Clinical trial results:
A Multicenter, Open-Label Proof-of-Concept Trial of Ganaxolone in Children with PCDH19 Female Pediatric Epilepsy

Summary

EudraCT number	2015-001324-36
Trial protocol	IT
Global end of trial date	04 January 2019

Results information

Result version number	v1 (current)
This version publication date	29 December 2023
First version publication date	29 December 2023

Trial information

Trial identification

Sponsor protocol code	1042-900

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02358538
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Marinus Pharmaceuticals, Inc.
Sponsor organisation address	5 Radnor Corporate Center, 100 Matsonford Rd, Suite 500, Radnor, United States, PA 19087
Public contact	Marinus Pharmaceuticals, Inc., Safety Department, 001 4846792138, clinicaltrials@marinuspharma.com
Scientific contact	Marinus Pharmaceuticals, Inc., Safety Department, 001 4846792138, clinicaltrials@marinuspharma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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	04 January 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of open-label ganaxolone as adjunctive therapy for uncontrolled seizures in female children with PCDH19 mutation.

Protection of trial subjects:

At the first visit, prior to initiation of any study-related procedures, the parent(s) or legal guardian(s) of the subjects gave their written consent to participate in the study after having been informed about the nature and purpose of the study, participation / termination conditions, and risks and benefits. Before the informed consent document was signed, the investigator, or a person designated by the investigator, provided the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial were answered to the satisfaction of the subject or the subject's legally acceptable representative.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 November 2015
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: 23
Country: Number of subjects enrolled	Italy: 7
Worldwide total number of subjects	30
EEA total number of subjects	7

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)	24
Adolescents (12-17 years)	6

Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment period May 08, 2015

Pre-assignment

Screening details:

None

Period 1

Period 1 title	Through Week 26
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	CDKL5

Arm description:

Cyclin-dependent kinase-like 5

Arm type	Experimental
Investigational medicinal product name	Ganaxolone
Investigational medicinal product code	
Other name	CCD 1042
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Participants were administered with Maximum of 1800 milligrams per day (mg/day) or 63 milligrams per kilograms per day (mg/kg/day).

Arm title	CSWS

Arm description:

Continuous Spike Wave in Sleep

Arm type	Experimental
Investigational medicinal product name	Ganaxolone
Investigational medicinal product code	
Other name	CCD 1042
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Participants were administered with Maximum of 1800 mg/day or 63 mg/kg/day

Arm title	Lennox-Gastaut

Arm description:

Lennox-Gastaut Syndrome pediatric epilepsy

Arm type	Experimental
Investigational medicinal product name	Ganaxolone
Investigational medicinal product code	
Other name	CCD 1042
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:
Participants were administered with Maximum of 1800 mg/day or 63 mg/kg/day

Arm title	PCDH19
Arm description: Protocadherin-19	
Arm type	Experimental
Investigational medicinal product name	Ganaxolone
Investigational medicinal product code	
Other name	CCD 1042
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:
Participants were administered with Maximum of 1800 mg/day or 63 mg/kg/day

Number of subjects in period 1	CDKL5	CSWS	Lennox-Gastaut
Started	7	2	10
Completed	4	0	5
Not completed	3	2	5
Consent withdrawn by subject	1	-	-
Family did not see benefit from IP	1	-	-
Adverse event, non-fatal	-	1	1
Non- Compliance	-	-	1
Lack of efficacy	1	1	3

Number of subjects in period 1	PCDH19
Started	11
Completed	6
Not completed	5
Consent withdrawn by subject	-
Family did not see benefit from IP	-
Adverse event, non-fatal	2
Non- Compliance	-
Lack of efficacy	3

Period 2

Period 2 title	52 Week Extension Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	CDKL5

Arm description:

Cyclin-dependent kinase-like 5

Arm type	Experimental
Investigational medicinal product name	Ganaxolone
Investigational medicinal product code	
Other name	CCD 1042
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Participants were administered with Maximum of 1800 mg/day or 63 mg/kg/day

Arm title	CSWS

Arm description:

Continuous Spike Wave in Sleep

Arm type	Experimental
Investigational medicinal product name	Ganaxolone
Investigational medicinal product code	
Other name	CCD 1042
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Participants were administered with Maximum of 1800 mg/day or 63 mg/kg/day

Arm title	Lennox-Gastaut

Arm description:

Lennox-Gastaut Syndrome pediatric epilepsy

Arm type	Experimental
Investigational medicinal product name	Ganaxolone
Investigational medicinal product code	
Other name	CCD 1042
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Participants were administered with Maximum of 1800 mg/day or 63 mg/kg/day

Arm title	PCDH19

Arm description:

Protocadherin-19

Arm type	Experimental
Investigational medicinal product name	Ganaxolone
Investigational medicinal product code	
Other name	CCD 1042
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:
Participants were administered with Maximum of 1800 mg/day or 63 mg/kg/day

Number of subjects in period 2	CDKL5	CSWS	Lennox-Gastaut
Started	4	2	4
Completed	4	0	2
Not completed	0	2	2
Adverse event, non-fatal	-	1	-
Lack of efficacy	-	1	2

Number of subjects in period 2	PCDH19
Started	6
Completed	2
Not completed	4
Adverse event, non-fatal	-
Lack of efficacy	4

Baseline characteristics

Reporting groups	
Reporting group title	CDKL5
Reporting group description: Cyclin-dependent kinase-like 5	
Reporting group title	CSWS
Reporting group description: Continuous Spike Wave in Sleep	
Reporting group title	Lennox-Gastaut
Reporting group description: Lennox-Gastaut Syndrome pediatric epilepsy	
Reporting group title	PCDH19
Reporting group description: Protocadherin-19	

Reporting group values	CDKL5	CSWS	Lennox-Gastaut
Number of subjects	7	2	10
Age categorical Units: Subjects			
Children (2-11 years)	6	1	9
Adolescents (12-17 years)	1	1	1
Age continuous Units: years			
arithmetic mean	7.57	11.55	9.12
standard deviation	± 5.167	± 5.728	± 2.352
Gender categorical Units: Subjects			
Female	6	1	7
Male	1	1	3

Reporting group values	PCDH19	Total	
Number of subjects	11	30	
Age categorical Units: Subjects			
Children (2-11 years)	8	24	
Adolescents (12-17 years)	3	6	
Age continuous Units: years			
arithmetic mean	9.00		
standard deviation	± 3.956	-	
Gender categorical Units: Subjects			
Female	11	25	
Male	0	5	

End points

End points reporting groups

Reporting group title	CDKL5
Reporting group description: Cyclin-dependent kinase-like 5	
Reporting group title	CSWS
Reporting group description: Continuous Spike Wave in Sleep	
Reporting group title	Lennox-Gastaut
Reporting group description: Lennox-Gastaut Syndrome pediatric epilepsy	
Reporting group title	PCDH19
Reporting group description: Protocadherin-19	
Reporting group title	CDKL5
Reporting group description: Cyclin-dependent kinase-like 5	
Reporting group title	CSWS
Reporting group description: Continuous Spike Wave in Sleep	
Reporting group title	Lennox-Gastaut
Reporting group description: Lennox-Gastaut Syndrome pediatric epilepsy	
Reporting group title	PCDH19
Reporting group description: Protocadherin-19	

Primary: Summary of 28-day Seizure Frequency for Sum of Individual Seizures and Clusters for 52-week OLE Period (Mean Percent Change & Standard Deviation)

End point title	Summary of 28-day Seizure Frequency for Sum of Individual Seizures and Clusters for 52-week OLE Period (Mean Percent Change & Standard Deviation)[1]

End point description:

Percentage change from baseline in 28-day seizure frequency at 3 months (day 91), 26 weeks, 52 week OLE (Mean Percent Change & Standard Deviation). Modified Intent-to-Treat Population (mITT Population) included all subjects who entered into the study and received at least 1 dose of Ganaxolone and provided at least 1 day of post-baseline seizure calendar data. 99999 indicated both subjects (2 for CSWS) discontinued so data is not available. Only those subjects with data available at specified timepoints has been presented (represented by n=X in the category titles).

End point type	Primary

End point timeframe:

Baseline through 52 week open label period

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: Per protocol, statistical analysis was not planned for this endpoint.

End point values	CDKL5	CSWS	Lennox-Gastaut	PCDH19
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	2	10	11
Units: percentage of change of frequency				
arithmetic mean (standard deviation)				
At Day 91, n=7,2,10,11	-31.23 (± 41.438)	99999 (± 99999)	122.10 (± 321.124)	52.83 (± 234.084)
At Week 26, n=7,2,10,11	-20.55 (± 60.588)	99999 (± 99999)	125.38 (± 319.051)	46.36 (± 235.661)
52 Week OLE through month 6, n=4,2,2,6	-54.41 (± 40.286)	99999 (± 99999)	-38.74 (± 9.292)	-19.98 (± 63.644)
52 Week OLE period, n=4,2,2,6	-49.20 (± 50.206)	99999 (± 99999)	-37.75 (± 7.891)	-19.95 (± 63.571)

Statistical analyses

No statistical analyses for this end point

Primary: Summary of 28-day Seizure Frequency for Sum of Individual Seizures and Clusters Through 52-week OLE (Median Percent Change)

End point title	Summary of 28-day Seizure Frequency for Sum of Individual Seizures and Clusters Through 52-week OLE (Median Percent Change)[2]

End point description:

Percentage change from baseline in 28-day seizure frequency at 3 months (day 91), 26 weeks, 52 week OLE (Median Percent Change). 99999 indicates both subjects (2 for CSWS) discontinued so data is not available. 88888 indicates there is no data available to support this row for this arm. One subject in the CDKL5 cohort had duplications of data on 6 days. These data appeared to the investigator and sponsor to be erroneous. Excluding these days changes the median percent change from baseline at Week 26 to 44.4 for the CDKL5 cohort. This is reflected in the CDKL5 arm. Only those subjects with data available at specified timepoints has been presented (represented by n=X in the category titles)

End point type	Primary

End point timeframe:

Baseline through 52-week open- label period

Notes:

[2] - 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: Per protocol, statistical analysis was not planned for this endpoint.

End point values	CDKL5	CSWS	Lennox-Gastaut	PCDH19
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	2	10	11
Units: Median Percent Change in Frequency				
median (full range (min-max))				
At Day 91, n=7,2,10,11	-47.34 (-80.9 to 36.8)	99999 (99999 to 99999)	-10.22 (-68.1 to 904.3)	-25.98 (-100.00 to 723.2)
At Week 26, n=7,2,10,11	-37.70 (-85.3 to 99.9)	99999 (99999 to 99999)	-9.19 (-71.2 to 904.3)	-24.59 (-100.00 to 723.2)
At Week 26 (duplicate entries deleted,n=7,2,10,11	-44.4 (-85.3 to 99.9)	99999 (99999 to 99999)	88888 (88888 to 88888)	88888 (88888 to 88888)

52 week OLE through month 6, n=4,2,10,2	-58.94 (-89.4 to -10.4)	99999 (99999 to 99999)	-38.74 (-45.3 to -32.2)	-13.48 (-100.0 to 59.6)
52 week OLE period, n=7,2,10,11	-61.93 (-89.5 to 16.6)	99999 (99999 to 99999)	-37.75 (-43.3 to -32.2)	-13.48 (-99.0 to 59.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of CGII-C

End point title	Summary of CGII-C

End point description:

Clinician Global Impression of Change score as assessed by questionnaire. [Time Frame: 78 Weeks] CGII-C scale is qualitative values and not quantitative. Only those subjects with data available at specified timepoints has been presented (represented by n=X in the category titles). 99999 indicates both subjects (2 for CSWS) discontinued so data is not available.

End point type	Secondary

End point timeframe:

End of Week 4, End of Week 8, End of Week 17, End of Week 26, Week 44, Week 62, Week 78

End point values	CDKL5	CSWS	Lennox-Gastaut	PCDH19
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	2	8	11
Units: participants				
number (not applicable)				
End of Week 4-Very much improved, n= 7, 2, 8, 11	0	99999	2	1
End of Week 4-much improved, n= 7, 2, 8, 11	3	99999	4	4
End of Week 4-minimally improved, n= 7, 2, 8, 11	2	99999	2	3
End of Week 4-No change, n= 7, 2, 8, 11	2	99999	0	3
End of Week 4-minimally worse, n= 7, 2, 8, 11	0	99999	0	0
End of Week 4- much worse, n= 7, 2, 8, 11	0	99999	0	0
End of Week 4- very much worse, n= 7, 2, 8, 11	0	99999	0	0
End of Week 8-Very much improved, n= 7, 2, 8, 7	0	99999	1	0
End of Week 8-much improved, n= 7, 2, 8, 7	4	99999	4	2
End of Week 8-minimally improved, n= 7, 2, 8, 7	2	99999	2	2
End of Week 8-No change, n= 7, 2, 8, 7	1	99999	1	1
End of Week 8-minimally worse, n= 7, 2, 8, 7	0	99999	0	2
End of Week 8- much worse, n= 7, 2, 8, 7	0	99999	0	0

End of Week 8- very much worse, n= 7, 2, 8, 7	0	99999	0	0
End of Week 17-Very much improved, n= 5, 2, 6, 6	1	99999	2	1
End of Week 17-much improved, n= 5, 2, 6, 6	2	99999	3	1
End of Week 17-minimally improved, n= 5, 2, 6, 6	2	99999	0	4
End of Week 17-No change, n= 5, 2, 6, 6	0	99999	1	0
End of Week 17-minimally worse, n= 5, 2, 6, 6	0	99999	0	0
End of Week 17- much worse, n= 5, 2, 6, 6	0	99999	0	0
End of Week 17- very much worse, n= 5, 2, 6, 6	0	99999	0	0
End of Week 26-Very much improved, n= 7, 2, 9, 9	0	99999	1	2
End of Week 26-much improved, n= 7, 2, 9, 9	3	99999	1	2
End of Week 26-minimally improved, n= 7, 2, 9, 9	1	99999	1	2
End of Week 26-No change, n=7, 2, 9, 9	2	99999	2	2
End of Week 26-minimally worse, n= 7, 2, 9, 9	0	99999	1	0
End of Week 26- much worse, n= 7, 2, 9, 9	1	99999	1	1
End of Week 26- very much worse, n= 7, 2, 9, 9	0	99999	0	0
End of Week 44-Very much improved, n= 4, 2, 2, 2	0	99999	0	2
End of Week 44-much improved, n= 4, 2, 2, 2	3	99999	0	0
End of Week 44-minimally improved, n= 4, 2, 2, 2	1	99999	0	0
End of Week 44-No change, n=4, 2, 2, 2	0	99999	1	0
End of Week 44-minimally worse, n= 4, 2, 2, 2	0	99999	1	0
End of Week 44- much worse, n= 4, 2, 2, 2	0	99999	0	0
End of Week 44- very much worse, n= 4, 2, 2, 2	0	99999	0	0
End of Week 62-Very much improved, n= 4, 2, 1, 2	0	99999	0	2
End of Week 62-much improved, n= 4, 2, 1, 2	4	99999	0	0
End of Week 62-minimally improved, n= 4, 2, 1, 2	0	99999	1	0
End of Week 62-No change, n=4, 2, 1, 2	0	99999	0	0
End of Week 62-minimally worse, n= 4, 2, 1, 2	0	99999	0	0
End of Week 62- much worse, n= 4, 2, 1, 2	0	99999	0	0
End of Week 62- very much worse, n= 4, 2, 1, 2	0	99999	0	0
End of Week 78-Very much improved, n= 3, 2, 1, 4	0	99999	0	2
End of Week 78-much improved, n= 3, 2, 1, 4	3	99999	0	0

End of Week 78-minimally improved, n= 3, 2, 1, 4	0	99999	1	0
End of Week 78-No change, n=3, 2, 1, 4	0	99999	0	0
End of Week 78-minimally worse, n= 3, 2, 1, 4	0	99999	0	1
End of Week 78 much worse, n= 3, 2, 1, 4	0	99999	0	1
End of Week 78- very much worse, n= 3, 2, 1, 4	0	99999	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of CGII-P

End point title	Summary of CGII-P

End point description:

Patient Global Impression of Change score as assessed by questionnaire. [Time Frame: 78 Weeks] CGII-P scale is qualitative values and not quantitative. 99999 indicates both subjects (2 for CSWS) discontinued so data is not available. Only those subjects with data available at specified timepoints has been presented (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

Patient Global Impression of Change score as assessed by questionnaire. [Time Frame: 78 Weeks]

End point values	CDKL5	CSWS	Lennox-Gastaut	PCDH19
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	2	8	11
Units: participants				
number (not applicable)				
End of Week 4-Very much improved, n= 7, 2, 8, 11	0	99999	3	1
End of Week 4-much improved, n= 7, 2, 8, 11	1	99999	2	2
End of Week 4-minimally improved, n= 7, 2, 8, 11	4	99999	3	5
End of Week 4-No change, n= 7, 2, 8, 11	2	99999	0	3
End of Week 4-minimally worse, n= 7, 2, 8, 11	0	99999	0	0
End of Week 4- much worse, n= 7, 2, 8, 11	0	99999	0	0
End of Week 4- very much worse, n= 7, 2, 8, 11	0	99999	0	0
End of Week 8-Very much improved, n= 7, 2, 8, 7	0	99999	2	0
End of Week 8-much improved, n= 7, 2, 8, 7	1	99999	2	2
End of Week 8-minimally improved, n= 7, 2, 8, 7	5	99999	3	2

End of Week 8-No change, n= 7, 2, 8, 7	0	99999	1	1
End of Week 8-minimally worse, n= 7, 2, 8, 7	1	99999	0	1
End of Week 8- much worse, n= 7, 2, 8, 7	0	99999	0	1
End of Week 8- very much worse, n= 7, 2, 8, 7	0	99999	0	0
End of Week 17-Very much improved, n= 5, 2, 6, 6	1	99999	1	1
End of Week 17-much improved, n= 5, 2, 6, 6	2	99999	1	1
End of Week 17-minimally improved, n= 5, 2, 6, 6	2	99999	3	4
End of Week 17-No change, n= 5, 2, 6, 6	0	99999	0	0
End of Week 17-minimally worse, n= 5, 2, 6, 6	0	99999	1	0
End of Week 17- much worse, n= 5, 2, 6, 6	0	99999	0	0
End of Week 17- very much worse, n= 5, 2, 6, 6	0	99999	0	0
End of Week 26-Very much improved, n= 7, 2, 7, 9	0	99999	1	2
End of Week 26-much improved, n= 7, 2, 7, 9	4	99999	1	2
End of Week 26-minimally improved, n= 7, 2, 7, 9	0	99999	3	3
End of Week 26-No change, n=7, 2, 7, 9	1	99999	1	0
End of Week 26-minimally worse, n= 7, 2, 7, 9	1	99999	0	1
End of Week 26- much worse, n= 7, 2, 7, 9	1	99999	1	1
End of Week 26- very much worse, n= 7, 2, 7, 9	0	99999	0	0
End of Week 44-Very much improved, n= 4, 2, 2, 2	0	99999	0	2
End of Week 44-much improved, n= 4, 2, 2, 2	2	99999	0	0
End of Week 44-minimally improved, n= 4, 2, 2, 2	0	99999	0	0
End of Week 44-No change, n=4, 2, 2, 2	2	99999	1	0
End of Week 44-minimally worse, n= 4, 2, 2, 2	0	99999	1	0
End of Week 44- much worse, n= 4, 2, 2, 2	0	99999	0	0
End of Week 44- very much worse, n= 4, 2, 2, 2	0	99999	0	0
End of Week 62-Very much improved, n= 4, 2, 1, 2	2	99999	0	2
End of Week 62-much improved, n= 4, 2, 1, 2	2	99999	0	0
End of Week 62-minimally improved, n= 4, 2, 1, 2	0	99999	1	0
End of Week 62-No change, n=4, 2, 1, 2	0	99999	0	0
End of Week 62-minimally worse, n= 4, 2, 1, 2	0	99999	0	0
End of Week 62- much worse, n= 4, 2, 1, 2	0	99999	0	0

End of Week 62- very much worse, n= 4, 2, 1, 2	0	99999	0	0
End of Week 78-Very much improved, n= 3, 2, 1, 4	1	99999	0	2
End of Week 78-much improved, n= 3, 2, 1, 4	2	99999	0	0
End of Week 78-minimally improved, n= 3, 2, 1, 4	0	99999	1	1
End of Week 78-No change, n=3, 2, 1, 4	0	99999	0	0
End of Week 78-minimally worse, n= 3, 2, 1, 4	0	99999	0	0
End of Week 78 much worse, n= 3, 2, 1, 4	0	99999	0	1
End of Week 78- very much worse, n= 3, 2, 1, 4	0	99999	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Responder Rate of Seizure Frequency

End point title	Number of Participants With Responder Rate of Seizure Frequency

End point description:

Responder Rate in Terms of 28-day Seizure Frequency Based on the Sum of Individual Seizures and Clusters. 99999 indicates both subjects (2 for CSWS) discontinued so data is not available.

End point type	Secondary

End point timeframe:

Month 3 and Week 26

End point values	CDKL5	CSWS	Lennox-Gastaut	PCDH19
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	2	10	11
Units: Participants				
number (not applicable)				
Post-baseline through Month 3 - 25% Responder	4	99999	4	6
Post-baseline through Month 3 - 50% Responder	3	99999	2	4
Post-baseline through Month 3 - 75% Responder	1	99999	0	1
Post-baseline 26-week open-label - 25% Responder	4	99999	3	5
Post-baseline 26-week open-label - 50% Responder	2	99999	1	3
Post-baseline 26-week open-label - 75% Responder	1	99999	0	1

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Percentage Change of Individual Seizure-free Days

End point title	Mean Percentage Change of Individual Seizure-free Days

End point description:

Mean Percentage Change of Individual Seizure-free days per 28-day period (through 52-week OLE) period relative to baseline. 99999 indicates both subjects (2 for CSWS) discontinued so data is not available. Only those subjects with data available at specified time points has been presented (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

Baseline, Day 91, Week 26, 52-week OLE through month 6, 52-week OLE Period

End point values	CDKL5	CSWS	Lennox-Gastaut	PCDH19
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	2	10	11
Units: Percentage Change				
arithmetic mean (standard deviation)				
Baseline to Day 91, n=7, 2, 10, 11	11.84 (± 18.472)	99999 (± 99999)	-1.12 (± 24.928)	7.87 (± 17.843)
Baseline to Week 26, n=7, 2, 10, 11	11.80 (± 20.968)	99999 (± 99999)	-2.13 (± 22.042)	7.94 (± 18.016)
Baseline to 52-week OLE (181 days), n=4, 2, 2, 6	21 (± 30.85)	99999 (± 99999)	16.35 (± 2.916)	17.12 (± 27.040)
Baseline to 52-week OLE period, n=4, 2, 2, 6	20.44 (± 28.788)	99999 (± 99999)	14.95 (± 4.897)	17.02 (± 26.904)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Combined 26-week open label period and 52-week open label extension period	
Adverse event reporting additional description:	
Overall Summary of Adverse Events (Safety Population)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups	
Reporting group title	CDKL5
Reporting group description: -	
Reporting group title	CSWS
Reporting group description: -	
Reporting group title	Lennox-Gastaut
Reporting group description: -	
Reporting group title	PCDH19
Reporting group description: -	

Serious adverse events	CDKL5	CSWS	Lennox-Gastaut
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 7 (14.29%)	1 / 2 (50.00%)	2 / 10 (20.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Seizure			
subjects affected / exposed	0 / 7 (0.00%)	0 / 2 (0.00%)	0 / 10 (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
Somnolence			
subjects affected / exposed	0 / 7 (0.00%)	1 / 2 (50.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
General disorders and administration site conditions			
Unintentional Medical Device Removal			

subjects affected / exposed	1 / 7 (14.29%)	0 / 2 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 7 (0.00%)	0 / 2 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 7 (0.00%)	0 / 2 (0.00%)	0 / 10 (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
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 7 (0.00%)	1 / 2 (50.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 2 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Pneumonia Viral			
subjects affected / exposed	0 / 7 (0.00%)	0 / 2 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Serious adverse events	PCDH19		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 11 (27.27%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Seizure			

subjects affected / exposed	2 / 11 (18.18%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 4		
Somnolence			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Unintentional Medical Device Removal			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia Viral			

subjects affected / exposed	0 / 11 (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	CDKL5	CSWS	Lennox-Gastaut
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	1 / 2 (50.00%)	7 / 10 (70.00%)
Investigations			
Weight decreased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 2 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 7 (14.29%)	0 / 2 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Fall			
subjects affected / exposed	0 / 7 (0.00%)	0 / 2 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Surgical and medical procedures			
Gastrostomy			
subjects affected / exposed	2 / 7 (28.57%)	0 / 2 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 2 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Balance Disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 2 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Dizziness			
subjects affected / exposed	0 / 7 (0.00%)	1 / 2 (50.00%)	1 / 10 (10.00%)
occurrences (all)	0	2	1
Headache			

subjects affected / exposed	1 / 7 (14.29%)	0 / 2 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Hypersomnia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 2 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Sedation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 2 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Seizure			
subjects affected / exposed	1 / 7 (14.29%)	0 / 2 (0.00%)	2 / 10 (20.00%)
occurrences (all)	1	0	4
Somnolence			
subjects affected / exposed	0 / 7 (0.00%)	1 / 2 (50.00%)	2 / 10 (20.00%)
occurrences (all)	0	1	2
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 7 (0.00%)	0 / 2 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	5 / 7 (71.43%)	0 / 2 (0.00%)	1 / 10 (10.00%)
occurrences (all)	22	0	2
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 7 (0.00%)	0 / 2 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	3 / 7 (42.86%)	1 / 2 (50.00%)	1 / 10 (10.00%)
occurrences (all)	9	1	3
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 7 (0.00%)	0 / 2 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 2 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1

Rash			
subjects affected / exposed	1 / 7 (14.29%)	0 / 2 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Psychiatric disorders			
Abnormal behavior			
subjects affected / exposed	0 / 7 (0.00%)	0 / 2 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Emotional disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 2 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Restlessness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 2 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Enuresis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 2 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Fungal Infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 2 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Influenza			
subjects affected / exposed	2 / 7 (28.57%)	0 / 2 (0.00%)	1 / 10 (10.00%)
occurrences (all)	5	0	1
Nasopharyngitis			
subjects affected / exposed	2 / 7 (28.57%)	0 / 2 (0.00%)	0 / 10 (0.00%)
occurrences (all)	8	0	0
Otitis media			
subjects affected / exposed	0 / 7 (0.00%)	0 / 2 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 2 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	2
Rhinitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 2 (0.00%)	1 / 10 (10.00%)
occurrences (all)	3	0	1
Sinusitis			

subjects affected / exposed	0 / 7 (0.00%)	1 / 2 (50.00%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	3 / 7 (42.86%)	0 / 2 (0.00%)	0 / 10 (0.00%)
occurrences (all)	3	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 7 (0.00%)	0 / 2 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	PCDH19		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 11 (100.00%)		
Investigations			
Weight decreased			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Fall			
subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	3		
Surgical and medical procedures			
Gastrostomy			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Ataxia			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Balance Disorder			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Dizziness			

subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Headache subjects affected / exposed occurrences (all)	4 / 11 (36.36%) 4		
Hypersomnia subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0		
Sedation subjects affected / exposed occurrences (all)	2 / 11 (18.18%) 2		
Seizure subjects affected / exposed occurrences (all)	4 / 11 (36.36%) 6		
Somnolence subjects affected / exposed occurrences (all)	6 / 11 (54.55%) 6		
General disorders and administration site conditions			
Fatigue subjects affected / exposed occurrences (all)	4 / 11 (36.36%) 4		
Pyrexia subjects affected / exposed occurrences (all)	7 / 11 (63.64%) 16		
Gastrointestinal disorders			
Abdominal pain upper subjects affected / exposed occurrences (all)	2 / 11 (18.18%) 2		
Vomiting subjects affected / exposed occurrences (all)	3 / 11 (27.27%) 3		
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	2 / 11 (18.18%) 2		
Skin and subcutaneous tissue disorders			

Alopecia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Psychiatric disorders			
Abnormal behavior			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	2		
Emotional disorder			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Restlessness			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Renal and urinary disorders			
Enuresis			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Infections and infestations			
Fungal Infection			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	2		
Otitis media			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Pneumonia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Rhinitis			

subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 December 2014	Amendment 1: Minor edits and clarifications.
12 January 2015	Amendment 2: Minor edits and clarifications. Statement added to Section 9.5.4 regarding the blood collection to measure allopregnanolone and related neurosteroids at Visits 2 and 4.
23 January 2015	Amendment 3: Dosing regimen revised. A visit at Week 2 and procedures for unscheduled visits added. Collection of blood for Liver Function Test and other laboratory assessments added at the Week 26 visit. Guidance on missed doses for the capsules and suspension clarified.
08 June 2015	Amendment 4: Collection of electroencephalograms (EEG's) added to Visits 2, 5 and 7.
15 July 2015	Amendment 5: Addition of cyclin-dependent kinase-like 5 (CDKL5) Deficiency Disorder (CDD) and Dravet Syndrome Subjects. Background section updated. Seizure criteria updated for CDD and Dravet Syndrome subjects. Contraindicated medications for Dravet patients added. Male children became eligible for inclusion. Age increased from 2 to 10 years to 2 to 18 years age. Pregnancy testing was added for women of childbearing potential (WCBP). Tanner Scale score added under Physical Exam.
30 September 2015	Amendment 5.1 Local Amendment: Stiripentol was added as an Exclusion Criteria in Section 9.3.3 and to the list in Appendix 3 of "Prohibited Strong and Moderate CYP 3A4 Inhibitors".
08 April 2016	Amendment 6.0 Local Amendment: Inclusion of other genetic epilepsies added. These included, but were not limited to children with PCDH19 mutation, CDD, Dravet Syndrome and other epileptic syndromes such as LGS, CSWS, and other potential genetic or clinical conditions with or without corresponding genetic condition (referred as genetic epilepsies) in an open-label proof-of concept study. Inclusion of additional EEG assessments. Addition of the Visual Analogue Scale (VAS)-Targeted Behavior at baseline, Visits 5, Visit 7, Visit 9 and Visit 10. Stiripentol (Italy specific) added as an Exclusion Criteria in Section 9.3.3 and added to the list in Appendix 3 of "Prohibited Strong and Moderate CYP 3A4 Inhibitors."
14 September 2016	Amendment 7: Sponsor address and Sponsor Medical Representative updated. Minor editorial changes made. Removed "and other potential genetic or clinical conditions with or without corresponding genetic condition (referred to as genetic epilepsies) or similar throughout the clinical study protocol. Primary and Secondary Efficacy evaluations modified. Columbia-Suicide Severity Rating Scale (C-SSRS) added to Safety evaluations Statistical Methods clarified; EEG added. Background on Ganaxolone – double-blind, Phase 3 study information added and relevant sections summarizing the Phase 2 data modified. Inclusion Criteria 2 and 3 revised. Addition of a 24-hour continuous EEG at baseline, Visit 4 and Visit 7 for the Continuous Spike Wave in Sleep (CSWS) subjects. Intent-to-treat (ITT) population changed to modified intent to treat (MITT) population throughout the clinical study protocol. Analysis of Primary and Secondary Efficacy Variables modified. Interim Analysis text added. Serious adverse events (SAE) reporting medical telephone number changed.

22 June 2017	Amendment 8: Synopsis-Study Population and Main Criteria for Inclusion/Exclusion revised Inclusion criteria #10 revised. Exclusion criteria #6 and #11 revised • Section 9.5.5.11 Visit 11 (Post drug follow-up visit) revised. Section 10.5.3.1 SAE Reporting – administrative change made.
24 August 2017	Amendment 8.1 Local Amendment: Minor editorial and format changes made. Section 9.3.4.2 Early Termination Procedures revised. Section 9.5.3 Safety Assessments revised. Section 9.5.4.1 Laboratory Samples revised. Section 9.5.4.2 Efficacy Assessments revised. Section 9.5.4.3 VAS revised. Section 9.5.5.10 Visit 10 (End of Week 78 ±Days, Final Investigative Visit) revised. Section 9.5.5.12 Visit 12-Visit 97 added. Section 9.5.5.13 Visit 98 added. Section 9.5.5.14 Visit 99 added. Section 13.3 Appendix 2 and Appendix 3, minor deletion/addition; footnote 7 added. Section 13.4 Appendix 4 added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

CSWS cohort was not included in efficacy summaries as only 2 subjects were enrolled in cohort; however, cohort was included in the subject data listings. Overall number of participants affected is associated with all TEAEs and not >-5%.

Notes: