Clinical trial results:
Efficacy and Safety Study of Vatiquinone for the Treatment of Mitochondrial Disease Subjects With Refractory Epilepsy (MIT-E)

Summary

EudraCT number	2020-002100-39
Trial protocol	ES FR IT SE PL
Global end of trial date	27 December 2023

Results information

Result version number	v1
This version publication date	19 July 2024
First version publication date	19 July 2024

Trial information

Trial identification

Sponsor protocol code	PTC743-MIT-001-EP

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04378075
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	PTC Therapeutics, Inc.
Sponsor organisation address	500 Warren Corp Centre Dr, Warren, United States, NJ 07059
Public contact	Medical Information, PTC Therapeutics, Inc., +011 44 1-866-562-4620, medinfo@ptcbio.com
Scientific contact	Medical Information, PTC Therapeutics International Limited, +353 19068700, medinfo@ptcbio.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001238-PIP02-20
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 February 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 December 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to demonstrate the effect of vatiquinone (PTC743) on reduction in observable motor seizure frequency in participants with genetically confirmed mitochondrial disease, as assessed by a seizure diary.

Protection of trial subjects:

This study was designed and monitored in accordance with sponsor procedures, which comply with the ethical principles of Good Clinical Practice (GCP) as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 September 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 31
Country: Number of subjects enrolled	Japan: 11
Country: Number of subjects enrolled	Poland: 8
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	Italy: 1
Worldwide total number of subjects	68
EEA total number of subjects	22

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23	5

months)	
Children (2-11 years)	47
Adolescents (12-17 years)	15
Adults (18-64 years)	1
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 82 participants were screened, of which 14 were not randomized due to screen failure.

Period 1

Period 1 title	Double-blind (24 Weeks)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Carer, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Double-blind Period: Vatiquinone

Arm description:

Participants received vatiquinone 15 milligrams (mg)/kilogram (kg) if body weight <13 kg, and 200 mg if body weight ≥13 kg, administered orally, 3 times per day (TID) for up to 24 weeks during the double-blind period.

Arm type	Experimental
Investigational medicinal product name	Vatiquinone
Investigational medicinal product code	
Other name	PTC743, EPI-743
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Vatiquinone was administered per the treatment arm description.

Arm title	Double-blind Period: Placebo

Arm description:

Participants received vatiquinone-matched placebo, administered orally, TID for up to 24 weeks during the double-blind period.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	PTC743, EPI-743
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Vatiquinone-matching placebo was administered per the treatment arm description

Number of subjects in period 1	Double-blind Period: Vatiquinone	Double-blind Period: Placebo
Started	34	34
Received at least 1 dose of study drug	34	34
Completed	28	29
Not completed	6	5
Adverse event, serious fatal	3	-
Consent withdrawn by subject	-	1
Adverse event, non-fatal	2	2
Other than specified	-	2
Protocol deviation	1	-

Period 2

Period 2 title	Long-term Extension (48 Weeks)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Long-term Extension: Vatiquinone/Vatiquinone

Arm description:

Participants who received vatiquinone for 24 weeks in the double-blind period continued to received vatiquinone 15 mg/kg if body weight <13 kg, and 200 mg if body weight ≥13 kg, administered orally, TID for 48 weeks during the long-term extension period.

Arm type	Experimental
Investigational medicinal product name	Vatiquinone
Investigational medicinal product code	
Other name	PTC743, EPI-743
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Vatiquinone was administered per the treatment arm description.

Arm title	Long-term Extension: Placebo/Vatiquinone

Arm description:

Participants who received placebo for 24 weeks in the double-blind period, received vatiquinone 15 mg/kg if body weight <13 kg, and 200 mg if body weight ≥13 kg, administered orally, TID for 48 weeks during the long-term extension period.

Arm type	Experimental
Investigational medicinal product name	Vatiquinone
Investigational medicinal product code	
Other name	PTC743, EPI-743
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Vatiquinone was administered per the treatment arm description.

Number of subjects in period 2	Long-term Extension: Vatiquinone/Vatiquinone	Long-term Extension: Placebo/Vatiquinone
Started	28	29
Completed	16	18
Not completed	12	11
Sponsor's decision	1	1
Adverse event, serious fatal	2	2
Other than specified	9	7
Lack of efficacy	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Double-blind Period: Vatiquinone
Reporting group description:	
Participants received vatiquinone 15 milligrams (mg)/kilogram (kg) if body weight <13 kg, and 200 mg if body weight ≥13 kg, administered orally, 3 times per day (TID) for up to 24 weeks during the double-blind period.	
Reporting group title	Double-blind Period: Placebo
Reporting group description:	
Participants received vatiquinone-matched placebo, administered orally, TID for up to 24 weeks during the double-blind period.	

Reporting group values	Double-blind Period: Vatiquinone	Double-blind Period: Placebo	Total
Number of subjects	34	34	68
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	8.7	6.6	
standard deviation	± 5.34	± 4.84	-
Gender Categorical Units: Subjects			
Female	14	20	34
Male	20	14	34
Race Units: Subjects			
American Indian/Alaska Native	0	1	1
Asian	3	9	12
Black/African American	1	3	4
White/Caucasian	24	20	44
Other	1	0	1
Not Reported	5	1	6
Ethnicity Units: Subjects			
Hispanic or Latino	2	1	3
Not Hispanic or Latino	26	30	56
Not Reported	5	1	6
Unknown	1	2	3
Number of Observable Motor Seizures per 28 Days			
The 28-day motor seizure frequency in the double-blind period was calculated as the (number of motor seizures)/ (the number of valid days where motor seizure count information is present) * 28 within the double-blind period.			
Units: motor seizures/28 days			
median	112.5	237.0	
full range (min-max)	6 to 3139	15 to 2918	-

End points

End points reporting groups

Reporting group title	Double-blind Period: Vatiquinone
Reporting group description:	
Participants received vatiquinone 15 milligrams (mg)/kilogram (kg) if body weight <13 kg, and 200 mg if body weight ≥13 kg, administered orally, 3 times per day (TID) for up to 24 weeks during the double-blind period.	
Reporting group title	Double-blind Period: Placebo
Reporting group description:	
Participants received vatiquinone-matched placebo, administered orally, TID for up to 24 weeks during the double-blind period.	
Reporting group title	Long-term Extension: Vatiquinone/Vatiquinone
Reporting group description:	
Participants who received vatiquinone for 24 weeks in the double-blind period continued to received vatiquinone 15 mg/kg if body weight <13 kg, and 200 mg if body weight ≥13 kg, administered orally, TID for 48 weeks during the long-term extension period.	
Reporting group title	Long-term Extension: Placebo/Vatiquinone
Reporting group description:	
Participants who received placebo for 24 weeks in the double-blind period, received vatiquinone 15 mg/kg if body weight <13 kg, and 200 mg if body weight ≥13 kg, administered orally, TID for 48 weeks during the long-term extension period.	
Subject analysis set title	Overall Period: Vatiquinone/Vatiquinone
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Participants received vatiquinone 15 mg/kg if body weight <13 kg, and 200 mg if body weight ≥13 kg, administered orally, TID for up to 72 weeks.	
Subject analysis set title	Overall Period: Placebo/Vatiquinone
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Participants received vatiquinone-matched placebo, administered orally, TID for up to 24 weeks followed by vatiquinone 15 mg/kg if body weight <13 kg, and 200 mg if body weight ≥13 kg, administered orally, TID for up to 48 weeks.	

Primary: Percent Change From Baseline to Week 24 in the Number of Observable Motor Seizures per 28 Days During the Double-blind Period

End point title	Percent Change From Baseline to Week 24 in the Number of Observable Motor Seizures per 28 Days During the Double-blind Period
End point description:	
The 28-day motor seizure frequency in the double-blind period was calculated as the (number of motor seizures)/ (the number of valid days where motor seizure count information is present) * 28 within the double-blind period. The baseline of the seizure frequency used the 28 days observations immediately prior to treatment start date for this calculation. Intent-to-treat (ITT) population included all randomized participants who received at least 1 dose of treatment.	
End point type	Primary
End point timeframe:	
Baseline to Week 24	

End point values	Double-blind Period: Vatiquinone	Double-blind Period: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	34		
Units: percent change				
median (confidence interval 95%)	-12.74 (-28.67 to 9.42)	-0.33 (-28.97 to 17.06)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Double-blind Period: Vatiquinone v Double-blind Period: Placebo
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.173
Method	ANCOVA
Parameter estimate	Median difference (final values)
Point estimate	-8.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.3
upper limit	16.4

Secondary: Change From Baseline to Week 24 in Number of Disease-Related Hospitalization Days per 28 Days in Double-Blind Period

End point title	Change From Baseline to Week 24 in Number of Disease-Related Hospitalization Days per 28 Days in Double-Blind Period

End point description:

The disease-related hospitalization days per 28 days in the double-blind period was calculated as the (number of disease-related hospitalizations)/(the number of days within the double-blind period) * 28. The baseline hospitalization used the 28 days observations immediately prior to treatment start date for this calculation. ITT population included all randomized participants who received at least 1 dose of treatment.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Double-blind Period: Vatiquinone	Double-blind Period: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	34		
Units: days				
median (confidence interval 95%)	0 (0 to 1.160)	0 (0 to 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 72 in Number of Disease-Related Hospitalization Days Per 28 days in Overall Period

End point title	Change From Baseline to Week 72 in Number of Disease-Related Hospitalization Days Per 28 days in Overall Period

End point description:

The disease-related hospitalization days per 28 days in the overall period was calculated as the (number of disease-related hospitalizations)/(the number of days within the overall treatment period) * 28.
The baseline hospitalization used the 28 days observations immediately prior to treatment start date for this calculation. ITT population included all randomized participants who received at least 1 dose of treatment.

End point type	Secondary

End point timeframe:

Baseline to Week 72

End point values	Overall Period: Vatiquinone/Vatiquinone	Overall Period: Placebo/Vatiquinone		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	34	34		
Units: days				
median (confidence interval 95%)	0.363 (0 to 1.304)	0.166 (0 to 0.515)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 72 in Occurrence/Recurrence of Status Epilepticus per 28 Days in Overall Period

End point title	Change From Baseline to Week 72 in Occurrence/Recurrence of Status Epilepticus per 28 Days in Overall Period

End point description:

The status epilepticus per 28 Days in the overall period was calculated as the (number of status epilepticus incidences)/(the number of days in the overall period) * 28.
The baseline status epilepticus incidences used the 28 days observations immediately prior to treatment start date for this calculation. ITT population included all randomized participants who received at least 1 dose of treatment.

End point type	Secondary
End point timeframe: Baseline to Week 72	

End point values	Overall Period: Vatiquinone/Vatiquinone	Overall Period: Placebo/Vatiquinone		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	34	34		
Units: status epilepticus per 28 days				
arithmetic mean (standard deviation)	0.036 (± 0.6444)	-0.102 (± 1.0094)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 24 in Occurrence/Recurrence of Status Epilepticus per 28 Days in Double-blind Period

End point title	Change From Baseline to Week 24 in Occurrence/Recurrence of Status Epilepticus per 28 Days in Double-blind Period

End point description:

The status epilepticus per 28 Days in the double-blind period was calculated as the (number of status epilepticus incidences)/(the number of days in the double-blind period) * 28.
The baseline status epilepticus incidences used the 28 days observations immediately prior to treatment start date for this calculation. ITT population included all randomized participants who received at least 1 dose of treatment.

End point type	Secondary
End point timeframe: Baseline to Week 24	

End point values	Double-blind Period: Vatiquinone	Double-blind Period: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	34		
Units: status epilepticus per 28 days				
arithmetic mean (standard deviation)	0.039 (± 0.9564)	-0.026 (± 1.1083)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Disease-Related Emergency Room Visits in Double-Blind Period

End point title	Number of Participants With Disease-Related Emergency Room Visits in Double-Blind Period

End point description:

Disease-related emergency room visits per 28 days in the double-blind period was calculated as the (number of disease-related emergency room visits)/(the number of days in the double-blind period) * 28.
The baseline disease-related emergency room visits used the 28 days observations immediately prior to treatment start date for this calculation. Number of participants with disease-related emergency room visits for either seizure or epilepticus per 28 days in double-blind period are reported. ITT population included all randomized participants who received at least 1 dose of treatment.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Double-blind Period: Vatiquinone	Double-blind Period: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	34		
Units: participants	9	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Disease-Related In-Patient Hospitalizations in Overall Period

End point title	Number of Participants with Disease-Related In-Patient Hospitalizations in Overall Period

End point description:

In-patient hospitalization per 28 days in the overall period was calculated as the (number of in-patient hospitalization)/(the number of days in the overall period) * 28.
The baseline in-patient hospitalization used the 28 days observations immediately prior to treatment start date for this calculation. Number of participants with in-patient hospitalizations for either seizure or epilepticus per 28 days in overall period are reported. ITT population included all randomized participants who received at least 1 dose of treatment.

End point type	Secondary

End point timeframe:

Baseline to Week 72

End point values	Overall Period: Vatiquinone/Vatiquinone	Overall Period: Placebo/Vatiquinone		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	34	34		
Units: participants	11	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Disease-Related In-Patient Hospitalizations in Double-Blind Period

End point title	Number of Participants with Disease-Related In-Patient Hospitalizations in Double-Blind Period

End point description:

In-patient hospitalization per 28 days in the double-blind period was calculated as the (number of in-patient hospitalization)/(the number of days in the double-blind period) * 28.
The baseline in-patient hospitalization used the 28 days observations immediately prior to treatment start date for this calculation. Number of participants with in-patient hospitalizations for either seizure or epilepticus per 28 days in double-blind period are reported. ITT population included all randomized participants who received at least 1 dose of treatment.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Double-blind Period: Vatiquinone	Double-blind Period: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	34		
Units: participants	6	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Disease-Related In-Patient Hospitalizations in Double-Blind Period

End point title	Number of Disease-Related In-Patient Hospitalizations in Double-Blind Period

End point description:

In-patient hospitalization per 28 days in the double-blind period was calculated as the (number of in-patient hospitalization)/(the number of days in the double-blind period) * 28.
The baseline in-patient hospitalization used the 28 days observations immediately prior to treatment start date for this calculation. Number of participants with number of in-patient hospitalizations for either seizure or epilepticus per 28 days in double-blind period are reported. ITT population included all randomized participants who received at least 1 dose of treatment.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Double-blind Period: Vatiquinone	Double-blind Period: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	34		
Units: participants				
0 Hospitalization	28	32		
1 Hospitalization	4	1		
2 Hospitalizations	1	0		
7 Hospitalizations	0	1		
10 Hospitalizations	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Disease-Related In-Patient Hospitalizations in Overall Period

End point title	Number of Disease-Related In-Patient Hospitalizations in Overall Period

End point description:

In-patient hospitalization per 28 days in the overall period was calculated as the (number of in-patient hospitalization)/(the number of days in the overall period) * 28.
The baseline in-patient hospitalization used the 28 days observations immediately prior to treatment start date for this calculation. Number of participants with number in-patient hospitalizations for either seizure or epilepticus per 28 days in overall period are reported. ITT population included all randomized participants who received at least 1 dose of treatment.

End point type	Secondary

End point timeframe:

Baseline to Week 72

End point values	Overall Period: Vatiquinone/Vatiquinone	Overall Period: Placebo/Vatiquinone		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	34	34		
Units: participants				
0 Hospitalization	23	31		
1 Hospitalization	7	1		
2 Hospitalizations	0	1		
5 Hospitalizations	1	0		
6 Hospitalizations	1	0		
7 Hospitalizations	0	1		
8 Hospitalizations	1	0		

10 Hospitalizations	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Disease-Related Emergency Room Visits in Overall Period

End point title	Number of Participants With Disease-Related Emergency Room Visits in Overall Period

End point description:

Disease-related emergency room visits per 28 days in the overall period was calculated as the (number of disease-related emergency room visits)/(the number of days in the overall period) * 28.
The baseline disease-related emergency room visits used the 28 days observations immediately prior to treatment start date for this calculation. Number of participants with disease-related emergency room visits for either seizure or epilepticus per 28 days in overall period are reported. ITT population included all randomized participants who received at least 1 dose of treatment.

End point type	Secondary

End point timeframe:

Baseline to Week 72

End point values	Overall Period: Vatiquinone/Vatiquinone	Overall Period: Placebo/Vatiquinone		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	34	34		
Units: participants	14	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Disease-Related Emergency Room Visits in Double-Blind Period

End point title	Number of Disease-Related Emergency Room Visits in Double-Blind Period

End point description:

Disease-related emergency room visits per 28 days in the double-blind period was calculated as the (number of disease-related emergency room
visits)/(the number of days in the double-blind period) * 28.
The baseline disease-related emergency room visits used the 28 days observations immediately prior to treatment start date for this calculation. Number of participants with number of emergency room visits for either seizure or epilepticus per 28 days in double-blind period are reported. ITT population included all randomized participants who received at least 1 dose of treatment.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Double-blind Period: Vatiquinone	Double-blind Period: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	34		
Units: participants				
0 Visit	25	30		
1 Visit	7	4		
2 Visits	1	0		
10 Visits	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Disease-Related Emergency Room Visits in Overall Period

End point title	Number of Disease-Related Emergency Room Visits in Overall Period

End point description:

Disease-related emergency room visits per 28 days in the overall period was calculated as the (number of disease-related emergency room visits)/(the number of days in the overall period) * 28.
The baseline disease-related emergency room visits used the 28 days observations immediately prior to treatment start date for this calculation. Number of participants with number of emergency room visits for either seizure or epilepticus per 28 days in overall period are reported. ITT population included all randomized participants who received at least 1 dose of treatment.

End point type	Secondary

End point timeframe:

Baseline to Week 72

End point values	Overall Period: Vatiquinone/Vatiquinone	Overall Period: Placebo/Vatiquinone		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	34	34		
Units: participants				
0 Visit	20	29		
1 Visit	8	4		
2 Visits	2	1		
6 Visits	2	0		
8 Visits	1	0		
10 Visits	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline to Week 72 in Total Seizure Frequency per 28 Days in Overall Period

End point title	Percent Change From Baseline to Week 72 in Total Seizure Frequency per 28 Days in Overall Period

End point description:

Overall period was defined as the period from the first dosing date of investigational product (IP) during double-blind period to the end of study (double-blind + open-label period).
The 28 day total seizure frequency in the overall period was calculated as the (number of total seizures)/(the number of valid days where total seizure count information is present) * 28 within the overall period.
The baseline of the seizure frequency used the 28 days observations immediately prior to treatment start date for this calculation. ITT population included all randomized participants who received at least 1 dose of treatment.

End point type	Secondary

End point timeframe:

Baseline, Week 72

End point values	Overall Period: Vatiquinone/Vatiquinone	Overall Period: Placebo/Vatiquinone		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	34	34		
Units: percent change				
median (confidence interval 95%)	-17.03 (-42.38 to 0)	-7.52 (-35.46 to 17.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 24 in Health-Related Quality of Life as Measured by the Care-Related Quality of Life of Informal Caregivers (CarerQoL-7D) Questionnaire Score in Double-blind Period

End point title	Change From Baseline to Week 24 in Health-Related Quality of Life as Measured by the Care-Related Quality of Life of Informal Caregivers (CarerQoL-7D) Questionnaire Score in Double-blind Period

End point description:

The CarerQol-7D consists of 5 negative and 2 positive dimensions of providing informal care. The negative dimensions are relational problems, mental health problems, problems combining daily activities with care, financial problems and physical health problems because of providing informal care.

The 2 positive dimensions are fulfilment from caregiving and support with lending care. For each dimension, there are 3 possible responses: no, some and a lot. Utility tariffs for CarerQol have been developed to calculate a weighted sum score of CarerQol-7D from the responses on the 7 dimensions, ranging from 0 (worst imaginable caregiving situation) to 100 (best imaginable caregiving situation), for which discrete choice experiments were used. Higher sum scores reflect better care-related quality of life. ITT population included all randomized participants who received at least 1 dose of treatment. 'Overall number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Double-blind Period: Vatiquinone	Double-blind Period: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	2		
Units: units on a scale				
arithmetic mean (standard deviation)	-10.38 (± 18.207)	-5.25 (± 10.112)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline to Week 24 in Total Seizure Frequency per 28 Days in Double-Blind Period

End point title	Percent Change From Baseline to Week 24 in Total Seizure Frequency per 28 Days in Double-Blind Period

End point description:

The total seizure frequency per 28 days in the double-blind period was calculated as the (number of total seizures)/(the number of valid days where total seizure count information is present) * 28 within the double-blind period.
The baseline of the seizure frequency used the 28 days observations immediately prior to treatment start date for this calculation. ITT population included all randomized participants who received at least 1 dose of treatment.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Double-blind Period: Vatiquinone	Double-blind Period: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	34		
Units: percent change				
median (confidence interval 95%)	-14.27 (-34.52 to 21.85)	-5.73 (-31.59 to 7.79)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Taking Rescue Medications in the Overall Period

End point title	Number of Participants Taking Rescue Medications in the Overall Period

End point description:

Number of participants taking rescue medications for epilepsy in overall period are reported. ITT population included all randomized participants who received at least 1 dose of treatment.

End point type	Secondary

End point timeframe:

Baseline to Week 72

End point values	Overall Period: Vatiquinone/Vatiquinone	Overall Period: Placebo/Vatiquinone		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	34	34		
Units: participants	24	23		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Taking Rescue Medications in the Double-blind Period

End point title	Number of Participants Taking Rescue Medications in the Double-blind Period

End point description:

Number of participants taking rescue medications for epilepsy in double-blind period are reported. ITT population included all randomized participants who received at least 1 dose of treatment.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Double-blind Period: Vatiquinone	Double-blind Period: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	34		
Units: participants	24	22		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 72 in Health-Related Quality of Life as Measured by the CarerQoL-7D Questionnaire Score in Overall Period

End point title	Change From Baseline to Week 72 in Health-Related Quality of Life as Measured by the CarerQoL-7D Questionnaire Score in Overall Period

End point description:

The CarerQol-7D consists of 5 negative and 2 positive dimensions of providing informal care. The negative dimensions are relational problems, mental health problems, problems combining daily activities with care, financial problems and physical health problems because of providing informal care. The 2 positive dimensions are fulfilment from caregiving and support with lending care. For each dimension, there are 3 possible responses: no, some and a lot. Utility tariffs for CarerQol have been developed to calculate a weighted sum score of CarerQol-7D from the responses on the 7 dimensions, ranging from 0 (worst imaginable caregiving situation) to 100 (best imaginable caregiving situation), for which discrete choice experiments were used. Higher sum scores reflect better care-related quality of life. ITT population included all randomized participants who received at least 1 dose of treatment. 'Overall number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 72

End point values	Overall Period: Vatiquinone/Vatiquinone	Overall Period: Placebo/Vatiquinone		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	10		
Units: units on a scale				
arithmetic mean (standard deviation)	-0.95 (± 14.235)	-3.14 (± 13.675)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Motor Seizure Clusters in Double-Blind Period

End point title	Number of Participants with Motor Seizure Clusters in Double-Blind Period

End point description:

Seizure clusters were defined by "too many to count" entries in the seizure diaries. The motor seizure clusters per 28 days in the double-blind period was calculated as the (number of motor seizure clusters)/(the number of valid days where motor seizure clusters count information was present) * 28 within the double-blind period.
The baseline of the seizure frequency used the 28 days observations immediately prior to treatment start date for this calculation. ITT population included all randomized participants who received at least 1 dose of treatment.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Double-blind Period: Vatiquinone	Double-blind Period: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	34		
Units: participants	19	25		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Motor Seizure Clusters in Overall Period

End point title	Number of Participants with Motor Seizure Clusters in Overall Period

End point description:

Seizure clusters were defined by "too many to count" entries in the seizure diaries. The motor seizure clusters per 28 days in the overall period was calculated as the (number of motor seizure clusters)/(the number of valid days where motor seizure clusters count information was present) * 28 within the overall period.
The baseline of the seizure frequency used the 28 days observations immediately prior to treatment start date for this calculation. ITT population included all randomized participants who received at least 1 dose of treatment.

End point type	Secondary

End point timeframe:

Baseline to Week 72

End point values	Overall Period: Vatiquinone/Vatiquinone	Overall Period: Placebo/Vatiquinone		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	34	34		
Units: participants	21	26		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With >30%, 30% to -30%, < -30% to -60%, < -60% to -100% Reduction in Motor Seizures per 28 Days During the Double-blind Period

End point title	Number of Participants With >30%, 30% to -30%, < -30% to -60%, < -60% to -100% Reduction in Motor Seizures per 28 Days During the Double-blind Period

End point description:

Number of participants whose motor seizure frequency reduction per 28 days was more than the specified percentage compared to baseline were reported.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Double-blind Period: Vatiquinone	Double-blind Period: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	34		
Units: participants				
>30%	7	9		
30% to -30%	17	14		
< -30% to -60%	7	7		
< -60% to -100%	3	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With >30%, 30% to -30%, < -30% to -60%, < -60% to -100% Reduction in Total Seizures per 28 Days During the Double-blind Period

End point title	Number of Participants With >30%, 30% to -30%, < -30% to -60%, < -60% to -100% Reduction in Total Seizures per 28 Days During the Double-blind Period

End point description:

Number of participants whose total seizure frequency reduction per 28 days was more than the specified percentage compared to baseline were reported.

End point type	Secondary

End point timeframe:

Baseline to Week 24

End point values	Double-blind Period: Vatiquinone	Double-blind Period: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	34		
Units: participants				
>30%	7	7		
30% to -30%	13	15		
< -30% to -60%	10	9		
< -60% to -100%	4	3		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to Week 77

Adverse event reporting additional description:

Double-blind phase: Safety analysis set included all randomized participants who received at least 1 dose of treatment.

On-Vatiquinone period: On-Vatiquinone safety analysis set included all randomized participants who received at least 1 dose of Vatiquinone anytime during the study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Double-blind Period: Vatiquinone

Reporting group description:

Participants received vatiquinone 15 mg/kg if body weight <13 kg, and 200 mg if body weight ≥13 kg, administered orally, TID for up to 24 weeks during the double-blind period.

Reporting group title	On-Vatiquinone Period: Placebo/Vatiquinone

Reporting group description:

Participants who received placebo for 24 weeks in the double-blind period, received vatiquinone 15 mg/kg if body weight <13 kg, and 200 mg if body weight ≥13 kg, administered orally, TID for 48 weeks during the long-term extension period.

Reporting group title	On-Vatiquinone Period: Vatiquinone/Vatiquinone

Reporting group description:

Participants who received vatiquinone for 24 weeks in the double-blind period continued to received vatiquinone 15 mg/kg if body weight <13 kg, and 200 mg if body weight ≥13 kg, administered orally, TID for 48 weeks during the long-term extension period.

Reporting group title	Double-blind Period: Placebo

Reporting group description:

Participants received vatiquinone-matched placebo, administered orally, TID for up to 24 weeks during the double-blind period.

Serious adverse events	Double-blind Period: Vatiquinone	On-Vatiquinone Period: Placebo/Vatiquinone	On-Vatiquinone Period: Vatiquinone/Vatiquinone
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 34 (52.94%)	16 / 29 (55.17%)	26 / 34 (76.47%)
number of deaths (all causes)	1	1	1
number of deaths resulting from adverse events			
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 34 (0.00%)	0 / 29 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 34 (2.94%)	1 / 29 (3.45%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Hypothermia			
subjects affected / exposed	0 / 34 (0.00%)	0 / 29 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	0 / 34 (0.00%)	0 / 29 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 34 (2.94%)	2 / 29 (6.90%)	3 / 34 (8.82%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	1 / 34 (2.94%)	0 / 29 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory arrest			
subjects affected / exposed	1 / 34 (2.94%)	1 / 29 (3.45%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis aspiration			
subjects affected / exposed	1 / 34 (2.94%)	0 / 29 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			

subjects affected / exposed	1 / 34 (2.94%)	0 / 29 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 34 (2.94%)	0 / 29 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute pulmonary oedema			
subjects affected / exposed	1 / 34 (2.94%)	0 / 29 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract congestion			
subjects affected / exposed	1 / 34 (2.94%)	0 / 29 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Increased upper airway secretion			
subjects affected / exposed	0 / 34 (0.00%)	0 / 29 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atelectasis			
subjects affected / exposed	0 / 34 (0.00%)	0 / 29 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 34 (0.00%)	0 / 29 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 34 (0.00%)	1 / 29 (3.45%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheal stenosis			

subjects affected / exposed	0 / 34 (0.00%)	1 / 29 (3.45%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 34 (0.00%)	0 / 29 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inappropriate affect			
subjects affected / exposed	0 / 34 (0.00%)	0 / 29 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Urine output decreased			
subjects affected / exposed	1 / 34 (2.94%)	0 / 29 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Joint dislocation			
subjects affected / exposed	0 / 34 (0.00%)	0 / 29 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 34 (2.94%)	0 / 29 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 34 (0.00%)	1 / 29 (3.45%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Status epilepticus			

subjects affected / exposed	1 / 34 (2.94%)	0 / 29 (0.00%)	2 / 34 (5.88%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	4 / 34 (11.76%)	1 / 29 (3.45%)	7 / 34 (20.59%)
occurrences causally related to treatment / all	0 / 8	0 / 2	0 / 15
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Change in seizure presentation			
subjects affected / exposed	0 / 34 (0.00%)	0 / 29 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile convulsion			
subjects affected / exposed	0 / 34 (0.00%)	1 / 29 (3.45%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 34 (2.94%)	1 / 29 (3.45%)	3 / 34 (8.82%)
occurrences causally related to treatment / all	1 / 1	0 / 1	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 34 (0.00%)	1 / 29 (3.45%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspepsia			
subjects affected / exposed	0 / 34 (0.00%)	1 / 29 (3.45%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Excessive granulation tissue			
subjects affected / exposed	0 / 34 (0.00%)	0 / 29 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Urinary retention			
subjects affected / exposed	0 / 34 (0.00%)	0 / 29 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 34 (0.00%)	0 / 29 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	2 / 34 (5.88%)	0 / 29 (0.00%)	5 / 34 (14.71%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia viral			
subjects affected / exposed	1 / 34 (2.94%)	0 / 29 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 34 (0.00%)	0 / 29 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhinovirus infection			
subjects affected / exposed	1 / 34 (2.94%)	0 / 29 (0.00%)	3 / 34 (8.82%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 34 (2.94%)	0 / 29 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 34 (2.94%)	1 / 29 (3.45%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	2 / 34 (5.88%)	4 / 29 (13.79%)	2 / 34 (5.88%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasopharyngitis			
subjects affected / exposed	1 / 34 (2.94%)	0 / 29 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			
subjects affected / exposed	1 / 34 (2.94%)	0 / 29 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 34 (2.94%)	1 / 29 (3.45%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metapneumovirus infection			
subjects affected / exposed	0 / 34 (0.00%)	0 / 29 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 34 (2.94%)	1 / 29 (3.45%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 34 (0.00%)	1 / 29 (3.45%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis viral			
subjects affected / exposed	0 / 34 (0.00%)	1 / 29 (3.45%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			

subjects affected / exposed	0 / 34 (0.00%)	1 / 29 (3.45%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterovirus infection			
subjects affected / exposed	0 / 34 (0.00%)	0 / 29 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Norovirus infection			
subjects affected / exposed	0 / 34 (0.00%)	1 / 29 (3.45%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 34 (0.00%)	2 / 29 (6.90%)	2 / 34 (5.88%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pseudomonal			
subjects affected / exposed	0 / 34 (0.00%)	0 / 29 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 34 (0.00%)	1 / 29 (3.45%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear infection			
subjects affected / exposed	0 / 34 (0.00%)	0 / 29 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 34 (0.00%)	1 / 29 (3.45%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular device infection			

subjects affected / exposed	0 / 34 (0.00%)	0 / 29 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Metabolic acidosis			
subjects affected / exposed	0 / 34 (0.00%)	0 / 29 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitochondrial cytopathy			
subjects affected / exposed	0 / 34 (0.00%)	0 / 29 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Double-blind Period: Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 34 (26.47%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 34 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 34 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypothermia			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Disease progression			

subjects affected / exposed	0 / 34 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 34 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory distress			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory arrest			
subjects affected / exposed	0 / 34 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonitis aspiration			
subjects affected / exposed	0 / 34 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	0 / 34 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	0 / 34 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute pulmonary oedema			
subjects affected / exposed	0 / 34 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory tract congestion			

subjects affected / exposed	0 / 34 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Increased upper airway secretion			
subjects affected / exposed	0 / 34 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atelectasis			
subjects affected / exposed	0 / 34 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 34 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	0 / 34 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tracheal stenosis			
subjects affected / exposed	0 / 34 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 34 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Inappropriate affect			
subjects affected / exposed	0 / 34 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			

Urine output decreased			
subjects affected / exposed	0 / 34 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Joint dislocation			
subjects affected / exposed	0 / 34 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 34 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	0 / 34 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Status epilepticus			
subjects affected / exposed	2 / 34 (5.88%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	0 / 34 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Change in seizure presentation			
subjects affected / exposed	0 / 34 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Febrile convulsion			

subjects affected / exposed	0 / 34 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	0 / 34 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspepsia			
subjects affected / exposed	0 / 34 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Excessive granulation tissue			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 34 (2.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
COVID-19			

subjects affected / exposed	0 / 34 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia viral				
subjects affected / exposed	0 / 34 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory syncytial virus infection				
subjects affected / exposed	1 / 34 (2.94%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rhinovirus infection				
subjects affected / exposed	1 / 34 (2.94%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	0 / 34 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	0 / 34 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	2 / 34 (5.88%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Nasopharyngitis				
subjects affected / exposed	0 / 34 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal infection				

subjects affected / exposed	0 / 34 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	0 / 34 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metapneumovirus infection				
subjects affected / exposed	1 / 34 (2.94%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	1 / 34 (2.94%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	0 / 34 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchitis viral				
subjects affected / exposed	0 / 34 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	0 / 34 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Enterovirus infection				
subjects affected / exposed	0 / 34 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Norovirus infection				

subjects affected / exposed	0 / 34 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	0 / 34 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia pseudomonal				
subjects affected / exposed	0 / 34 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	0 / 34 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ear infection				
subjects affected / exposed	0 / 34 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	0 / 34 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular device infection				
subjects affected / exposed	0 / 34 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Metabolic acidosis				
subjects affected / exposed	0 / 34 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mitochondrial cytopathy				

subjects affected / exposed	0 / 34 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Double-blind Period: Vatiquinone	On-Vatiquinone Period: Placebo/Vatiquinone	On-Vatiquinone Period: Vatiquinone/Vatiquinone
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 34 (76.47%)	19 / 29 (65.52%)	30 / 34 (88.24%)
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 34 (5.88%)	0 / 29 (0.00%)	4 / 34 (11.76%)
occurrences (all)	2	0	4
Fall			
subjects affected / exposed	0 / 34 (0.00%)	1 / 29 (3.45%)	2 / 34 (5.88%)
occurrences (all)	0	1	2
Tooth fracture			
subjects affected / exposed	0 / 34 (0.00%)	0 / 29 (0.00%)	2 / 34 (5.88%)
occurrences (all)	0	0	3
Nervous system disorders			
Change in seizure presentation			
subjects affected / exposed	0 / 34 (0.00%)	2 / 29 (6.90%)	0 / 34 (0.00%)
occurrences (all)	0	2	0
Somnolence			
subjects affected / exposed	1 / 34 (2.94%)	0 / 29 (0.00%)	2 / 34 (5.88%)
occurrences (all)	1	0	2
Headache			
subjects affected / exposed	2 / 34 (5.88%)	0 / 29 (0.00%)	2 / 34 (5.88%)
occurrences (all)	2	0	2
Seizure			
subjects affected / exposed	4 / 34 (11.76%)	1 / 29 (3.45%)	8 / 34 (23.53%)
occurrences (all)	4	1	10
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	4 / 34 (11.76%)	1 / 29 (3.45%)	9 / 34 (26.47%)
occurrences (all)	6	1	12
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	7 / 34 (20.59%)	1 / 29 (3.45%)	10 / 34 (29.41%)
occurrences (all)	7	5	14
Reproductive system and breast disorders			
Intermenstrual bleeding			
subjects affected / exposed	2 / 34 (5.88%)	0 / 29 (0.00%)	2 / 34 (5.88%)
occurrences (all)	2	0	2
Respiratory, thoracic and mediastinal disorders			
Respiratory disorder			
subjects affected / exposed	0 / 34 (0.00%)	1 / 29 (3.45%)	3 / 34 (8.82%)
occurrences (all)	0	1	3
Dyspnoea			
subjects affected / exposed	1 / 34 (2.94%)	0 / 29 (0.00%)	2 / 34 (5.88%)
occurrences (all)	1	0	2
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	0 / 34 (0.00%)	0 / 29 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Eczema			
subjects affected / exposed	1 / 34 (2.94%)	0 / 29 (0.00%)	3 / 34 (8.82%)
occurrences (all)	1	0	5
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 34 (2.94%)	0 / 29 (0.00%)	3 / 34 (8.82%)
occurrences (all)	1	0	3
Insomnia			
subjects affected / exposed	0 / 34 (0.00%)	0 / 29 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 34 (0.00%)	0 / 29 (0.00%)	2 / 34 (5.88%)
occurrences (all)	0	0	2

Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 34 (2.94%)	2 / 29 (6.90%)	2 / 34 (5.88%)
occurrences (all)	1	2	2
Conjunctivitis			
subjects affected / exposed	0 / 34 (0.00%)	0 / 29 (0.00%)	2 / 34 (5.88%)
occurrences (all)	0	0	2
Ear infection			
subjects affected / exposed	1 / 34 (2.94%)	0 / 29 (0.00%)	4 / 34 (11.76%)
occurrences (all)	1	0	4
COVID-19			
subjects affected / exposed	1 / 34 (2.94%)	2 / 29 (6.90%)	3 / 34 (8.82%)
occurrences (all)	1	2	3
Influenza			
subjects affected / exposed	1 / 34 (2.94%)	3 / 29 (10.34%)	2 / 34 (5.88%)
occurrences (all)	1	3	2
Gastroenteritis			
subjects affected / exposed	0 / 34 (0.00%)	2 / 29 (6.90%)	0 / 34 (0.00%)
occurrences (all)	0	3	0
Pharyngitis			
subjects affected / exposed	0 / 34 (0.00%)	2 / 29 (6.90%)	0 / 34 (0.00%)
occurrences (all)	0	3	0
Pneumonia			
subjects affected / exposed	1 / 34 (2.94%)	2 / 29 (6.90%)	1 / 34 (2.94%)
occurrences (all)	2	3	2
Pneumonia aspiration			
subjects affected / exposed	0 / 34 (0.00%)	2 / 29 (6.90%)	0 / 34 (0.00%)
occurrences (all)	0	2	0
Respiratory tract infection			
subjects affected / exposed	1 / 34 (2.94%)	1 / 29 (3.45%)	2 / 34 (5.88%)
occurrences (all)	1	1	2
Respiratory tract infection viral			
subjects affected / exposed	1 / 34 (2.94%)	0 / 29 (0.00%)	2 / 34 (5.88%)
occurrences (all)	1	0	2
Rhinitis			

subjects affected / exposed	0 / 34 (0.00%)	0 / 29 (0.00%)	2 / 34 (5.88%)
occurrences (all)	0	0	4
Sinusitis			
subjects affected / exposed	1 / 34 (2.94%)	0 / 29 (0.00%)	4 / 34 (11.76%)
occurrences (all)	1	0	4
Upper respiratory tract infection			
subjects affected / exposed	2 / 34 (5.88%)	7 / 29 (24.14%)	5 / 34 (14.71%)
occurrences (all)	3	10	10
Urinary tract infection			
subjects affected / exposed	3 / 34 (8.82%)	2 / 29 (6.90%)	4 / 34 (11.76%)
occurrences (all)	4	6	11
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 34 (0.00%)	2 / 29 (6.90%)	2 / 34 (5.88%)
occurrences (all)	0	2	2
Nasopharyngitis			
subjects affected / exposed	2 / 34 (5.88%)	0 / 29 (0.00%)	3 / 34 (8.82%)
occurrences (all)	2	0	4
Hordeolum			
subjects affected / exposed	0 / 34 (0.00%)	0 / 29 (0.00%)	0 / 34 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 34 (0.00%)	2 / 29 (6.90%)	0 / 34 (0.00%)
occurrences (all)	0	2	0

Non-serious adverse events	Double-blind Period: Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 34 (58.82%)		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 34 (0.00%)		
occurrences (all)	0		
Fall			
subjects affected / exposed	0 / 34 (0.00%)		
occurrences (all)	0		
Tooth fracture			

subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0		
Nervous system disorders Change in seizure presentation subjects affected / exposed occurrences (all) Somnolence subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Seizure subjects affected / exposed occurrences (all)	 2 / 34 (5.88%) 3 1 / 34 (2.94%) 1 0 / 34 (0.00%) 0 1 / 34 (2.94%) 1		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	 1 / 34 (2.94%) 1		
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all)	 0 / 34 (0.00%) 0		
Reproductive system and breast disorders Intermenstrual bleeding subjects affected / exposed occurrences (all)	 0 / 34 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Respiratory disorder subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all)	 0 / 34 (0.00%) 0 0 / 34 (0.00%) 0		
Skin and subcutaneous tissue disorders			

Blister subjects affected / exposed occurrences (all) Eczema subjects affected / exposed occurrences (all)	2 / 34 (5.88%) 2 0 / 34 (0.00%) 0		
Psychiatric disorders Agitation subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0 3 / 34 (8.82%) 3		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Conjunctivitis subjects affected / exposed occurrences (all) Ear infection subjects affected / exposed occurrences (all) COVID-19 subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all) Gastroenteritis subjects affected / exposed occurrences (all)	2 / 34 (5.88%) 3 0 / 34 (0.00%) 0 0 / 34 (0.00%) 0 0 / 34 (0.00%) 0 1 / 34 (2.94%) 1 1 / 34 (2.94%) 1		

Pharyngitis				
subjects affected / exposed	2 / 34 (5.88%)			
occurrences (all)	3			
Pneumonia				
subjects affected / exposed	1 / 34 (2.94%)			
occurrences (all)	1			
Pneumonia aspiration				
subjects affected / exposed	2 / 34 (5.88%)			
occurrences (all)	2			
Respiratory tract infection				
subjects affected / exposed	3 / 34 (8.82%)			
occurrences (all)	5			
Respiratory tract infection viral				
subjects affected / exposed	0 / 34 (0.00%)			
occurrences (all)	0			
Rhinitis				
subjects affected / exposed	0 / 34 (0.00%)			
occurrences (all)	0			
Sinusitis				
subjects affected / exposed	0 / 34 (0.00%)			
occurrences (all)	0			
Upper respiratory tract infection				
subjects affected / exposed	3 / 34 (8.82%)			
occurrences (all)	4			
Urinary tract infection				
subjects affected / exposed	2 / 34 (5.88%)			
occurrences (all)	2			
Viral upper respiratory tract infection				
subjects affected / exposed	0 / 34 (0.00%)			
occurrences (all)	0			
Nasopharyngitis				
subjects affected / exposed	0 / 34 (0.00%)			
occurrences (all)	0			
Hordeolum				
subjects affected / exposed	2 / 34 (5.88%)			
occurrences (all)	3			

Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all)	 0 / 34 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 March 2020	The overall reason for this amendment was to change the name of the study Sponsor, subsequently the drug name, and to incorporate health authorities' feedback on the previous version of the protocol.
22 May 2020	The overall reasons for this amendment were to add urinalysis assessment and an additional pharmacokinetic (PK) timepoint and to give additional training for seizure diaries, if needed.
30 September 2020	The overall reasons for this amendment were to revise the electrocariogram (ECG) collection schedule so as to time match it with the 4-hour postdose PK, to add PK samples to 4 hours postdose at Weeks 48 and 72, to revise the definition of compliance with study drug dosing, to separate the secondary endpoints into key and other endpoints, and refinement of statistical considerations.
31 March 2021	The overall reasons for this amendment were to add Pediatric Quality of Life Inventory (PedsQL) questionnaire at Weeks 24 and 72; revise the number of study sites from approximately 12 to approximately 30; clarify that historical electroencephalogram (EEG) may be within 6 months prior to the Screening Visit; revise inclusion and exclusion criteria to clarify genetic confirmation of mitochondrial disease, clarify use of antiepileptic drugs (AEDs), clarify aspartate aminotransferase (AST) and alanine aminotransferase (ALT) range for participants with underlying Alpers-Huttenlocher syndrome/DNA polymerase subunit gamma (POLG) subtypes, and clarify exclusion of artisanal (non-Epidiolex cannabidiol) cannabidiol; add a weight-based dosing table for study drug; and clarify that the statistical anlysis plan (SAP) will be finalized prior to unblinding of the study and revise the text regarding the sample size and statistical powering.
04 June 2021	The overall reasons for this amendment were to clarify that male participants must use contraception and that all participants must use contraceptive measures from the time consent was signed until 30 days after treatment discontinuation and to add an appendix of prohibited medications.
06 January 2022	The overall reason for this amendment was to incorporate feedback from health authorities.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported