



## Clinical trial results:

### A Double-blind, Randomized, Placebo-controlled Trial of Adjunctive Ganaxolone Treatment in Children and Young Adults with Cyclin-dependent Kinase-like 5 (CDKL5) Deficiency Disorder (CDD) Followed by Long-term Open-label Treatment

#### Summary

EudraCT number	2018-001180-23
Trial protocol	GB IT FR PL
Global end of trial date	28 May 2021

#### Results information

Result version number	v1 (current)
This version publication date	20 June 2025
First version publication date	20 June 2025

#### Trial information

##### Trial identification

Sponsor protocol code	1042-CDD-3001
-----------------------	---------------

##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03572933
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Marinus Pharmaceuticals, Inc.
Sponsor organisation address	5 Radnor Corporate Center, 100 Matsonford Road, Suite 500, Radnor, PA, United States, 19087
Public contact	Safety Department, Marinus Pharmaceuticals, Inc., +46 853339500, clinical@immedica.com
Scientific contact	Safety Department, Marinus Pharmaceuticals, Inc., +46 853339500, clinical@immedica.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	28 May 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	28 May 2021
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To assess the efficacy, safety, and tolerability of adjunctive ganaxolone therapy compared to placebo for the treatment of seizures in children and young adults with genetically confirmed CDKL5 gene 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	30 June 2018
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	Australia: 6
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Russian Federation: 14
Country: Number of subjects enrolled	United States: 42
Country: Number of subjects enrolled	Poland: 10
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Italy: 15
Worldwide total number of subjects	101
EEA total number of subjects	31

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)	82
Adolescents (12-17 years)	17
Adults (18-64 years)	2
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

The study was to evaluate the efficacy, safety, and tolerability of adjunctive ganaxolone therapy compared to placebo for the treatment of seizures in children and young adults with genetically confirmed CDKL5 gene mutation.

### 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:

Placebo was administered

<b>Arm title</b>	Ganaxolone
------------------	------------

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:

Ganaxolone was administered

<b>Number of subjects in period 1</b>	Placebo	Ganaxolone
Started	51	50
Completed	47	48
Not completed	4	2
Consent withdrawn by subject	-	1
Adverse event, non-fatal	4	1

## Baseline characteristics

### 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

Reporting group values	Placebo	Ganaxolone	Total
Number of subjects	51	50	101
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)	41	41	82
Adolescents (12-17 years)	9	8	17
Adults (18-64 years)	1	1	2
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	7.73	6.78	
standard deviation	± 4.382	± 4.705	-
Gender categorical Units: Subjects			
Female	41	39	80
Male	10	11	21
Race Units: Subjects			
Asian	3	2	5
White	47	46	93
Unknown or Not Reported	1	2	3
Ethnicity Units: Subjects			
Hispanic or Latino	6	4	10
Not Hispanic or Latino	43	44	87
Unknown or Not Reported	2	2	4

## 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 for Major Motor Seizure Types

End point title	Summary of 28-day Seizure Frequency for Major Motor Seizure Types <sup>[1]</sup>
End point description:	
Summary of 28-day seizure frequency for Major Motor Seizure Types during the double-blind treatment period relative to the 6-week prospective baseline period. Summaries are based on the sum of the individual seizures, the countable seizures, and the clusters with uncountable seizures (each cluster with uncountable seizures counts as 1 seizure). Within the baseline and post baseline intervals, 28-day seizure frequency was calculated as the total number of seizures in the interval divided by the number of days with available seizure data in the interval, multiplied by 28. Intent-to-Treat (ITT) population: included all randomized participants who received at least one dose of study drug.	
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: No statistical analysis was performed for this outcome measure.

End point values	Placebo	Ganaxolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	49		
Units: Seizures per day				
median (confidence interval 95%)				
Baseline	49.17 (32.20 to 60.67)	54.00 (38.24 to 106.67)		
17 week-post baseline phase	55.50 (35.75 to 80.14)	45.03 (31.83 to 76.03)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Caregiver Global Impression of Change in Attention

End point title	Caregiver Global Impression of Change in Attention
End point description:	
Caregiver global impression of change in attention during the double-blind treatment period of ganaxolone compared to placebo. Investigators and caregivers reported improvements in attention, mood, behavior and sleep via investigator narratives. Per Protocol population: included ITT participants	

who received study drug for at least 6 weeks, provided at least 5 weeks of post-baseline seizure data, and had no major protocol violations. Only those participants with data available at the specified data points were analyzed.

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	47	45		
Units: Participants				
number (not applicable)				
Very Much Improved - Visit 5 (End of Week 17)	1	1		
Much Improved - Visit 5 (End of Week 17)	7	2		
Minimally Improved - Visit 5 (End of Week 17)	14	21		
No Change - Visit 5 (End of Week 17)	23	18		
Minimally Worse - Visit 5 (End of Week 17)	1	1		
Much Worse - Visit 5 (End of Week 17)	1	1		
Very Much Worse - Visit 5 (End of Week 17)	0	1		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Caregiver Global Impression of Change in Target Behavior

End point title	Caregiver Global Impression of Change in Target Behavior
End point description:	
Caregiver global impression of change in target behavior during the double-blind treatment period of ganaxolone compared to placebo. Investigators and caregivers reported improvements in attention, mood, behavior and sleep via investigator narratives. Only those participants with data available at the specified data points were analyzed.	
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	46	45		
Units: Participants				
number (not applicable)				
Very Much Improved - Visit 5 (End of Week 17)	0	0		
Much Improved - Visit 5 (End of Week 17)	6	4		
Minimally Improved - Visit 5 (End of Week 17)	14	20		
No Change - Visit 5 (End of Week 17)	22	19		
Minimally Worse - Visit 5 (End of Week 17)	1	2		
Much Worse - Visit 5 (End of Week 17)	2	0		
Very Much Worse - Visit 5 (End of Week 17)	1	0		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Clinical Global Impression of Improvement - Parent/Caregiver (P/C)

End point title	Clinical Global Impression of Improvement - Parent/Caregiver (P/C)
-----------------	--

End point description:

Clinical global impression of improvement during the double-blind treatment period of ganaxolone compared to placebo. The CGI is rated on a 7-point scale, with the severity of illness scale using a range of responses. Only those participants with data available at the specified data points were analyzed.

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	48	48		
Units: Participants				
number (not applicable)				
Very Much Improved - Visit 5 (End of Week 17)- P/C	1	0		
Much Improved - Visit 5 (End of Week 17) - P/C	7	13		
Minimally Improved - Visit 5 (End of Week 17)-P/C	13	17		
No Change - Visit 5 (End of Week 17) - P/C	22	14		
Minimally Worse - Visit 5 (End of Week 17) - P/C	4	2		
Much Worse - Visit 5 (End of Week 17) - P/C	1	2		

Very Much Worse - Visit 5 (End of Week 17) - P/C	0	0		
--	---	---	--	--

## Statistical analyses

No statistical analyses for this end point

## Secondary: Clinical Global Impression of Improvement - Clinician (C)

End point title	Clinical Global Impression of Improvement - Clinician (C)
-----------------	---

End point description:

Clinical global impression of improvement during the double-blind treatment period of ganaxolone compared to placebo. Only those participants with data available at the specified data points were analyzed.

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	48	48		
Units: Participants				
number (not applicable)				
Very Much Improved - Visit 5 (End of Week 17)- C	0	0		
Much Improved - Visit 5 (End of Week 17) - C	7	7		
Minimally Improved - Visit 5 (End of Week 17) - C	13	19		
No Change - Visit 5 (End of Week 17) - C	19	16		
Minimally Worse - Visit 5 (End of Week 17) - C	9	2		
Much Worse - Visit 5 (End of Week 17) - C	0	3		
Very Much Worse - Visit 5 (End of Week 17) - C	0	1		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Seizure-free Days for Major Motor Seizure Types

End point title	Percentage of Seizure-free Days for Major Motor Seizure Types
-----------------	---

End point description:

Percentage of Seizure-free Days for Major Motor Seizure types during the double-blind treatment period of ganaxolone compared to placebo. The major motor seizure types include bilateral tonic (sustained

motor activity = 3 seconds), generalized tonic-clonic, atonic/drop, bilateral clonic, and focal to bilateral tonic-clonic.

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	51	50		
Units: Percent of seizure-free days				
arithmetic mean (standard deviation)				
Baseline	30.32 (± 27.070)	22.57 (± 25.761)		
17-week-Post-Baseline Phase	36.17 (± 30.932)	32.29 (± 30.615)		
Arithmetic Change from Baseline	5.86 (± 15.350)	9.62 (± 21.364)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Arithmetic Change in Longest Seizure Free Interval, Based on Primary Seizure Types

End point title	Arithmetic Change in Longest Seizure Free Interval, Based on Primary Seizure Types
-----------------	--

End point description:

Arithmetic change in longest seizure free interval, based on primary seizure types during the double-blind treatment period of ganaxolone compared to placebo. Only those participants with data available at the specified data points were analyzed.

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	51	49		
Units: Days				
arithmetic mean (standard deviation)	-4.68 (± 14.831)	-0.02 (± 9.376)		

### Statistical analyses

No statistical analyses for this end point

## Secondary: Caregiver Global Impression of Change in Seizure Intensity and Duration

End point title	Caregiver Global Impression of Change in Seizure Intensity and Duration
-----------------	---

End point description:

Caregiver global impression of change in seizure intensity and duration during the double-blind treatment period of ganaxolone compared to placebo. CGI-C is a 7 point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of the intervention. Only those participants with data available at the specified data points were analyzed.

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	47	45		
Units: Participants				
number (not applicable)				
Very Much Improved - Visit 5 (End of Week 17)	1	2		
Much Improved - Visit 5 (End of Week 17)	5	15		
Minimally Improved - Visit 5 (End of Week 17)	11	11		
No Change - Visit 5 (End of Week 17)	21	10		
Minimally Worse - Visit 5 (End of Week 17)	5	3		
Much Worse - Visit 5 (End of Week 17)	4	2		
Very Much Worse - Visit 5 (End of Week 17)	0	2		

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Screening through 17-week Double-blind Phase

Assessment type	Systematic
-----------------	------------

### Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	23.0
--------------------	------

### 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

Serious adverse events	Placebo	Ganaxolone	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 51 (9.80%)	6 / 50 (12.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Oxygen saturation decreased			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal disorders			
Faecaloma			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Pneumonia aspiration			

subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypotonia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Seizure			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Unresponsive to stimuli			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia mycoplasmal			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia viral			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Rhinovirus infection			

subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary tract infection			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Food refusal			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 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	45 / 51 (88.24%)	43 / 50 (86.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign breast neoplasm			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 51 (7.84%)	9 / 50 (18.00%)	
occurrences (all)	5	10	
Gait disturbance			
subjects affected / exposed	1 / 51 (1.96%)	2 / 50 (4.00%)	
occurrences (all)	1	2	
Fatigue			

subjects affected / exposed	1 / 51 (1.96%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
Asthenia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Crying			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Discomfort			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Pain			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences (all)	9	0	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 51 (0.00%)	3 / 50 (6.00%)	
occurrences (all)	0	3	
Reproductive system and breast disorders			
Spontaneous penile erection			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 51 (5.88%)	0 / 50 (0.00%)	
occurrences (all)	3	0	
Nasal congestion			
subjects affected / exposed	1 / 51 (1.96%)	2 / 50 (4.00%)	
occurrences (all)	1	2	
Rhinorrhoea			
subjects affected / exposed	2 / 51 (3.92%)	1 / 50 (2.00%)	
occurrences (all)	2	1	
Choking			



subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	1
Dysphonia		
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences (all)	1	0
Dyspnoea		
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	1
Epistaxis		
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences (all)	1	0
Hiccups		
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	1
Hypoxia		
subjects affected / exposed	1 / 51 (1.96%)	1 / 50 (2.00%)
occurrences (all)	1	3
Increased bronchial secretion		
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	1
Lower respiratory tract congestion		
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	1
Nasal flaring		
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	1
Oropharyngeal pain		
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences (all)	1	0
Productive cough		
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	1
Respiratory disorder		
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	1
Respiratory failure		

subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Increased upper airway secretion			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 51 (3.92%)	2 / 50 (4.00%)	
occurrences (all)	3	2	
Irritability			
subjects affected / exposed	2 / 51 (3.92%)	2 / 50 (4.00%)	
occurrences (all)	2	2	
Anxiety			
subjects affected / exposed	1 / 51 (1.96%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
Sleep disorder			
subjects affected / exposed	1 / 51 (1.96%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
Attention-seeking behaviour			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Bruxism			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Inappropriate affect			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Middle insomnia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Mood altered			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Nervousness			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	

Restlessness subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1	0 / 50 (0.00%) 0	
Stereotypy subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1	0 / 50 (0.00%) 0	
Investigations			
Body temperature increased subjects affected / exposed occurrences (all)	2 / 51 (3.92%) 3	0 / 50 (0.00%) 0	
Blood urea increased subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1	0 / 50 (0.00%) 0	
Hepatic enzyme increased subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	1 / 50 (2.00%) 1	
Influenza virus test positive subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	1 / 50 (2.00%) 1	
Oxygen saturation decreased subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	1 / 50 (2.00%) 2	
Platelet count decreased subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1	0 / 50 (0.00%) 0	
Urine output decreased subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	1 / 50 (2.00%) 1	
Anticonvulsant drug level decreased subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	1 / 50 (2.00%) 1	
Injury, poisoning and procedural complications			
Incorrect dose administered subjects affected / exposed occurrences (all)	2 / 51 (3.92%) 3	0 / 50 (0.00%) 0	
Fall			

subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	1 / 50 (2.00%) 3	
Lip injury subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	1 / 50 (2.00%) 1	
Sedation complication subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	1 / 50 (2.00%) 1	
Thermal burn subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1	0 / 50 (0.00%) 0	
Cardiac disorders Tachycardia paroxysmal subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1	0 / 50 (0.00%) 0	
Nervous system disorders Somnolence subjects affected / exposed occurrences (all)	8 / 51 (15.69%) 8	18 / 50 (36.00%) 20	
Seizure subjects affected / exposed occurrences (all)	9 / 51 (17.65%) 12	7 / 50 (14.00%) 8	
Sedation subjects affected / exposed occurrences (all)	2 / 51 (3.92%) 2	3 / 50 (6.00%) 3	
Lethargy subjects affected / exposed occurrences (all)	2 / 51 (3.92%) 2	2 / 50 (4.00%) 2	
Hyperaesthesia subjects affected / exposed occurrences (all)	2 / 51 (3.92%) 2	0 / 50 (0.00%) 0	
Hypersomnia subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	2 / 50 (4.00%) 2	
Balance disorder			

subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Circadian rhythm sleep disorder			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences (all)	2	0	
Disturbance in attention			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Drooling			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Dyskinesia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Hypotonia			
subjects affected / exposed	1 / 51 (1.96%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
Poor quality sleep			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Psychomotor hyperactivity			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Unresponsive to stimuli			
subjects affected / exposed	1 / 51 (1.96%)	1 / 50 (2.00%)	
occurrences (all)	2	2	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Lacrimation decreased			

subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Ocular hyperaemia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	10 / 51 (19.61%)	5 / 50 (10.00%)	
occurrences (all)	12	6	
Constipation			
subjects affected / exposed	3 / 51 (5.88%)	3 / 50 (6.00%)	
occurrences (all)	3	3	
Diarrhoea			
subjects affected / exposed	4 / 51 (7.84%)	1 / 50 (2.00%)	
occurrences (all)	5	1	
Salivary hypersecretion			
subjects affected / exposed	1 / 51 (1.96%)	3 / 50 (6.00%)	
occurrences (all)	1	3	
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 51 (5.88%)	0 / 50 (0.00%)	
occurrences (all)	3	0	
Abdominal pain			
subjects affected / exposed	2 / 51 (3.92%)	0 / 50 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorder			
subjects affected / exposed	1 / 51 (1.96%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
Abdominal discomfort			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Abdominal pain upper			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Aphthous ulcer			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	
occurrences (all)	1	0	

Dental caries subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1	0 / 50 (0.00%) 0	
Faecaloma subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 2	0 / 50 (0.00%) 0	
Faeces soft subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1	0 / 50 (0.00%) 0	
Nausea subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	1 / 50 (2.00%) 1	
Hepatobiliary disorders Hepatic steatosis subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	1 / 50 (2.00%) 1	
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	4 / 51 (7.84%) 4	3 / 50 (6.00%) 3	
Alopecia subjects affected / exposed occurrences (all)	2 / 51 (3.92%) 2	0 / 50 (0.00%) 0	
Blister subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1	0 / 50 (0.00%) 0	
Psoriasis subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1	0 / 50 (0.00%) 0	
Renal and urinary disorders Pollakiuria subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1	0 / 50 (0.00%) 0	
Polyuria subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1	0 / 50 (0.00%) 0	
Urinary retention			

subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	1 / 50 (2.00%) 1	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	3 / 51 (5.88%)	5 / 50 (10.00%)	
occurrences (all)	3	6	
Rhinitis			
subjects affected / exposed	4 / 51 (7.84%)	2 / 50 (4.00%)	
occurrences (all)	5	4	
Ear infection			
subjects affected / exposed	3 / 51 (5.88%)	2 / 50 (4.00%)	
occurrences (all)	3	2	
Nasopharyngitis			
subjects affected / exposed	5 / 51 (9.80%)	0 / 50 (0.00%)	
occurrences (all)	5	0	
Respiratory tract infection viral			
subjects affected / exposed	3 / 51 (5.88%)	1 / 50 (2.00%)	
occurrences (all)	3	1	
Urinary tract infection			
subjects affected / exposed	3 / 51 (5.88%)	1 / 50 (2.00%)	
occurrences (all)	3	2	
Gastrointestinal viral infection			
subjects affected / exposed	2 / 51 (3.92%)	1 / 50 (2.00%)	
occurrences (all)	2	1	
Influenza			
subjects affected / exposed	1 / 51 (1.96%)	2 / 50 (4.00%)	
occurrences (all)	1	2	
Gastroenteritis			
subjects affected / exposed	1 / 51 (1.96%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
Sinusitis			
subjects affected / exposed	2 / 51 (3.92%)	0 / 50 (0.00%)	
occurrences (all)	2	0	
Varicella			
subjects affected / exposed	2 / 51 (3.92%)	0 / 50 (0.00%)	
occurrences (all)	3	0	



Viral upper respiratory tract infection		
subjects affected / exposed	1 / 51 (1.96%)	1 / 50 (2.00%)
occurrences (all)	1	1
Anal fungal infection		
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	1
Bronchitis		
subjects affected / exposed	0 / 51 (0.00%)	2 / 50 (4.00%)
occurrences (all)	0	2
Conjunctivitis		
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	1
Gastrointestinal infection		
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences (all)	1	0
Laryngitis		
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	1
Lower respiratory tract infection		
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	1
Oral candidiasis		
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	1
Otitis media		
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences (all)	1	0
Pneumonia		
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	1
Respiratory tract infection		
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	1
Roseola		
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)
occurrences (all)	1	0

Viral infection subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	1 / 50 (2.00%) 1	
Metabolism and nutrition disorders			
Abnormal weight gain subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	1 / 50 (2.00%) 1	
Decreased appetite subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	1 / 50 (2.00%) 1	
Dehydration subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1	0 / 50 (0.00%) 0	
Hypophagia subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	1 / 50 (2.00%) 1	
Increased appetite subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	1 / 50 (2.00%) 1	
Iron deficiency subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1	0 / 50 (0.00%) 0	
Vitamin D deficiency subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1	0 / 50 (0.00%) 0	
Zinc deficiency subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1	0 / 50 (0.00%) 0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 May 2019	Allowed for an increase in patient enrolment from N=70 to N=100 and for use of concomitant Epidiolex® during the double-blind phase if it was accompanied by a prescription. This amendment also removed the option for a capsule formulation and replaced two open-label study drug pharmacokinetic tests without time parameters to testing to be done 1-5 hours post dose. Updates to investigational product dose modifications clarified minimal dosing and alternative dosing paradigms that would need to be discussed with the medical monitor. To help address any tolerability issues, there was an increase in the number of phone follow-up calls during both double-blind titration and the open-label transition periods. Background information was updated to align with the current Investigator's Brochure (05-Dec-2018) with no new safety concerns noted. Patients with neurosteroids ALLO-S $\geq 6$ ng/mL would be excluded from trial enrolment. Changes to inclusion criteria related to genetic testing information was clarified. An interim analysis was added and select secondary endpoints were updated.
26 May 2020	Minor changes involving grammar, wordsmithing, punctuation, and other editorial changes have been made throughout the document. Revised: Prior to unblinding or immediately following, the sponsor's Medical Monitor must be contacted, Primary Efficacy Endpoint, Key Secondary Efficacy Endpoints, Secondary Efficacy Endpoints (Seizure control), Secondary Efficacy Endpoints (Behavioral/Neuropsychiatric), Exploratory Endpoints and Open-Label Phase Endpoints. Updated The Per-Protocol (PP) population definition to include all ITT subjects who received study drug for at least 6 weeks, provided at least 5 weeks of post-baseline seizure data, and without major protocol violations (defined prior to database lock). Revised: To examine the effect of GNX compared to PBO among subjects with low Allo-S levels. Added: The following subgroup summarizations of the primary efficacy parameter are planned as outlined in the SAP: Allo-S levels [(low ( $\leq 2.5$ nanograms per milliliter [ng/mL]), middle ( $> 2.5$ ng/mL and $< 6.0$ ng/mL) or high ( $\geq 6.0$ ng/mL)]; Safety assessments include: AEs, Clinical laboratory tests, Vital signs including temperature, blood pressure, pulse rate, and weight, 12-lead ECG, Physical, neurological and developmental examinations, Tanner staging (OL phase only), Concomitant AED levels (If available); and Key Secondary Efficacy Endpoints. Revised: Subjects that fall below 80% compliance at 2 consecutive visits during the double-blind phase will not be included in the per-protocol population; The clinical research associate (CRA)/study monitor will review all data in accordance with the clinical monitoring plan. If the data are unclear or contradictory to source data, queries are sent for corrections or verification of data; The CRA/study monitor will verify the contents of the eDiary data in accordance with the clinical monitoring plan.

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported