



## Clinical trial results:

### A Phase 3, Double-blind, Randomized, Placebo-controlled Trial of Adjunctive Ganaxolone (GNX) Treatment in Children and Adults with Tuberous Sclerosis Complex (TSC)-related Epilepsy (TrustTSC)

#### Summary

EudraCT number	2021-003441-38
Trial protocol	FR DE ES IT BE
Global end of trial date	14 October 2024

#### Results information

Result version number	v1 (current)
This version publication date	10 July 2025
First version publication date	10 July 2025

#### Trial information

##### Trial identification

Sponsor protocol code	1042-TSC-3001
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05323734
WHO universal trial number (UTN)	-
Other trial identifiers	IND Number: 155634

Notes:

#### Sponsors

Sponsor organisation name	Marinus Pharmaceuticals, Inc.
Sponsor organisation address	5 Radnor Corporate Center, 100 Matsonford Road, Suite 500, Radnor, PA, India, 19087
Public contact	Global Integrated Evidence Generation, Marinus Pharmaceuticals, Inc., +46 853339500, clinical@immedica.com
Scientific contact	Global Integrated Evidence Generation, 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	14 October 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 September 2024
Global end of trial reached?	Yes
Global end of trial date	14 October 2024
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

To assess the safety and efficacy of ganaxolone compared to placebo as adjunctive therapy for seizures associated with TSC in children and adults as assessed by the change from baseline in the frequency of countable major motor and focal seizures (primary endpoint seizures) during the double-blind phase.

Protection of trial subjects:

Not Applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 March 2022
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: 8
Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	China: 21
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Spain: 19
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	United States: 42
Worldwide total number of subjects	129
EEA total number of subjects	38

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)	3
Children (2-11 years)	59
Adolescents (12-17 years)	21
Adults (18-64 years)	46
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

This was a Phase 3, global, double-blind, randomized, placebo-controlled study of adjunctive ganaxolone treatment in children and adults with TSC-related epilepsy.

### Pre-assignment

Screening details:

A total of 129 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

### Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Ganaxolone
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Arm description:

Participants were randomized to receive an oral suspension of ganaxolone based on their body weight. ganaxolone 63 milligrams/kilograms/day (mg/kg/day) was administered orally three times a day (TID) to participants weighing 28 kg or less. ganaxolone 1800 mg/day TID was administered orally to participants weighing more than 28 kg.

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 as oral suspension, 3 times a day (TID)

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

Participants were administered with matching placebo as oral suspension TID based on the body weight.

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 as oral suspension TID.

<b>Number of subjects in period 1</b>	Ganaxolone	Placebo
Started	64	65
Completed	55	60
Not completed	9	5
Adverse event, serious fatal	5	2
Physician decision	1	-
Consent withdrawn by subject	2	-
Participant Withdrawn Due	-	1
Lack of efficacy	1	2

## Baseline characteristics

### Reporting groups

Reporting group title	Ganaxolone
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Reporting group description:

Participants were randomized to receive an oral suspension of ganaxolone based on their body weight. ganaxolone 63 milligrams/kilograms/day (mg/kg/day) was administered orally three times a day (TID) to participants weighing 28 kg or less. ganaxolone 1800 mg/day TID was administered orally to participants weighing more than 28 kg.

Reporting group title	Placebo
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Reporting group description:

Participants were administered with matching placebo as oral suspension TID based on the body weight.

Reporting group values	Ganaxolone	Placebo	Total
Number of subjects	64	65	129
Age categorical			
Units: Subjects			
Infants and toddlers (28 days-23 months)	2	1	3
Children (2-11 years)	31	28	59
Adolescents (12-17 years)	11	10	21
Adults (18-64 years)	20	26	46
Age continuous			
Units: years			
arithmetic mean	14.7	16.1	
standard deviation	± 11.0	± 11.2	-
Gender categorical			
Units: Subjects			
Female	36	29	65
Male	28	36	64

## End points

### End points reporting groups

Reporting group title	Ganaxolone
Reporting group description: Participants were randomized to receive an oral suspension of ganaxolone based on their body weight. ganaxolone 63 milligrams/kilograms/day (mg/kg/day) was administered orally three times a day (TID) to participants weighing 28 kg or less. ganaxolone 1800 mg/day TID was administered orally to participants weighing more than 28 kg.	
Reporting group title	Placebo
Reporting group description: Participants were administered with matching placebo as oral suspension TID based on the body weight.	

### Primary: Percent Change From Baseline in 28-day Seizure Frequency for Primary Seizure Type During Double Blind Period

End point title	Percent Change From Baseline in 28-day Seizure Frequency for Primary Seizure Type During Double Blind Period
End point description: Primary seizures include atonic/drop, bilateral clonic, bilateral tonic, focal motor with altered awareness, focal motor with intact awareness, focal to bilateral tonic-clonic seizures, focal with hypotonia impaired awareness, and generalized tonic-clonic. Seizure frequency was calculated as the total number of seizures divided by the number of days with seizure data in the period, multiplied by 28. Percent change from Baseline in 28-day seizure frequency was calculated as follows for each participant: post-baseline 28-day seizure frequency minus baseline 28-day seizure frequency whole divided by baseline 28-day seizure frequency and multiplied by 100. Intent-to-treat (ITT) Set comprises of randomized participants who dosed and had at least one post-baseline efficacy assessment.	
End point type	Primary
End point timeframe: Baseline (Day 1), Day 28	

End point values	Ganaxolone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	65		
Units: Percent change				
arithmetic mean (standard deviation)	-7.50 (± 60.430)	13.57 (± 77.374)		

### Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Ganaxolone v Placebo

Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0904 <sup>[1]</sup>
Method	Wilcoxon Rank-Sum
Parameter estimate	Mean difference (final values)
Point estimate	-14.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.04
upper limit	2.48

Notes:

[1] - Wilcoxon Rank-Sum statistic is applied using a 2-sided significance level of 0.05.

### Secondary: Number of Participants Who Were Considered as Treatment Responders During Double Blind Period

End point title	Number of Participants Who Were Considered as Treatment Responders During Double Blind Period
End point description:	Treatment responders are defined as those participants with $\geq 50\%$ reduction from Baseline in primary seizure type frequency during the given period. The analysis was performed in ITT population.
End point type	Secondary
End point timeframe:	
Up to 16 weeks	

End point values	Ganaxolone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	65		
Units: Participants				
number (not applicable)	12	8		

### Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Ganaxolone
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3407
Method	Fisher exact
Parameter estimate	Difference in percentage
Point estimate	6.4



Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.4
upper limit	20.1

## Secondary: Number of Responders to Clinical Global Impression of Improvement (CGI-I) Scale as Assessed by Parent/Caregiver

End point title	Number of Responders to Clinical Global Impression of Improvement (CGI-I) Scale as Assessed by Parent/Caregiver
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### End point description:

The CGI-I is a 7-point Likert scale that the parent(s)/caregiver(s)/ legally authorized representative (LAR) and clinician uses to rate the change in overall seizure control, behavior, safety, and tolerability after initiation of the investigational product (IP) relative to baseline (prior to treatment with the IP). The participant was rated as follows: 1 – very much improved, 2 – much improved, 3 – minimally improved, 4 – no change, 5 – minimally worse, 6 – much worse, and 7 – very much worse. Higher scores indicated worse condition. Number of responders to each score on the scale has been presented. The estimated odds ratio of the ganaxolone group compared to the placebo group based on proportional odds logistic regression with treatment as a factor. The participants in ITT Set who responded to CGI-I scale has been presented. The estimated odds ratio of the ganaxolone group compared to the placebo group based on proportional odds logistic regression with treatment as a factor.

End point type	Secondary
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### End point timeframe:

Baseline (Day 1) through 16 weeks

End point values	Ganaxolone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	58		
Units: Participants				
number (not applicable)				
Very Much Improved	5	8		
Much Improved	16	15		
Minimally Improved	14	12		
No Change	19	19		
Minimally Worse	2	4		
Much Worse	2	0		
Very Much Worse	0	0		

## Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Ganaxolone v Placebo

Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7069
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	1.7

### Secondary: Number of Responders to Clinical Global Impression of Improvement (CGI-I) Scale as Assessed by Clinician

End point title	Number of Responders to Clinical Global Impression of Improvement (CGI-I) Scale as Assessed by Clinician
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End point description:

The CGI-I is a 7-point Likert scale that the parent(s)/caregiver(s)/ LAR and clinician uses to rate the change in overall seizure control, behavior, safety, and tolerability after initiation of the IP relative to baseline (prior to treatment with the IP). The participant was rated as follows: 1 – very much improved, 2 – much improved, 3 – minimally improved, 4 – no change, 5 – minimally worse, 6 – much worse, and 7 – very much worse. Higher scores indicated worse outcomes. The participants in ITT Set and who responded to each score on the scale has been presented.

End point type	Secondary
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End point timeframe:

Baseline (Day 1) through 16 weeks

End point values	Ganaxolone	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	53		
Units: Participants				
number (not applicable)				
Very Much Improved	0	3		
Much Improved	14	13		
Minimally Improved	12	11		
No Change	22	25		
Minimally Worse	2	1		
Much Worse	1	0		
Very Much Worse	0	0		

### Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Ganaxolone v Placebo

Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6434
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	1.72

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 16 Weeks

Adverse event reporting additional description:

Serious treatment emergent adverse events and treatment emergent adverse events were collected in Safety Analysis Set which comprises of all randomized participants who received at least 1 dose of the IP.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	25.0
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### Reporting groups

Reporting group title	Ganaxolone
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Reporting group description:

Participants were randomized to receive an oral suspension of ganaxolone based on their body weight. ganaxolone 63 milligrams/kilograms/day (mg/kg/day) was administered orally three times a day (TID) to participants weighing 28 kg or less. ganaxolone 1800 mg/day TID was administered orally to participants weighing more than 28 kg.

Reporting group title	Placebo
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Reporting group description:

Participants were administered with matching placebo as oral suspension TID based on the body weight.

Serious adverse events	Ganaxolone	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 64 (7.81%)	6 / 65 (9.23%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Craniocerebral Injury			
subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Seizure			
subjects affected / exposed	1 / 64 (1.56%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Respiratory Failure			

subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
<b>Infections and infestations</b>			
Cellulitis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
<b>Erysipelas</b>			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
<b>Influenza</b>			
subjects affected / exposed	1 / 64 (1.56%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
<b>Pneumonia Aspiration</b>			
subjects affected / exposed	1 / 64 (1.56%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
<b>Pneumonia</b>			
subjects affected / exposed	1 / 64 (1.56%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	

Frequency threshold for reporting non-serious adverse events: 3 %

<b>Non-serious adverse events</b>	Ganaxolone	Placebo	
<b>Total subjects affected by non-serious adverse events</b>			
subjects affected / exposed	58 / 64 (90.63%)	49 / 65 (75.38%)	
<b>Investigations</b>			
Weight Decreased			
subjects affected / exposed	2 / 64 (3.13%)	0 / 65 (0.00%)	
occurrences (all)	2	0	
Weight Increased			

subjects affected / exposed occurrences (all)	3 / 64 (4.69%) 3	0 / 65 (0.00%) 0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 64 (1.56%)	2 / 65 (3.08%)	
occurrences (all)	1	2	
Fall			
subjects affected / exposed	3 / 64 (4.69%)	3 / 65 (4.62%)	
occurrences (all)	4	4	
Skin Abrasion			
subjects affected / exposed	2 / 64 (3.13%)	0 / 65 (0.00%)	
occurrences (all)	2	0	
Upper Limb Fracture			
subjects affected / exposed	2 / 64 (3.13%)	0 / 65 (0.00%)	
occurrences (all)	2	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 64 (3.13%)	1 / 65 (1.54%)	
occurrences (all)	2	1	
Nervous system disorders			
Balance Disorder			
subjects affected / exposed	3 / 64 (4.69%)	0 / 65 (0.00%)	
occurrences (all)	3	0	
Dizziness			
subjects affected / exposed	2 / 64 (3.13%)	1 / 65 (1.54%)	
occurrences (all)	2	1	
Headache			
subjects affected / exposed	6 / 64 (9.38%)	2 / 65 (3.08%)	
occurrences (all)	7	3	
Lethargy			
subjects affected / exposed	2 / 64 (3.13%)	2 / 65 (3.08%)	
occurrences (all)	2	2	
Psychomotor Hyperactivity			
subjects affected / exposed	3 / 64 (4.69%)	0 / 65 (0.00%)	
occurrences (all)	7	0	
Sedation			

subjects affected / exposed occurrences (all)	3 / 64 (4.69%) 3	0 / 65 (0.00%) 0	
Seizure subjects affected / exposed occurrences (all)	9 / 64 (14.06%) 21	7 / 65 (10.77%) 13	
Somnolence subjects affected / exposed occurrences (all)	18 / 64 (28.13%) 25	11 / 65 (16.92%) 14	
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	3 / 64 (4.69%) 3	0 / 65 (0.00%) 0	
Fatigue subjects affected / exposed occurrences (all)	9 / 64 (14.06%) 9	6 / 65 (9.23%) 8	
Pyrexia subjects affected / exposed occurrences (all)	10 / 64 (15.63%) 14	11 / 65 (16.92%) 11	
Gastrointestinal disorders			
Abdominal Pain Upper subjects affected / exposed occurrences (all)	0 / 64 (0.00%) 0	2 / 65 (3.08%) 2	
Constipation subjects affected / exposed occurrences (all)	4 / 64 (6.25%) 4	4 / 65 (6.15%) 5	
Dental Caries subjects affected / exposed occurrences (all)	2 / 64 (3.13%) 2	1 / 65 (1.54%) 1	
Diarrhoea subjects affected / exposed occurrences (all)	4 / 64 (6.25%) 4	2 / 65 (3.08%) 3	
Mouth Ulceration subjects affected / exposed occurrences (all)	3 / 64 (4.69%) 3	1 / 65 (1.54%) 2	
Toothache			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vomiting</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 64 (3.13%)</p> <p>2</p> <p>5 / 64 (7.81%)</p> <p>7</p>	<p>1 / 65 (1.54%)</p> <p>1</p> <p>4 / 65 (6.15%)</p> <p>4</p>	
<p>Reproductive system and breast disorders</p> <p>Menstruation Irregular</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 64 (3.13%)</p> <p>2</p>	<p>0 / 65 (0.00%)</p> <p>0</p>	
<p>Respiratory, thoracic and mediastinal disorders</p> <p>Adenoidal Hypertrophy</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 64 (3.13%)</p> <p>2</p> <p>6 / 64 (9.38%)</p> <p>6</p>	<p>0 / 65 (0.00%)</p> <p>0</p> <p>3 / 65 (4.62%)</p> <p>3</p>	
<p>Skin and subcutaneous tissue disorders</p> <p>Rash</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>3 / 64 (4.69%)</p> <p>3</p>	<p>1 / 65 (1.54%)</p> <p>1</p>	
<p>Psychiatric disorders</p> <p>Affect Lability</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Aggression</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Insomnia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Irritability</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Sleep Disorder</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 64 (3.13%)</p> <p>2</p> <p>1 / 64 (1.56%)</p> <p>1</p> <p>1 / 64 (1.56%)</p> <p>1</p> <p>2 / 64 (3.13%)</p> <p>2</p> <p>2 / 64 (3.13%)</p> <p>2</p>	<p>0 / 65 (0.00%)</p> <p>0</p> <p>2 / 65 (3.08%)</p> <p>2</p> <p>2 / 65 (3.08%)</p> <p>2</p> <p>4 / 65 (6.15%)</p> <p>7</p> <p>3 / 65 (4.62%)</p> <p>3</p>	



Infections and infestations Conjunctivitis subjects affected / exposed occurrences (all)	2 / 64 (3.13%) 2	1 / 65 (1.54%) 1	
Covid-19 subjects affected / exposed occurrences (all)	2 / 64 (3.13%) 2	3 / 65 (4.62%) 3	
Gastrointestinal Infection subjects affected / exposed occurrences (all)	0 / 64 (0.00%) 0	2 / 65 (3.08%) 2	
Influenza subjects affected / exposed occurrences (all)	4 / 64 (6.25%) 4	1 / 65 (1.54%) 1	
Nasopharyngitis subjects affected / exposed occurrences (all)	5 / 64 (7.81%) 6	4 / 65 (6.15%) 5	
Respiratory Tract Infection subjects affected / exposed occurrences (all)	2 / 64 (3.13%) 2	2 / 65 (3.08%) 2	
Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	3 / 64 (4.69%) 3	6 / 65 (9.23%) 7	
Urinary Tract Infection subjects affected / exposed occurrences (all)	2 / 64 (3.13%) 2	1 / 65 (1.54%) 1	
Metabolism and nutrition disorders Decreased Appetite subjects affected / exposed occurrences (all)	6 / 64 (9.38%) 7	4 / 65 (6.15%) 7	
Increased Appetite subjects affected / exposed occurrences (all)	2 / 64 (3.13%) 2	0 / 65 (0.00%) 0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 February 2022	The rationale for the major changes in this protocol amendment are as follows: <ul style="list-style-type: none"><li>• The availability of new Phase 2 data raised the question of a cannabidiol (CBD) interaction. As a result, participants taking CBD will be monitored closely for adverse events (AEs), and specifically sedation-related AEs throughout the study. Participants were also stratified according to concomitant CBD use.</li><li>• The allowance of an additional 2 weeks of titration after the 4 weeks titration period at the start of the maintenance period was removed as were specific dosing paradigms for participants taking Epidiolex &gt; 10 milligrams (mg)/kg/day. This change will ensure that all participants will have the same target dose regardless of their background CBD therapy.</li></ul>
07 December 2022	The following changes are made in this global protocol amendment from version 2.0 to version 3.0 to: <ul style="list-style-type: none"><li>• Revise inclusion criteria to include participants aged 2 to 65 years of age.</li><li>• Add a section on contraception use to include acceptable barrier methods and donation of sperm and ova.</li><li>• Add details on pregnancy testing.</li><li>• Elaborate on dose adjustments and rescue medications.</li><li>• Update endpoint analyses to incorporate analyses related to European Medicines Agency (EMA).</li><li>• Add details on blood volumes approval by investigator for participants &lt; 15 kilograms (kg) weight.</li><li>• The dosing instructions for the oral suspension were updated to match the package insert.</li></ul>
08 December 2022	The following changes are made in this protocol amendment from version 3.0 (applicable to Europe [EU], Middle East and North Africa [MENA] and Oceania [OC]) to version 3.1 (applicable to North America [United States and Canada] and China) to: <ul style="list-style-type: none"><li>• Revise inclusion criteria to include participants aged 1 to 65 years of age.</li><li>• Specify that genetic testing will not be permitted under this protocol in China.</li><li>• Specified that investigational product will be stored in accordance with applicable requirements under the Controlled Substance Act and Drug Enforcement Administration regulations.</li></ul>
12 September 2023	The following changes are made in this global protocol amendment from version 3.0 to version 4.0 to: <ul style="list-style-type: none"><li>• Include updated information regarding completed and ongoing clinical studies.</li><li>• Editorial updates throughout.</li><li>• Sample size, participant age, and inclusion criteria were updated.</li><li>• References to interim analysis were removed as no interim analysis was performed.</li><li>• Serious adverse event (SAE) contact details were updated.</li><li>• Country-specific amendment for China/North America has been combined with the global protocol.</li></ul>

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported