TESAEs by SOC and PT
- TEAEs leading to discontinuation by SOC and PT

Subjects who die, who have SAE and AE leading to discontinuation during the study will be provided in three separate data listings.

5.2. Clinical Laboratory Parameters

Laboratory parameters (Table 1) values and the change from baseline will be summarized for each visit.

A by-subject listing of laboratory results will be provided for hematology, coagulation, biochemistry, and urinalysis respectively.

Table 1: Clinical Laboratory Parameters

Type	Parameters
Hematology	Basophils, Eosinophils, Erythrocytes, Hematocrit, Hemoglobin, Leukocytes, Lymphocytes, Monocytes, Neutrophils, Platelets
Biochemistry	Alanine Aminotransferase, Albumin, Alkaline Phosphatase, Aspartate Aminotransferase, Bilirubin, Blood Urea Nitrogen, Calcium, Chloride, Cholesterol, Creatinine, Direct Bilirubin, Gamma Glutamyl Transferase, Glucose, Lactate Dehydrogenase, Potassium, Protein, Sodium, Triglycerides, Glutathione
Urinalysis	Ketones, Urine Glucose, Urine Protein, Pregnancy Test
Coagulation	Activated Partial Thromboplastin Time, Prothrombin Time, Intl. Normalized Ratio

5.3. Vital Signs

Vital signs (temperature, respiratory rate, systolic blood pressure, diastolic blood pressure, heart rate, oxygen saturation, weight, and BMI) and the change from baseline will be summarized for each visit.

A by-subject level listing of vital signs will be provided.

5.4. Electrocardiogram (ECG)

ECG results and the change from baseline (heart rate, PR interval, RR interval, QRS interval, QTc interval) along with ECG interpretations will be summarized for each visit.

A subject data listing of ECG results will be generated.

5.5. Physical examinations

A by-subject data listing of physical examination will be generated.

6. EXPLORATORY ANALYSIS

6.1. Seizure Frequency

Number of seizures for motor and non-motor seizures are collected in the seizure log. 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. Only "valid days" will be used in the calculations of seizures frequency per 28 days. A "valid day" is defined as the day where seizure counts information is present.

6.2. Newcastle Pediatric Mitochondrial Disease Scale (NPMDS)

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.

6.3. CarerQoL-7D and PedsQL

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.

7. MOCK TABLES, LISTINGS, AND GRAPHS

The tables, listings, and graphs shells for the study will be provided in a separate document.

8. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study PTC743-CNS-005-LSEP is based on the protocol Version 3.0 dated 25Jan2023.

SAP Version	Approval Date	Change	Rationale
1.0	04APR2025	Not Applicable	Original version

9. REFERENCES

None

APPENDIX 1. SCHEDULE OF EVENTS

Table 2: Schedule of Assessments – Rollover Subjects

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.

Table 3: Schedule of Assessments – De Novo Subjects (France)

Study Period	Screening/ Run-In[a]	Baseline	Treatment				
	Day -42 to Day -1	Day 0 (±7 Days)	Month 1 (28±7 Days)	Month 3 (56±7 Days)	Month 6 (84±7 Days)	Month 12[b] (168±7 Days)	ET (6 Weeks After D/C)[c]
Informed consent	X[d]						
Demographics	X						
Medical history	X						
Vital signs	X	X	X	X	X	X	X
Height	X	X					
Weight	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X
12-lead ECG	X	X	X	X	X	X	X
Electroencephalogram (EEG)	X						X
Urine pregnancy test (WOCBP)[i]	X	X	X	X	X	X	X
Hematology (CBC w/differential)	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]
Serum chemistry	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]
Coagulation panel	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]
Urinalysis[e]	X	X	X	X	X	X	X
NPMDS		X			X	X	X
CarerQoL-7D		X			X	X	X
PEDsQL		X			X	X	X
Drug dispensed[f]		X		X	X	X	
Drug compliance[g]				X	X	X	X
AE/SAE assessment	X	X	X	X	X	X	X
Prior/Concomitant medication	X	X	X	X	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; WOCBP, women of childbearing potential

[a] Screening will be conducted and completed in a maximum of 42 days (up to 14 days Screening and 28 days Run-in Period) prior to the Baseline Visit. Before the Run-in Period subjects will be trained in diary completion. The Run-in phase and initiation of the seizure diary completed during this phase of the study, will contain a minimum of 28 consecutive days of seizure data collected prior to the Baseline Visit. Ideally the subject will be instructed to start entering diary information the day after screening, so that the requisite number of days can be collected prior to the Baseline Visit. Laboratory tests from within 30 days of Screening are acceptable for entry to the study.

[b] After the Month 12 visits, subjects will return for on-site visits every 6 months and will have telephone visits every 3 months after the on-site visits, following the Schedule of Assessments for rollover subjects (Table 2).

[c] Subjects who discontinue vatiquinone prematurely should complete an Early Termination Visit.

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

[e] Urinalysis by dipstick collection.

[f] Drug will be dispensed to the subject every 3 months. For Month 9, the 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.
[g] 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.
[h] Approximately 7.7 mL of blood will be drawn per visit.
[i] In the event of pregnancy and, if the subject objects to their parents or guardians being informed, consultation without the presence of parents or guardians should be conducted.

Table 4: Schedule of Assessments – De Novo Subjects (Italy)

Study Period	Screening/ Run-In[a]	Baseline	Treatment				
	Day -42 to Day -1	Day 0 (±7 Days)	Month 1 (28±7 Days)	Month 3 (56±7 Days)	Month 6 (84±7 Days)	Month 12[b] (168±7 Days)	ET (6 Weeks After D/C)[c]
Informed consent	X[d]						
Demographics	X						
Medical history	X						
Vital signs	X	X	X	X	X	X	X
Height	X	X					
Weight	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X
12-lead ECG	X	X	X	X	X	X	X
Electroencephalogram (EEG)	X						X
Urine pregnancy test (WOCBP)	X	X	X	X	X	X	X
Hematology (CBC w/differential)	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]
Serum chemistry	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]
Coagulation panel	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]
Urinalysis[e]	X	X	X	X	X	X	X
Glutathione		X	X	X	X	X	X
NPMDS		X			X	X	
CarerQoL-7D		X			X	X	
PEDsQL		X			X	X	
Drug dispensed[f]		X		X	X	X	
Drug compliance[g]				X	X	X	X
AE/SAE assessment	X	X	X	X	X	X	X
Prior/Concomitant medication	X	X	X	X	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; WOCBP, women of childbearing potential

[a] Screening will be conducted and completed in a maximum of 42 days (up to 14 days Screening and 28 days Run-in Period) prior to the Baseline Visit. Before the Run-in Period subjects will be trained in diary completion. The Run-in phase and initiation of the seizure diary completed during this phase of the study, will contain a minimum of 28 consecutive days of seizure data collected prior to the Baseline Visit. Ideally the subject will be instructed to start entering diary information the day after screening, so that the requisite number of days can be collected prior to the Baseline Visit. Laboratory tests from within 30 days of Screening are acceptable for entry to the study.

[b] After the Month 12 visits, subjects will return for on-site visits every 6 months and will have telephone visits every 3 months after the on-site visits, following the Schedule of Assessments for rollover subjects (Table 2).

[c] Subjects who discontinue vatiquinone prematurely should complete an Early Termination Visit.

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

[e] Urinalysis by dipstick collection or serum test.

[f] Drug will be dispensed to the subject every 3 months. For Month 9, the 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.
[g] 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.
[h] Approximately 7.7 mL of blood will be drawn per visit.