Clinical trial results:
A Multicenter, Open-label, Pilot Study of TAK-935 (OV935) in Patients With 15Q Duplication Syndrome or CDKL5 Deficiency Disorder (ARCADE Study)

Summary

EudraCT number	2022-001315-44
Trial protocol	Outside EU/EEA
Global end of trial date	31 July 2020

Results information

Result version number	v1 (current)
This version publication date	15 July 2022
First version publication date	15 July 2022

Trial information

Trial identification

Sponsor protocol code	TAK-935-18-002 (OV935)

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03694275
WHO universal trial number (UTN)	U1111-1219-5787

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	95 Hayden Avenue, Lexington, MA, United States, 02421
Public contact	Study Director, Takeda, TrialDisclosures@takeda.com
Scientific contact	Study Director, Takeda, TrialDisclosures@takeda.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-002572-PIP01-19
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 July 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to investigate the effect of TAK-935 (soticlestat) on the frequency of motor seizures for participants with 15q duplication syndrome (Dup15q) or cyclin-dependent kinase-like 5 deficiency disorder (CDD) during the Maintenance Period.

Protection of trial subjects:

Study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 September 2018
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: 20
Worldwide total number of subjects	20
EEA total number of subjects	0

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 months)	0
Children (2-11 years)	9
Adolescents (12-17 years)	9
Adults (18-64 years)	2
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 8 investigative sites in the United States from 10 September 2018 to 31 July 2020.

Pre-assignment

Screening details:

Participants with a diagnosis of Dup15q or CDD were enroled in 2 cohorts to receive treatment with TAK-935 for up to 20 weeks Treatment Period (8-week Dose Optimisation Period and 12-week Maintenance Period).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Soticlestat Dup15q

Arm description:

Soticlestat tablets twice daily (BID) orally or via gastrostomy tube (G-tube)/ percutaneous endoscopic gastrostomy (PEG) tube, BID. Participants with Dup15q weighing <60 kg at Baseline received total daily dose of study drug calculated based on body weight. Participants weighing ≥60 kg at Baseline, were administered with 200 mg/day followed by 400 mg/day, then 600 mg/day, up to Week 20.

Arm type	Experimental
Investigational medicinal product name	Soticlestat
Investigational medicinal product code	
Other name	TAK-935
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

TAK-935 tablets

Arm title	Soticlestat CDD

Arm description:

Soticlestat tablets BID orally or via G-tube/ PEG tube, BID. Participants with CDD weighing <60 kg at Baseline received total daily dose of study drug calculated based on body weight. Participants weighing ≥60 kg at Baseline, were administered with 200 mg/day followed by 400 mg/day, then 600 mg/day, up to Week 20.

Arm type	Experimental
Investigational medicinal product name	Soticlestat
Investigational medicinal product code	
Other name	TAK-935
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

TAK-935 tablets

Number of subjects in period 1	Soticlestat Dup15q	Soticlestat CDD
Started	8	12
Completed	8	10
Not completed	0	2
Adverse event, non-fatal	-	1
Reason not Specified	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Soticlestat Dup15q
Reporting group description:	
Soticlestat tablets twice daily (BID) orally or via gastrostomy tube (G-tube)/ percutaneous endoscopic gastrostomy (PEG) tube, BID. Participants with Dup15q weighing <60 kg at Baseline received total daily dose of study drug calculated based on body weight. Participants weighing ≥60 kg at Baseline, were administered with 200 mg/day followed by 400 mg/day, then 600 mg/day, up to Week 20.	
Reporting group title	Soticlestat CDD
Reporting group description:	
Soticlestat tablets BID orally or via G-tube/ PEG tube, BID. Participants with CDD weighing <60 kg at Baseline received total daily dose of study drug calculated based on body weight. Participants weighing ≥60 kg at Baseline, were administered with 200 mg/day followed by 400 mg/day, then 600 mg/day, up to Week 20.	

Reporting group values	Soticlestat Dup15q	Soticlestat CDD	Total
Number of subjects	8	12	20
Age Categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	15.4	7.6	
standard deviation	± 6.00	± 5.30	-
Gender categorical Units: Subjects			
Male	5	3	8
Female	3	9	12
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	8	12	20
Unknown or Not Reported	0	0	0
Race Units: Subjects			
White	8	11	19
Unknown or Not Reported	0	1	1
Height Units: cm			
arithmetic mean	148.54	124.59	
standard deviation	± 14.965	± 26.882	-
Weight Units: kg			
arithmetic mean	43.40	26.28	
standard deviation	± 13.678	± 12.511	-
Body Mass Index (BMI)			
BMI= weight (kg)/height (m^2).			
Units: kg/m^2			
arithmetic mean	19.21	16.00	

standard deviation	± 4.149	± 1.874	-

End points

End points reporting groups

Reporting group title	Soticlestat Dup15q

Reporting group description:

Soticlestat tablets twice daily (BID) orally or via gastrostomy tube (G-tube)/ percutaneous endoscopic gastrostomy (PEG) tube, BID. Participants with Dup15q weighing <60 kg at Baseline received total daily dose of study drug calculated based on body weight. Participants weighing ≥60 kg at Baseline, were administered with 200 mg/day followed by 400 mg/day, then 600 mg/day, up to Week 20.

Reporting group title	Soticlestat CDD

Reporting group description:

Soticlestat tablets BID orally or via G-tube/ PEG tube, BID. Participants with CDD weighing <60 kg at Baseline received total daily dose of study drug calculated based on body weight. Participants weighing ≥60 kg at Baseline, were administered with 200 mg/day followed by 400 mg/day, then 600 mg/day, up to Week 20.

Primary: Percent Change from Baseline in Motor Seizure Frequency per 28 Days During the Maintenance Period

End point title	Percent Change from Baseline in Motor Seizure Frequency per 28 Days During the Maintenance Period[1]

End point description:

Seizure frequency per 28 days was defined as total number of Seizures reported during the period divided by number of days with no missing seizure count during the period multiplied by 28. Percent Change from Baseline was defined as (frequency of seizures per 28 days during Maintenance Period – frequency of seizures per 28 days at Baseline) divided by frequency of seizures per 28 days at Baseline multiplied by 100. Positive percent change from Baseline indicates seizure increase and negative percent change from Baseline indicates seizure decrease. Modified Intent-to-Treat (mITT) Analysis Set included all participants who have received at least 1 dose of study drug and have been assessed for at least 1 day in the Treatment Period. Overall subjects analysed are the number of participants with data available for analyses.

End point type	Primary

End point timeframe:

Maintenance Period: Weeks 9 to 20

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics was planned to be reported for this endpoint.

End point values	Soticlestat Dup15q	Soticlestat CDD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	11		
Units: percent change				
median (full range (min-max))	11.7 (-90 to 39)	-23.6 (-100 to 107)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in Motor Seizure Frequency per 28 Days

During the Treatment Period

End point title	Percent Change from Baseline in Motor Seizure Frequency per 28 Days During the Treatment Period

End point description:

Seizure frequency per 28 days was defined as total number of Seizures reported during the period divided by number of days with no missing seizure count during the period multiplied by 28. Percent Change from Baseline was defined as (frequency of seizures per 28 days during the treatment period – frequency of seizures per 28 days at Baseline) divided by frequency of seizures per 28 days at Baseline multiplied by 100. Positive percent change from Baseline indicates seizure increase and negative percent change from Baseline indicates seizure decrease. mITT Analysis Set included all participants who have received at least 1 dose of study drug and have been assessed for at least 1 day in the Treatment Period.

End point type	Secondary

End point timeframe:

Treatment Period: Weeks 0 to 20

End point values	Soticlestat Dup15q	Soticlestat CDD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	12		
Units: percent change				
median (full range (min-max))	13.4 (-89 to 30)	-13.6 (-93 to 48)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Considered as Treatment Responders During the Maintenance Period

End point title	Percentage of Participants Considered as Treatment Responders During the Maintenance Period

End point description:

Responders were defined as having over 50% motor seizure reduction compared to Baseline. Percent reduction from Baseline (%) was defined as [(Maintenance Period motor Seizure Frequency -Baseline Period motor Seizure Frequency) divided by Baseline motor Seizure Frequency] multiplied by 100. Data is reported as reduction of 25%, 50%, 75% and 100% or more in motor seizures from Baseline. mITT Analysis Set included all participants who have received at least 1 dose of study drug and have been assessed for at least 1 day in the Treatment Period. Overall subjects analysed are the number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

Maintenance Period: Weeks 9 to 20

End point values	Soticlestat Dup15q	Soticlestat CDD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	11		
Units: percentage of participants				
number (not applicable)				
<=0% Reduction	62.5	27.3		
>0% to <25% Reduction	12.5	27.3		
>=25% to <50% Reduction	12.5	18.2		
>=50% to <75% Reduction	0	18.2		
>=75% to 100% Reduction	12.5	9.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in Frequency of Motor Seizures Longer Than 5 Minutes in Participants with CDD

End point title	Percent Change from Baseline in Frequency of Motor Seizures Longer Than 5 Minutes in Participants with CDD[2]

End point description:

Seizure frequency was defined as total number of Seizures reported during the period divided by number of days with no missing seizure count during the period. Percent Change from Baseline was defined as (frequency of seizures during Treatment period –frequency of seizures at Baseline) divided by frequency of seizures at Baseline multiplied by 100. Positive percent change from Baseline indicates seizure increase and negative percent change from Baseline indicates seizure decrease. The data is reported only for CDD participants. mITT Analysis Set included all participants who have received at least 1 dose of study drug and have been assessed for at least 1 day in the Treatment Period. Overall subjects analysed are all participants whose analyses were conducted using observed values and no imputation was done for missing data.

End point type	Secondary

End point timeframe:

Treatment Period: Weeks 0 to 20

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive statistics was planned to be reported for this endpoint.

End point values	Soticlestat CDD			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: percent change				
median (full range (min-max))	-54.0 (-86 to 11)			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Motor Seizure-free Days in Participants During the

Maintenance Period

End point title	Proportion of Motor Seizure-free Days in Participants During the Maintenance Period

End point description:

Seizure-free days was defined as number of days with zero motor seizure during the period the Maintenance Period divided by number of days participant was in the Maintenance Period. mITT Analysis Set included all participants who have received at least 1 dose of study drug and have been assessed for at least 1 day in the Treatment Period. Overall subjects analysed are the number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

Maintenance Period: Weeks 9 to 20

End point values	Soticlestat Dup15q	Soticlestat CDD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	11		
Units: days/28 days				
median (full range (min-max))	0.1 (0 to 1)	0.1 (0 to 1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Clinician's Global Impression of Severity (CGI-S) Responses of Investigator

End point title	Change From Baseline in Clinician's Global Impression of Severity (CGI-S) Responses of Investigator

End point description:

The CGI-S focuses on clinician's observations of the participant’s cognitive, functional, and behavioral performance since the beginning of the study. The CGI-S is rated on a 7-point scale, with the severity of illness scale using a range of responses where, 1= normal, not at all ill, 2= borderline mentally ill, 3= mildly ill, 4= moderately ill, 5= markedly ill, 6= severely ill and 7=amongst the most extremely ill participants. Negative change from Baseline indicates improvement. mITT Analysis Set included all participants who have received at least 1 dose of study drug and have been assessed for at least 1 day in the Treatment Period. 'n'= number analysed is the number of participants with data available for analyses at the given timepoint.

End point type	Secondary

End point timeframe:

Baseline to Week 20

End point values	Soticlestat Dup15q	Soticlestat CDD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	12		
Units: score on scale				
median (full range (min-max))				
Baseline (n=8,12)	5.0 (4 to 6)	5.0 (4 to 6)		

Change From Baseline at Week 20 (n=6,12)	0.0 (-2 to 0)	0.0 (-1 to 1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Clinical Global Impression of Change (CGI-C) Responses as per the Investigator Reported Impression

End point title	Percentage of Participants with Clinical Global Impression of Change (CGI-C) Responses as per the Investigator Reported Impression

End point description:

CGI-C treatment response ratings should take account of both therapeutic efficacy and treatment-related AEs. Each component of the CGI is rated separately; the instrument does not yield a global score. The CGI-C is rated on a 5-point scale, where, 0 = marked improvement and no side-effects, 1 = marked improvement and minimal side-effects, 2 = no change, 3 = minimal improvement and marked side-effects and 4 = unchanged or worse and side effects outweigh the therapeutic effect. Lower scores indicated improvement. mITT Analysis Set included all participants who have received at least 1 dose of study drug and have been assessed for at least 1 day in the Treatment Period. Overall subjects analysed are the number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

Week 20

End point values	Soticlestat Dup15q	Soticlestat CDD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	12		
Units: percentage of participants				
number (not applicable)				
Week 20, Score 0	33.3	33.3		
Week 20, Score 1	0	33.3		
Week 20, Score 2	50.0	33.3		
Week 20, Score 3	16.7	0		
Week 20, Score 4	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Care Clinical Global Impression of Change (CGI-C) Responses of Parent/Family

End point title	Percentage of Participants with Care Clinical Global Impression of Change (CGI-C) Responses of Parent/Family

End point description:

CGI-C treatment response ratings should take account of both therapeutic efficacy and treatment-related AEs. Each component of the CGI is rated separately; the instrument does not yield a global score. The CGI-C is rated on a 7-point scale where, 1 = very much improved, 2 = much improved, 3 = slightly improved, 4= no change, 5= slightly worse, 6= much worse and 7= very much worse and marked side-effects. Lower scores indicated improvement. mITT Analysis Set included all participants who have received at least 1 dose of study drug and have been assessed for at least 1 day in the Treatment Period. Overall subjects analysed are the number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

Week 20

End point values	Soticlestat Dup15q	Soticlestat CDD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	12		
Units: percentage of participants				
number (not applicable)				
Week 20, Score 1	0	16.7		
Week 20, Score 2	16.7	25.0		
Week 20, Score 3	33.3	50.0		
Week 20, Score 4	50.0	0		
Week 20, Score 5	0	8.3		
Week 20, Score 6	0	0		
Week 20, Score 7	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline of Plasma 24S-hydroxycholesterol (24HC) Levels

End point title	Change from Baseline of Plasma 24S-hydroxycholesterol (24HC) Levels

End point description:

mITT Analysis Set included all participants who have received at least 1 dose of study drug and have been assessed for at least 1 day in the Treatment Period. Overall subjects analysed is the number of participants with data available for analyses. 'n'=number analysed is the number of participants with data available for analyses at the given timepoint.

End point type	Secondary

End point timeframe:

Baseline to Week 20

End point values	Soticlestat Dup15q	Soticlestat CDD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	11		
Units: ng/mL				
arithmetic mean (standard deviation)				
Baseline (n=8,11)	57.08 (± 24.195)	115.29 (± 73.587)		
Change from Baseline at Week 20 (n=4,5)	-34.71 (± 16.578)	-75.64 (± 29.284)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Seizure Frequency in Participants Treated with TAK-935 as an Adjunctive Therapy

End point title	Change from Baseline in Seizure Frequency in Participants Treated with TAK-935 as an Adjunctive Therapy

End point description:

Seizure Frequency per 28 days was defined as total number of Seizures reported during the period divided by number of days with no missing seizure during the
period seizures were assessed multiplied by 28. Positive change from Baseline indicates seizure increase and negative change from Baseline indicates seizure decrease. mITT Analysis Set included all participants who have received at least 1 dose of study drug and have been assessed for at least 1 day in the Treatment Period.

End point type	Secondary

End point timeframe:

Baseline to Week 20

End point values	Soticlestat Dup15q	Soticlestat CDD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	12		
Units: seizures per 28 days				
median (full range (min-max))				
Baseline	128.4 (35 to 224)	77.8 (10 to 374)		
Change From Baseline at Week 20	13.2 (-31 to 67)	-3.4 (-210 to 28)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose to 30 days post-last dose of study treatment (Up to 24 weeks)

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the participant or observed by the investigator was recorded, irrespective of the relation to study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Soticlestat Dup15q

Reporting group description:

Soticlestat tablets twice daily (BID) orally or via gastrostomy tube (G-tube)/ percutaneous endoscopic gastrostomy (PEG) tube, BID. Participants with Dup15q weighing <60 kg at Baseline received total daily dose of study drug calculated based on body weight. Participants weighing ≥60 kg at Baseline, were administered with 200 mg/day followed by 400 mg/day, then 600 mg/day, up to Week 20.

Reporting group title	Soticlestat CDD

Reporting group description:

Soticlestat tablets BID orally or via G-tube/ PEG tube, BID. Participants with CDD weighing <60 kg at Baseline received total daily dose of study drug calculated based on body weight. Participants weighing ≥60 kg at Baseline, were administered with 200 mg/day followed by 400 mg/day, then 600 mg/day, up to Week 20.

Serious adverse events	Soticlestat Dup15q	Soticlestat CDD	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 8 (12.50%)	2 / 12 (16.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 8 (12.50%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Soticlestat Dup15q	Soticlestat CDD	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 8 (87.50%)	12 / 12 (100.00%)	
Investigations			
Blood bicarbonate decreased			
subjects affected / exposed	0 / 8 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	3	
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 8 (12.50%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Anticonvulsant drug level increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Blood cholesterol increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Blood triglycerides increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
C-reactive protein increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Electrocardiogram QT prolonged			

subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	2	
Electrocardiogram ST-T change			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Haematocrit increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
International normalised ratio increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Low density lipoprotein increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Oxygen saturation decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Neutrophil count decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Platelet count increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
White blood cell count increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Face injury			
subjects affected / exposed	1 / 8 (12.50%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Fall			
subjects affected / exposed	1 / 8 (12.50%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			

Seizure			
subjects affected / exposed	2 / 8 (25.00%)	1 / 12 (8.33%)	
occurrences (all)	2	1	
Lethargy			
subjects affected / exposed	2 / 8 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Partial seizures			
subjects affected / exposed	0 / 8 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	3	
Tonic convulsion			
subjects affected / exposed	0 / 8 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	3	
Atonic seizures			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Balance disorder			
subjects affected / exposed	1 / 8 (12.50%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Hypersomnia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Drooling			
subjects affected / exposed	1 / 8 (12.50%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Hypotonia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Somnolence			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Tremor			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Eosinophilia			

subjects affected / exposed	1 / 8 (12.50%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 8 (25.00%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Asthenia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Peripheral swelling			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 8 (0.00%)	4 / 12 (33.33%)	
occurrences (all)	0	5	
Diarrhoea			
subjects affected / exposed	1 / 8 (12.50%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Frequent bowel movements			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Apnoea			
subjects affected / exposed	1 / 8 (12.50%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Hyperventilation			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	

Pneumonia aspiration			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 8 (12.50%)	2 / 12 (16.67%)	
occurrences (all)	1	2	
Pruritus			
subjects affected / exposed	1 / 8 (12.50%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 8 (12.50%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Initial insomnia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Irritability			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	2	
Sleep disorder			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	2	
Renal and urinary disorders			
Neurogenic bladder			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Urinary retention			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Infections and infestations			
Ear infection			
subjects affected / exposed	0 / 8 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	3	
Nasopharyngitis			
subjects affected / exposed	1 / 8 (12.50%)	1 / 12 (8.33%)	
occurrences (all)	1	1	

Respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Sinusitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 January 2019	The changes implemented based on Amendment 1 were: -Revised study design. -Updated name of titration period to Dose Optimization Period due to change in the length of the treatment period. -Revised the primary and secondary objectives/endpoints. -Added secondary objectives/endpoints. -Revised exploratory objectives. -One exploratory objective/endpoint was added. -Study visits were changed to reflect the revised study design. -Timepoints for collection of samples for pharmacokinetic analysis were clarified. -The age for participation was increased to 35 years. -Route of administration was expanded to include G-tube/PEG tube/J-tube at all sites except those in China. -Perampanel was added as a prohibited medication. -The use of traditional Chinese medicines was clarified. -Clarified and revised inclusion and exclusion criteria. -An optional severity assessment for cyclin-dependent kinase-like 5 (CDKL5) deficiency syndrome was added. -Handling of missed doses was clarified. -Requirement was added to discontinue a patient if he/she exhibits signs of suicidal ideation. -Cytochrome P450 (CYP) 46A1 mutation analysis was removed and replaced with optional blood sample storage for exploratory research.
31 January 2019	-Two additional timepoints were added for collection of plasma 24HC. -Amount of blood samples was changed to reflect additional visits. -Change in dose during the study was clarified. -Weight-based dosing was updated to reflect the administration of 100 mg tablets. -Use of an electroencephalogram (EEG) charter was removed. -An additional electrocardiogram (ECG) assessment was added. -Clarification was added for rolling over from the antecedent trial to the open-label extension. -Oxcarbazepine was added to the assay for concomitant antiepileptic drugs (AEDs). -An analysis population (Efficacy Analysis Population) was added. -Statistical analyses were revised. -Confidentiality of participant information was clarified. -The length of time participants must avoid pregnancy, donation of ova, and sperm donation after the last dose of study drug was clarified and instructions were included if urine cannot be collected at Visit 2. -End of study definition was added. -Description of the dosing card was added.
20 November 2019	The changes implemented based on Amendment 2 were: -Modified inclusion/exclusion criteria to increase the age for participation in the trial to 55 years old and expand the inclusion criteria to allow participants with a diagnosis of interstitial Dup15q. -Corrected an inadvertent error in the way the secondary endpoints CGI-S, CGI-C, and Care-CGI-C were defined, from “percent change” to “change”. -Added that Jejunostomy tube (J-tube) may be considered based on approval from Medical Monitor and Sponsor. -Allowed ad hoc analyses throughout the trial. -Added an additional subgroup in the treatment responder analysis (≥75% reduction in motor seizure frequency). -Made corrections in schedule of assessment table including, 1.Separated out CGI-S from CGI-C; 2.Removed collection seizure diary checks on Day 8, Day 22, Day 57, Day 113. -Removed the exploratory endpoint of EEG parameters in participants with Dup15q. -Removed the optional blood sample for research analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported