



## Clinical trial results:

### A double-blind, randomized, placebo-controlled trial of adjunctive ganaxolone treatment in female children with protocadherin 19 (PCDH19)- related epilepsy followed by long-term open-label treatment Summary

EudraCT number	2018-004496-12
Trial protocol	FR NL PL HU GB IT
Global end of trial date	20 June 2022

#### Results information

Result version number	v1 (current)
This version publication date	20 October 2023
First version publication date	20 October 2023

#### Trial information

##### Trial identification

Sponsor protocol code	1042-PCDH19-3002
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##### Additional study identifiers

ISRCTN number	ISRCTN000000000
ClinicalTrials.gov id (NCT number)	NCT03865732
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	Safety Department, Marinus Pharmaceuticals, Inc., 001 4846792138, clinicaltrials@marinuspharma.com
Scientific contact	Safety Department, Marinus Pharmaceuticals, Inc., 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	20 June 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 January 2021
Global end of trial reached?	Yes
Global end of trial date	20 June 2022
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To assess the efficacy of Ganaxolone (GNX) compared with Placebo, in biomarker-positive subjects, as adjunctive therapy for the treatment of seizures in children with genetically-confirmed PCDH19-related epilepsy at the end of the 17-week double-blind (DB) phase.

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	17 May 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	United States: 12
Worldwide total number of subjects	21
EEA total number of subjects	9

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)	19
Adolescents (12-17 years)	2
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

This was a global, biomarker-stratified, double-blind, randomized, placebo-controlled trial of adjunctive ganaxolone treatment of seizures in female children with a confirmed pathogenic or likely pathogenic PCDH19 mutation.

### Pre-assignment

Screening details:

A total of 21 participants were enrolled in the study.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Placebo

Arm description:

Placebo suspension 3x's/day for 17 weeks

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Participants were administered with inactive Placebo as oral suspension.

<b>Arm title</b>	Ganaxolone
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Arm description:

Ganaxolone suspension (50 mg/ml) 3x's /day for 17 weeks

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

Dosage and administration details:

Participants were administered with 50 mg/ml Ganaxolone as oral ssuspension.

<b>Number of subjects in period 1</b>	Placebo	Ganaxolone
Started	11	10
Completed	11	9
Not completed	0	1
Adverse event, non-fatal	-	1

## Baseline characteristics

### Reporting groups

Reporting group title	Placebo
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Reporting group description:

Placebo suspension 3x's/day for 17 weeks

Reporting group title	Ganaxolone
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Reporting group description:

Ganaxolone suspension (50 mg/ml) 3x's /day for 17 weeks

Reporting group values	Placebo	Ganaxolone	Total
Number of subjects	11	10	21
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	10	9	19
Adolescents (12-17 years)	1	1	2
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	11	10	21
Male	0	0	0
Race			
Units: Subjects			
American Indian or Alaska Native	0	1	1
Black or African American	1	0	1
White	10	7	17
More than one race	0	1	1
Unknown or Not Reported	0	1	1

## End points

### End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo suspension 3x's/day for 17 weeks	
Reporting group title	Ganaxolone
Reporting group description:	
Ganaxolone suspension (50 mg/ml) 3x's /day for 17 weeks	

### Primary: Summary of 28-day Seizure Frequency Through 17 Week Post-Baseline Phase (Median Percent Change)

End point title	Summary of 28-day Seizure Frequency Through 17 Week Post-Baseline Phase (Median Percent Change) <sup>[1]</sup>
End point description:	
Summary of 28-day Seizure Frequency for Seizure Types for Subjects in the Biomarker-positive Stratum through 17 weeks (Median Percent Change). Intent-to-Treat Population comprises all randomized subjects who received at least one dose of study drug and had at least one post-Baseline efficacy assessment.	
End point type	Primary
End point timeframe:	
End of the double-blind 17 week treatment 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	Placebo	Ganaxolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: Median % Change in Number of Seizures				
median (inter-quartile range (Q1-Q3))	-23.97 (-88.24 to 4.89)	-61.52 (-95.85 to -33.40)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Summary of 28-day Seizure Frequency for Subjects in the Biomarker-positive Stratum (Median Percent Change)

End point title	Summary of 28-day Seizure Frequency for Subjects in the Biomarker-positive Stratum (Median Percent Change)
End point description:	
Summary of 28-day Seizure Frequency for Seizure Types for Subjects in the Biomarker-positive Stratum through 17 weeks (Median Percent Change). Intent to treat Population (ITT) Population specific to subjects in the Biomarker-positive Stratum.	
End point type	Secondary

End point timeframe:  
End of the double-blind 17 week treatment period

End point values	Placebo	Ganaxolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: Median % Change in Number of Seizures				
median (inter-quartile range (Q1-Q3))	-18.71 (-85.74 to 70.73)	-35.90 (-86.48 to -24.32)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: 50% Primary Seizure Reduction

End point title	50% Primary Seizure Reduction
End point description: Percent of subjects experiencing a greater than or equal to 50% reduction in 28-day primary seizure frequency relative to the 12-week baseline.	
End point type	Secondary
End point timeframe: End of the double-blind 17 week treatment period	

End point values	Placebo	Ganaxolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	10		
Units: Participants	4	5		

### Statistical analyses

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Screening through Week 17

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	22
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### Reporting groups

Reporting group title	Placebo
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Reporting group description:

Placebo suspension 3x's/day for 17 weeks

Reporting group title	Ganaxolone
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Reporting group description:

Ganaxolone suspension (50 mg/ml) 3x's /day for 17 weeks

Serious adverse events	Placebo	Ganaxolone	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 11 (45.45%)	1 / 10 (10.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Febrile Convulsion			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Seizure			
subjects affected / exposed	3 / 11 (27.27%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 4	0 / 0	
Seizure cluster			
subjects affected / exposed	2 / 11 (18.18%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Psychiatric disorders			
Psychogenic seizure			

subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

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

<b>Non-serious adverse events</b>	Placebo	Ganaxolone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 11 (90.91%)	7 / 10 (70.00%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 11 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	2	
Protein urine present			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Eye injury			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Skin laceration			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Somnolence			
subjects affected / exposed	3 / 11 (27.27%)	4 / 10 (40.00%)	
occurrences (all)	3	4	
Ataxia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	

Lethargy subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 10 (10.00%) 2	
Seizure subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 10 (0.00%) 0	
General disorders and administration site conditions			
Fatigue subjects affected / exposed occurrences (all)	2 / 11 (18.18%) 2	2 / 10 (20.00%) 2	
Gait disturbance subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 10 (0.00%) 0	
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	2 / 11 (18.18%) 2	1 / 10 (10.00%) 1	
Constipation subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	1 / 10 (10.00%) 1	
Vomiting subjects affected / exposed occurrences (all)	2 / 11 (18.18%) 2	0 / 10 (0.00%) 0	
Abdominal pain subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 10 (0.00%) 0	
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 10 (0.00%) 0	
Dental caries subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 10 (10.00%) 1	
Eructation subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 10 (10.00%) 1	
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	2 / 11 (18.18%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Dermatitis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Papule			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Psychiatric disorders			
Aggression			
subjects affected / exposed	1 / 11 (9.09%)	2 / 10 (20.00%)	
occurrences (all)	1	2	
Agitation			
subjects affected / exposed	0 / 11 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	2	
Behaviour disorder			
subjects affected / exposed	1 / 11 (9.09%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Irritability			
subjects affected / exposed	1 / 11 (9.09%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Restlessness			
subjects affected / exposed	1 / 11 (9.09%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Disinhibition			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	1 / 11 (9.09%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			

Arthralgia subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 10 (0.00%) 0	
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	1 / 10 (10.00%) 1	
Impetigo subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 10 (0.00%) 0	
Pharyngitis streptococcal subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 10 (0.00%) 0	
Vulvovaginal candidiasis subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 10 (0.00%) 0	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	2 / 10 (20.00%) 2	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 March 2019	Updated to redefine the primary seizure types used to determine participant eligibility and conduct the primary/secondary endpoint analyses.
01 July 2019	Updated total enrollment from 50-70 to approximately 70 participants; Updated total number of sites up to 45 sites; Added: Acceptable historical seizure data must include at least 12 consecutive weeks prior to the Screening visit of documenting seizure type and frequency (also noting seizure-free days); Added: If a participant must be abruptly discontinued from investigational product, (e.g., severe rash), careful attention should be paid for possibility of withdrawal symptoms such as increase in seizure number or severity. Consideration should be made by the investigator for providing another GABA-A medication for 1-2 weeks such as clobazam to mitigate the potential risk of withdrawal from a positive modulator of GABA-A; Added: Adverse event in which the character, severity or frequency is new in comparison to the participant's existing risk profile with the exception of somnolence and seizures. Added: An Adverse Event that is associated with non-reversible target organ dysfunction, with the associated laboratory abnormalities as defined in exclusion criteria 11, 12 or 13. An allowance may be made for continued treatment if the abnormality is not medically significant; Added: A laboratory abnormality or vital sign change that is irreversible and considered medically significant, associated with use of the investigational product; Added: The Sponsor's Medical Monitor does not have to be contacted to initiate unblinding in the IWRS system; Added: Baseline Visit – Randomization (Visit 2, Week 0 + 6 days) The following study procedures/assessments to be completed, the results received, and the investigator must ensure the participant meets all inclusion and exclusion criteria prior to IP administration. The 8 weeks between Screening and Randomization can be no less than 56 days and no more than 62 days.
16 August 2019	Added: Exclusion Criteria - participants with $\leq 3$ primary seizures during the 12-week baseline period; Added: If a participant fails to qualify because of Exclusion Criteria #4 ( $\leq 3$ primary seizures during the 12-week baseline period), she will not be randomized. However, she can be rescreened after collecting another 12 or more weeks of seizure history that satisfies all eligibility criteria including Inclusion Criteria #5 and Exclusion Criteria #3. Each participant is allowed a maximum of 1 rescreening visit.
30 June 2020	Added: As enrollment in the study was discontinued early due to administrative reasons, and only 15 biomarker-positive participants are expected to be randomized, the study is not considered to have adequate power for formal testing of the statistical hypotheses. Since the reason for stopping enrollment is external to the study, the statistical analysis will be performed as planned. All p-values produced as part of the pre-specified analysis would therefore be considered as nominal; Added: In the event of unforeseen circumstances, in-person study visit assessments may not be able to be performed. To conduct the study according to protocol while preserving patient safety, operational alternatives such as those listed below can be employed as long as the site's actions are in compliance with the institution's IRB/EC policies and regulations: Telemedicine visits (video and/or audio communication methods); In-home visits; Local physician visits; Use of local and/or off-site laboratories; Site-to-patient IP distribution. Added: Retrospective entry of diary events (seizure and medication) can be completed by the caregiver up to 5 days later and proxy entry by the site is also available to the site staff (greater than 5 days), but neither method is encouraged.

Notes:

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## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

None reported