



Clinical trial results:

An Open-label Pilot Study With an Extension Phase to Evaluate the Pharmacokinetics, and to Generate Preliminary Safety, Tolerability, and Efficacy of Perampanel (E2007) Oral Suspension When Given as an Adjunctive Therapy in Pediatric Subjects From 2 to Less Than 12 Years of Age With Epilepsy

Summary

EudraCT number	2011-001105-28
Trial protocol	Outside EU/EEA
Global end of trial date	13 February 2015

Results information

Result version number	v2 (current)
This version publication date	07 December 2016
First version publication date	07 August 2016
Version creation reason	<ul style="list-style-type: none">• Correction of full data setCorrection of data

Trial information

Trial identification

Sponsor protocol code	E2007-G000-232
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01527006
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eisai Medical Research Inc.
Sponsor organisation address	155 Tice Boulevard, Woodcliff Lake, United States, 07677
Public contact	Eisai Medical Information, Eisai Inc., 888 274-2378, esi_medinfo@eisai.com
Scientific contact	Eisai Medical Information, Eisai Inc., 888 274-2378, esi_medinfo@eisai.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000467-PIP01-08
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	19 March 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	13 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the pharmacokinetics (PK) of perampanel following oral suspension administration given as an adjunctive therapy in pediatric subjects from 2 to less than 12 years old with epilepsy

Protection of trial subjects:

This study was conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki (World Medical Association, 2008)
- International Council on Harmonisation (ICH) E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
- Title 21 of the United States (US) Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and Institutional Review Board (IRB) regulations and applicable sections of US 21 CFR Part 312
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country. All suspected unexpected serious adverse reactions were reported, as required, to the Competent Authorities of all involved EU member states.
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP Subject Information and Informed Consent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 January 2012
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: 50
Worldwide total number of subjects	50
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	50
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Of the 63 participants who were screened, 13 participants were screen failures and 50 participants were eligible to continue in the Core Study. Of the 42 subjects who completed the Core Study, 41 subjects continued into the Extension Phase.

Period 1

Period 1 title	Core Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort (≥ 2 to < 7 years of age) - For Core Study

Arm description:

During the titration period, participants started at a set daily dose of 0.015 mg/kg perampanel oral suspension and had doses up-titrated at 1-week intervals (6 titration steps) to a maximum daily dose of 0.18 mg/kg. During the Maintenance Period, participants continued taking perampanel oral suspension once daily at the dose level they achieved at the end of the Titration Period. During the extension phase, participants continued taking perampanel oral suspension once daily, at the dose level achieved at the end of the treatment phase of the core study to a maximum daily dose of 0.18 mg/kg. The maximum total daily dose a participant was allowed was 12 mg perampanel.

Arm type	Experimental
Investigational medicinal product name	Perampanel
Investigational medicinal product code	E2007
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

During the titration period, participants started at a set daily dose of 0.015 mg/kg perampanel oral suspension and had doses up-titrated at 1-week intervals (6 titration steps) to a maximum daily dose of 0.18 mg/kg perampanel. During the Maintenance Period, participants continued taking perampanel oral suspension once daily at the dose level they achieved at the end of the Titration Period.

Arm title	Cohort (≥ 7 to < 12 years of age) - For Core Study
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Arm description:

During the titration period, participants started at a set daily dose of 0.015 mg/kg perampanel oral suspension and had doses up-titrated at 1-week intervals (6 titration steps) to a maximum daily dose of 0.18 mg/kg. During the Maintenance Period, participants continued taking perampanel oral suspension once daily at the dose level they achieved at the end of the Titration Period. During the extension phase, participants continued taking perampanel oral suspension once daily, at the dose level achieved at the end of the treatment phase of the core study to a maximum daily dose of 0.18 mg/kg. The maximum total daily dose a participant was allowed was 12 mg perampanel.

Arm type	Experimental
Investigational medicinal product name	Perampanel
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Dosage and administration details:

During the titration period, participants started at a set daily dose of 0.015 mg/kg perampanel oral suspension and had doses up-titrated at 1-week intervals (6 titration steps) to a maximum daily dose of

0.18 mg/kg perampanel. During the Maintenance Period, participants continued taking perampanel oral suspension once daily at the dose level they achieved at the end of the Titration Period.

Number of subjects in period 1	Cohort (≥ 2 to < 7 years of age) - For Core Study	Cohort (≥ 7 to < 12 years of age) - For Core Study
Started	22	28
Completed	20	22
Not completed	2	6
Adverse event, serious fatal	-	2
Participant choice	1	-
Not specified	-	2
Withdrawal by participant	-	1
Inadequate therapeutic effect	1	-
Lost to follow-up	-	1

Baseline characteristics

Reporting groups

Reporting group title	Cohort (≥ 2 to < 7 years of age) - For Core Study
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Reporting group description:

During the titration period, participants started at a set daily dose of 0.015 mg/kg perampanel oral suspension and had doses up-titrated at 1-week intervals (6 titration steps) to a maximum daily dose of 0.18 mg/kg. During the Maintenance Period, participants continued taking perampanel oral suspension once daily at the dose level they achieved at the end of the Titration Period. During the extension phase, participants continued taking perampanel oral suspension once daily, at the dose level achieved at the end of the treatment phase of the core study to a maximum daily dose of 0.18 mg/kg. The maximum total daily dose a participant was allowed was 12 mg perampanel.

Reporting group title	Cohort (≥ 7 to < 12 years of age) - For Core Study
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Reporting group description:

During the titration period, participants started at a set daily dose of 0.015 mg/kg perampanel oral suspension and had doses up-titrated at 1-week intervals (6 titration steps) to a maximum daily dose of 0.18 mg/kg. During the Maintenance Period, participants continued taking perampanel oral suspension once daily at the dose level they achieved at the end of the Titration Period. During the extension phase, participants continued taking perampanel oral suspension once daily, at the dose level achieved at the end of the treatment phase of the core study to a maximum daily dose of 0.18 mg/kg. The maximum total daily dose a participant was allowed was 12 mg perampanel.

Reporting group values	Cohort (≥ 2 to < 7 years of age) - For Core Study	Cohort (≥ 7 to < 12 years of age) - For Core Study	Total
Number of subjects	22	28	50
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	5	9	
full range (min-max)	2 to 6	7 to 11	-
Gender categorical Units: Subjects			
Female	7	9	16
Male	15	19	34

End points

End points reporting groups

Reporting group title	Cohort (≥ 2 to < 7 years of age) - For Core Study
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Reporting group description:

During the titration period, participants started at a set daily dose of 0.015 mg/kg perampanel oral suspension and had doses up-titrated at 1-week intervals (6 titration steps) to a maximum daily dose of 0.18 mg/kg. During the Maintenance Period, participants continued taking perampanel oral suspension once daily at the dose level they achieved at the end of the Titration Period. During the extension phase, participants continued taking perampanel oral suspension once daily, at the dose level achieved at the end of the treatment phase of the core study to a maximum daily dose of 0.18 mg/kg. The maximum total daily dose a participant was allowed was 12 mg perampanel.

Reporting group title	Cohort (≥ 7 to < 12 years of age) - For Core Study
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Reporting group description:

During the titration period, participants started at a set daily dose of 0.015 mg/kg perampanel oral suspension and had doses up-titrated at 1-week intervals (6 titration steps) to a maximum daily dose of 0.18 mg/kg. During the Maintenance Period, participants continued taking perampanel oral suspension once daily at the dose level they achieved at the end of the Titration Period. During the extension phase, participants continued taking perampanel oral suspension once daily, at the dose level achieved at the end of the treatment phase of the core study to a maximum daily dose of 0.18 mg/kg. The maximum total daily dose a participant was allowed was 12 mg perampanel.

Subject analysis set title	Cohort (≥ 2 to < 7 Years of Age) - For Core Study
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Subject analysis set type	Safety analysis
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Subject analysis set description:

During the titration period, participants started at a set daily dose of 0.015 mg/kg perampanel oral suspension and had doses up-titrated at 1-week intervals (6 titration steps) to a maximum daily dose of 0.18 mg/kg perampanel. During the Maintenance Period, participants continued taking perampanel oral suspension once daily at the dose level they achieved at the end of the Titration Period.

Subject analysis set title	Cohort (≥ 7 to < 12 Years of Age) - For Core Study
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Subject analysis set type	Safety analysis
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Subject analysis set description:

During the titration period, participants started at a set daily dose of 0.015 mg/kg perampanel oral suspension and had doses up-titrated at 1-week intervals (6 titration steps) to a maximum daily dose of 0.18 mg/kg perampanel. During the Maintenance Period, participants continued taking perampanel oral suspension once daily at the dose level they achieved at the end of the Titration Period.

Subject analysis set title	Cohort (≥ 2 to < 7 Years of Age) - For Extension Phase
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Subject analysis set type	Safety analysis
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Subject analysis set description:

During the extension phase, participants continued taking perampanel oral suspension once daily, at the dose level achieved at the end of the treatment phase of the core study to a maximum daily dose of 0.18 mg/kg perampanel. The maximum total daily dose a participant was allowed was 12 mg perampanel.

Subject analysis set title	Cohort (≥ 7 to < 12 Years of Age) - For Extension Phase
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Subject analysis set type	Safety analysis
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Subject analysis set description:

During the extension phase, participants continued taking perampanel oral suspension once daily, at the dose level achieved at the end of the treatment phase of the core study to a maximum daily dose of 0.18 mg/kg perampanel. The maximum total daily dose a participant was allowed was 12 mg perampanel.

Primary: Apparent Clearance (CL/F) of Perampanel [Core Study]

End point title	Apparent Clearance (CL/F) of Perampanel [Core Study] ^[1]
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End point description:

CL/F was defined as the volume of plasma cleared of the drug per unit time. Blood samples were collected at Day 8, Day 36, Day 64, and Day 78. The CL/F values were calculated for each visit and averaged to derive the total CL/F value per arm. Data was analyzed for 2 categories: CYP3A4/5 inducers (carbamazepine, oxcarbazepine and phenytoin) and non-inducers. Data is presented as mean Liter per hour +/- standard deviation. The pharmacokinetic (PK) analysis set was used and was defined as

participants with at least 1 PK assessment of perampanel with a documented dosing history.

End point type	Primary
End point timeframe:	
From Day 8 up to Day 78	

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 analyses for this end point.

End point values	Cohort (≥ 2 to < 7 years of age) - For Core Study	Cohort (≥ 7 to < 12 years of age) - For Core Study		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	22		
Units: Liters per hour				
arithmetic mean (standard deviation)				
Non-inducers (N = 14, 12)	0.732 (± 0.374)	0.956 (± 0.4)		
Inducers (N = 6, 10)	1.73 (± 1.18)	1.92 (± 0.517)		

Statistical analyses

No statistical analyses for this end point

Primary: Steady-state Average Concentration (C_{av,ss}) of Perampanel [Core Study]

End point title	Steady-state Average Concentration (C _{av,ss}) of Perampanel [Core Study] ^[2]
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End point description:

C_{av,ss} was calculated as 'Dose (mg)/Dosing Interval (24 h)/(CL/F [L/h]) x 1000'. C_{av,ss} during a dosing interval was dose-normalized to 0.12 mg/kg in participants aged ≥ 2 to less than 12 years (intended to correspond to 8 mg/70 kg in adults/adolescents). Blood samples were collected at day 8, Day 36, Day 64, and Day 78. C_{av,ss} values were calculated for each visit and averaged to derive the total C_{av,ss} value per arm. Data was analysed for 2 categories: CYP3A4/5 inducers (carbamazepine, oxcarbazepine and phenytoin) and non-inducers. Data is presented as mean Liter per hour +/- standard deviation. The PK analysis set was used and was defined as participants with at least 1 pharmacokinetic assessment of perampanel with a documented dosing history.

End point type	Primary
End point timeframe:	
From Day 8 up to Day 78	

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: No statistical analyses for this end point.

End point values	Cohort (≥ 2 to < 7 years of age) - For Core Study	Cohort (≥ 7 to < 12 years of age) - For Core Study		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	22		
Units: ng/mL				
arithmetic mean (standard deviation)				
Non-inducers (N = 14, 12)	179 (± 110)	266 (± 220)		
Inducers (N = 6, 10)	96.8 (± 90.4)	105 (± 38.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Seizure Frequency Per 28 Days in Treatment Phase [Core Study]

End point title	Percent Change From Baseline in Seizure Frequency Per 28 Days in Treatment Phase [Core Study]
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End point description:

Seizure frequency was derived from information (seizure count and type) recorded in participant diary. The seizure frequency per 28 days was calculated the number of seizures over the time interval multiplied by 28 and divided by the number of days in the interval. The percent change in 28-day seizure frequency from baseline was assessed for overall seizures, overall partial seizures, overall generalized seizures, and unclassified seizures. The data is presented as median percent change +/- standard deviation. The full analysis set (FAS) was used and was defined as participants who received study drug, had any seizure frequency data during the 2-week Pretreatment Phase plus the 4 weeks prior to the Pretreatment Phase (Visit 1), and during the Treatment Phase of the Core Study.

End point type	Secondary
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End point timeframe:

Baseline [Pretreatment Phase plus 4 weeks Prior Visit 1], Week 0 to Week 15

End point values	Cohort (≥ 2 to < 7 years of age) - For Core Study	Cohort (≥ 7 to < 12 years of age) - For Core Study		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	28		
Units: Percent change				
median (full range (min-max))				
Overall seizures	-43.6 (-100 to 95.4)	-33.9 (-100 to 1038.9)		
Overall partial seizures	-82.5 (-100 to 95.4)	-46.8 (-100 to 1722.2)		
Overall generalized seizures	-53.1 (-100 to 188.7)	305.4 (-62.9 to 1277.3)		
Unclassified seizures	-73.7 (-100 to 217.3)	-67.3 (-100 to -34.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: 50% Responder Rate During the Maintenance Period-LOCF [Core Study]

End point title	50% Responder Rate During the Maintenance Period-LOCF [Core Study]
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End point description:

Responder rate was defined as the proportion of participants with a 50% decrease in 28-day seizure frequency during the Maintenance Period compared to Baseline [Pretreatment Phase plus 4 weeks Prior to Visit 1] for overall seizures, overall partial seizures, overall generalized seizures, and unclassified seizures. The data is presented as percent responders. LOCF = Last Observation Carried Forward. The FAS was used.

End point type	Secondary
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End point timeframe:

Baseline [Pretreatment Phase plus 4 weeks Prior to Visit 1], Week 9 to Week 11

End point values	Cohort (≥ 2 to < 7 years of age) - For Core Study	Cohort (≥ 7 to < 12 years of age) - For Core Study		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	28		
Units: Percent responders				
number (not applicable)				
Overall seizures	72.7	53.8		
Overall partial seizures	82.4	60.9		
Overall generalized seizures	76.9	33.3		
Unclassified seizures	66.7	100		

Statistical analyses

No statistical analyses for this end point

Secondary: Seizure-free Rate During the Maintenance Period [Core Study]

End point title	Seizure-free Rate During the Maintenance Period [Core Study]
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End point description:

Seizure-free rate, defined as the percentage of participants who were seizure-free during the Maintenance Period. SG = Secondary Generalization. The FAS was used.

End point type	Secondary
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End point timeframe:

Week 9 to Week 11

End point values	Cohort (≥ 2 to < 7 years of age) - For Core Study	Cohort (≥ 7 to < 12 years of age) - For Core Study		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	28		
Units: Percentage of participants				
number (not applicable)				
Overall seizures	15	27.3		
Simple Partial without Motor Signs	100	100		
Simple Partial with Motor Signs	80	95.5		
Complex Partial	80	50		
Partial Seizures with SG	75	90.9		
Overall Partial Seizures	50	45.5		
Absence Generalized	95	90.9		
Myoclonic Generalized	80	86.4		
Clonic Generalized	100	100		
Tonic Generalized	85	90.9		
Tonic Clonic Generalized	80	90.9		
Atonic Generalized	95	95.5		
Overall Generalized Seizures	55	77.3		
Unclassified Seizures	100	95.5		

Statistical analyses

No statistical analyses for this end point

Secondary: The Clinical Global Impression of Change at the End of Treatment (EOT) [Core Study]

End point title	The Clinical Global Impression of Change at the End of Treatment (EOT) [Core Study]
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End point description:

The Clinical Global Impression (CGI) evaluated perceived seizure frequency and severity, the occurrence of adverse events (AEs), and overall functional status of the participant. The investigator performed the Clinical Global Impression of Severity for all participants at Baseline (Week 0). The evaluation used a 7-point scale where 1=normal, not at all ill and 7=extremely ill. The investigator performed the Clinical Global Impression of Change for all participants at the EOT (the duration after the day of first study drug dose up to 7 days after the last Core Phase drug dose, inclusive). The evaluation used a 7-point scale where 1=very much improved and 7=very much worse. This tool was used to assess the participant's status over the 4-week period prior to its completion compared to Baseline (Week 0). The FAS was used.

End point type	Secondary
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End point timeframe:

Week 0 (Baseline), Week 11 or EOT

End point values	Cohort (≥ 2 to < 7 years of age) - For Core Study	Cohort (≥ 7 to < 12 years of age) - For Core Study		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	28		
Units: Participants				
number (not applicable)				
Baseline - Normal, not at all ill (N=22, 27)	6	5		
Baseline - Borderline mentally ill (N=22, 27)	0	0		
Baseline - Mildly ill (N=22, 27)	3	4		
Baseline - Moderately ill (N=22,27)	10	11		
Baseline - Markedly ill (N=22, 27)	3	4		
Baseline - Severely ill (N=22, 27)	0	3		
Baseline - Extremely ill (N=22, 27)	0	0		
EOT - Very much improved (N=22, 25)	6	7		
EOT - Much improved (N=22, 25)	8	8		
EOT - Minimally improved (N=22, 25)	5	5		
EOT - No Change (N=22, 25)	2	3		
EOT - Minimally worse (N=22, 25)	0	1		
EOT - Much worse (N=22, 25)	0	1		
EOT - Very much worse (N=22, 25)	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-Emergent Non-Serious Adverse Events (AEs) and Treatment Emergent Serious Adverse Events (SAEs) as a Measure of Safety and Tolerability of Perampanel

End point title	Number of Participants With Treatment-Emergent Non-Serious Adverse Events (AEs) and Treatment Emergent Serious Adverse Events (SAEs) as a Measure of Safety and Tolerability of Perampanel
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End point description:

An AE was defined as any untoward medical occurrence in a participant administered with the study drug. A SAE was defined as any untoward medical occurrence that at any dose resulted in death, was life-threatening (ie, the participant was at immediate risk of death from the AE as it occurred; this did not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death), required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, or was as a congenital anomaly/birth defect (in the child of a participant who was exposed to the study drug). In this study, treatment-emergent AEs (defined as an AE (serious/non-serious) that started/increased in severity on/after the first dose of study drug up to 30 days after the final dose of study drug) were assessed. The details of the adverse events are presented in the safety section of the results.

End point type	Secondary
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End point timeframe:

For each participant, from the first treatment dose till 30 days after the last dose or up to Week 15 for Core Study and Week 56 for the Extension Phase

End point values	Cohort (≥ 2 to < 7 Years of Age) - For Core Study	Cohort (≥ 7 to < 12 Years of Age) - For Core Study	Cohort (≥ 2 to < 7 Years of Age) - For Extension Phase	Cohort (≥ 7 to < 12 Years of Age) - For Extension Phase
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	22	28	19	22
Units: Participants				
number (not applicable)				
Treatment-emergent non-serious AEs	22	25	19	22
Treatment-emergent SAEs	3	5	6	7

Statistical analyses

No statistical analyses for this end point

Secondary: Palatability Questionnaire Assessment - How Does This Medicine Taste [Core Study]

End point title	Palatability Questionnaire Assessment - How Does This Medicine Taste [Core Study]
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End point description:

The Palatability Questionnaire was answered directly by participants in Cohort (≥ 7 to < 12 years) and indirectly by participants in Cohort (≥ 2 to < 7 years) via their parents/caregivers. Participants selected their response from one of the five options (very good, good, not good-not bad, bad, very bad). The Safety Analysis Set was used and was defined as participants who received study drug treatment and had at least 1 postdose safety assessment.

End point type	Secondary
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End point timeframe:

Week 5 or at the time of early discontinuation

End point values	Cohort (≥ 2 to < 7 years of age) - For Core Study	Cohort (≥ 7 to < 12 years of age) - For Core Study		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	19		
Units: Participants				
number (not applicable)				
Very good	3	3		
Good	6	7		
Not good, not bad	2	3		
Bad	2	3		
Very bad	0	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Palatability Questionnaire Assessment - How Does This Medicine Smell [Core Study]

End point title	Palatability Questionnaire Assessment - How Does This Medicine Smell [Core Study]
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End point description:

The Palatability Questionnaire was answered directly by participants in Cohort (≥ 7 to ≤ 12 years) and indirectly by participants in Cohort (≥ 2 to ≤ 7 years) via their parents/caregivers. Participants selected their response from one of the five options (very good, good, not good-not bad, bad, very bad). The Safety Analysis Set was used and was defined as participants who received study drug treatment and had at least 1 postdose safety assessment.

End point type	Secondary
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End point timeframe:

Week 5 or at the time of early discontinuation

End point values	Cohort (≥ 2 to < 7 years of age) - For Core Study	Cohort (≥ 7 to < 12 years of age) - For Core Study		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	19		
Units: Participants				
number (not applicable)				
Very good	0	2		
Good	5	3		
Not good, not bad	7	13		
Bad	1	0		
Very bad	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Palatability Questionnaire Assessment - Based on Its Taste, Smell, and How it Felt in the Mouth, How Easy or Difficult Was it for You / Your Child to Take This Medicine Every Day [Core Study]

End point title	Palatability Questionnaire Assessment - Based on Its Taste, Smell, and How it Felt in the Mouth, How Easy or Difficult Was it for You / Your Child to Take This Medicine Every Day [Core Study]
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End point description:

The Palatability Questionnaire was answered directly by participants in Cohort (≥ 7 to ≤ 12 years) and indirectly by participants in Cohort (≥ 2 to ≤ 7 years) via their parents/caregivers. Participants selected their response from one of the five options (very easy, easy, neither easy or difficult, difficult and very difficult). The Safety Analysis Set was used and was defined as participants who received study drug treatment and had at least 1 postdose safety assessment.

End point type	Secondary
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End point timeframe:

Week 5 or at the time of early discontinuation

End point values	Cohort (≥ 2 to < 7 years of age) - For Core Study	Cohort (≥ 7 to < 12 years of age) - For Core Study		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	19		
Units: Participants				
number (not applicable)				
Very easy	6	7		
Easy	5	7		
Neither easy or difficult	3	3		
Difficult	0	1		
Very Difficult	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Palatability Questionnaire Assessment - Would You/Your Child Have Preferred This Medicine to Have Been Flavored, e.g. Fruity [Core Study]

End point title	Palatability Questionnaire Assessment - Would You/Your Child Have Preferred This Medicine to Have Been Flavored, e.g. Fruity [Core Study]
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End point description:

The Palatability Questionnaire was answered directly by participants in Cohort (≥ 7 to ≤ 12 years) and indirectly by participants in Cohort (≥ 2 to ≤ 7 years) via their parents/caregivers. Participants selected their response from one of the three options (yes, no and don't mind). The Safety Analysis Set was used and was defined as participants who received study drug treatment and had at least 1 postdose safety assessment.

End point type	Secondary
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End point timeframe:

Week 5 or at the time of early discontinuation

End point values	Cohort (≥ 2 to < 7 years of age) - For Core Study	Cohort (≥ 7 to < 12 years of age) - For Core Study		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	19		
Units: Participants				
number (not applicable)				
Yes	4	9		
No	2	5		
Don't mind	9	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change From Baseline in Seizure Frequency Per 28 Days During the Overall Treatment Duration by 13-week Intervals [Extension Phase]

End point title	Percentage Change From Baseline in Seizure Frequency Per 28 Days During the Overall Treatment Duration by 13-week Intervals [Extension Phase]
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End point description:

Seizure frequency was derived from information (seizure count and type) recorded in participant diary. The seizure frequency per 28 days was calculated as the number of seizures over the time interval multiplied by 28 and divided by the number of days in the interval. The percent change in 28-day seizure frequency from baseline was assessed for overall seizures, overall partial seizures, overall generalized seizures, and unclassified seizures. The data is presented as mean percent change +/- standard deviation. The FAS was used.

End point type	Secondary
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End point timeframe:

Baseline [Pretreatment Phase plus 4 weeks Prior to Visit 1], Weeks 1-13, Weeks 14-26, Weeks 27-39, and Weeks 40-52

End point values	Cohort (≥ 2 to < 7 Years of Age) - For Extension Phase	Cohort (≥ 7 to < 12 Years of Age) - For Extension Phase		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	22		
Units: Percent change				
median (full range (min-max))				
Overall Seizures- Weeks 1-13	-58.74 (-100 to 75.8)	-39.59 (-100 to 759.3)		
Overall Seizures- Weeks 14-26	-76.89 (-100 to 134.4)	-39.19 (-100 to 389.8)		
Overall Seizures- Weeks 27-39; N=18, 20	-80.93 (-100 to 129.9)	-45.6 (-100 to 474.6)		
Overall Seizures- Weeks 40-52; N=15, 15	-77.58 (-100 to -1.2)	-47.25 (-100 to 200)		
Overall Partial Seizures- Weeks 1-13; N=14,19	-79.62 (-100 to 75.8)	-56.04 (-100 to 290.5)		
Overall Partial Seizures- Weeks 14-26; N=14, 19	-78.69 (-100 to 134.4)	-67.3 (-100 to 87.9)		
Overall Partial Seizures- Weeks 27-39; N=14, 17	-89.49 (-100 to 129.9)	-53.57 (-100 to 165.2)		
Overall Partial Seizures- Weeks 40-52; N=14, 14	-89.89 (-100 to -1.2)	-39.46 (-100 to 100)		
Overall Generalized Seizures- Weeks 1-13; N=11, 6	-63.96 (-100 to 465.5)	177.58 (-65 to 1065.4)		

Overall Generalized Seizures- Weeks 14-26; N=11, 6	-79.08 (-100 to 440.7)	-14.13 (-87.3 to 389.8)		
Overall Generalized Seizures- Weeks 27-39; N=10, 6	-73.93 (-100 to -8.9)	-4.77 (-83.6 to 474.6)		
Overall Generalized Seizures- Weeks 40-52; N=7, 3	-76.91 (-100 to 182.8)	-5.86 (-61.5 to 700)		
Unclassified Epileptic Seizure- Weeks 1-13; N=2, 1	-88.74 (-100 to -77.5)	-41.61 (-41.61 to -41.61)		
Unclassified Epileptic Seizure- Weeks 14-26; N=2,1	-100 (-100 to 100)	-21.07 (-21.07 to -21.07)		
Unclassified Epileptic Seizure- Weeks 27-39; N=2,1	-58.24 (-100 to -16.5)	6.81 (6.81 to 6.81)		
Unclassified Epileptic Seizure- Weeks 40-52; N=2,1	-100 (-100 to 100)	-73.21 (-73.21 to -73.21)		

Statistical analyses

No statistical analyses for this end point

Secondary: 50 % Responder Rate During the Overall Treatment Duration by 13-week Intervals [Extension Phase]

End point title	50 % Responder Rate During the Overall Treatment Duration by 13-week Intervals [Extension Phase]
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End point description:

Responder rate was defined as the proportion of participants with a 50% decrease in 28-day seizure frequency during the overall treatment duration. The percentage of responders was assessed from Week 1 of perampanel treatment through successive 13-week intervals for overall seizures, overall partial seizures, overall generalized seizures, and unclassified seizures with baseline as Pretreatment Phase (Visit 1) of 2 weeks plus 4 weeks Prior to Pretreatment Phase. The data is presented as percentage of responders. The FAS was used.

End point type	Secondary
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End point timeframe:

Baseline [Pretreatment Phase plus 4 weeks Prior to Visit 1], Weeks 1-13, Weeks 14-26, Weeks 27-39, and Weeks 40-52

End point values	Cohort (≥ 2 to < 7 Years of Age) - For Extension Phase	Cohort (≥ 7 to < 12 Years of Age) - For Extension Phase		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	22		
Units: Percentage of responders				
number (not applicable)				
Overall Seizures- Weeks 1-13	57.9	45.5		
Overall Seizures- Weeks 14-26	84.2	45.5		
Overall Seizures- Weeks 27-39; N=18, 20	77.8	45		
Overall Seizures- Weeks 40-52; N=15, 15	80	46.7		
Overall Partial Seizures- Weeks 1-13; N=14,19	64.3	57.9		

Overall Partial Seizures- Weeks 14-26; N=14, 19	85.7	57.9		
Overall Partial Seizures- Weeks 27-39; N=14, 17	92.9	52.9		
Overall Partial Seizures- Weeks 40-52; N=14, 14	71.4	42.9		
Overall Generalized Seizures- Weeks 1-13; N=11, 6	72.7	16.7		
Overall Generalized Seizures- Weeks 14-26; N=11, 6	81.8	33.3		
Overall Generalized Seizures- Weeks 27-39; N=10, 6	70	16.7		
Overall Generalized Seizures- Weeks 40-52; N=7, 3	71.4	33.3		
Unclassified Epileptic Seizure- Weeks 1-13; N=2, 1	100	0		
Unclassified Epileptic Seizure- Weeks 14-26; N=2,1	100	0		
Unclassified Epileptic Seizure- Weeks 27-39; N=2,1	50	0		
Unclassified Epileptic Seizure- Weeks 40-52; N=2,1	100	100		

Statistical analyses

No statistical analyses for this end point

Secondary: Seizure-free Rate During the Overall Treatment Duration [Extension Phase]

End point title	Seizure-free Rate During the Overall Treatment Duration [Extension Phase]
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End point description:

Seizure-free rate, defined as the percentage of participants who were seizure-free during the Maintenance Period. The percentage of participants who were seizure free was assessed from Week 1 of perampanel treatment through successive 13-week intervals for overall seizures, overall partial seizures, overall generalized seizures, and unclassified seizures with baseline as Pretreatment Phase (Visit 1) of 2 weeks plus 4 weeks Prior to Pretreatment Phase. The data is presented as the percentage of participants. The FAS was used.

End point type	Secondary
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End point timeframe:

Baseline [2 weeks Pretreatment Phase (Visit 1) plus 4 weeks Prior to Pretreatment Phase], Weeks 1-13, Weeks 14-26, Weeks 27-39, and Weeks 40-52

End point values	Cohort (≥ 2 to < 7 Years of Age) - For Extension Phase	Cohort (≥ 7 to < 12 Years of Age) - For Extension Phase		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	22		
Units: Percentage of participants				
number (not applicable)				
Overall Seizures- Weeks 1-13	21.1	22.7		

Overall Seizures- Weeks 14-26;N=18, 20	22.2	30		
Overall Seizures- Weeks 27-39; N=15, 15	13.3	33.3		
Overall Seizures- Weeks 40-52; N=11, 11	27.3	36.4		
Overall Partial Seizures- Weeks 1-13	52.6	40.9		
Overall Partial Seizures- Weeks 14-26; N=18, 20	55.6	45		
Overall Partial Seizures- Weeks 27-39; N=15, 15	33.3	40		
Overall Partial Seizures- Weeks 40-52; N=11, 11	36.4	45.5		
Overall Generalized Seizures- Weeks 1-13	57.9	72.7		
Overall Generalized Seizures- Weeks 14-26; N=18,20	55.6	75		
Overall Generalized Seizures- Weeks 27-39; N=15,15	66.7	80		
Overall Generalized Seizures- Weeks 40-52; N=11,11	63.6	90.9		
Unclassified Epileptic Seizure- Weeks 1-13	100	90.9		
Unclassified Epileptic Seizure-Weeks 14-26;N=18,20	100	95		
Unclassified Epileptic Seizure-Weeks 27-39;N=15,15	93.3	93.3		
Unclassified Epileptic Seizure-Weeks 40-52;N=11,11	100	90.9		

Statistical analyses

No statistical analyses for this end point

Secondary: The Clinical Global Impression of Change During the Overall Treatment Duration by Visit and at EOT [Extension Phase]

End point title	The Clinical Global Impression of Change During the Overall Treatment Duration by Visit and at EOT [Extension Phase]
End point description:	The CGI evaluated perceived seizure frequency and severity, the occurrence of AEs, and overall functional status of the participant. The investigator performed the Clinical Global Impression of Severity for all participants at Baseline (Week 0). The evaluation used a 7-point scale where 1=normal, not at all ill and 7=extremely ill. The investigator performed the Clinical Global Impression of Change for all participants at planned visit and at EOT (the duration after the day of first study drug dose up to 7 days after the Extension Phase drug dose, inclusive). The evaluation used a 7-point scale where 1=very much improved and 7=very much worse. This tool was used to assess the participant's status over the 4-week period prior to the planned/EOT visits compared to Baseline (Week 0). The FAS was used.
End point type	Secondary
End point timeframe:	Week 0 (Baseline), Week 11, Week 28, Week 52 or EOT

End point values	Cohort (≥ 2 to < 7 Years of Age) - For Extension Phase	Cohort (≥ 7 to < 12 Years of Age) - For Extension Phase		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	22		
Units: Participants				
number (not applicable)				
Baseline- Normal, not at all ill	5	3		
Baseline- Borderline mentally ill	0	0		
Baseline- Mildly ill	3	4		
Baseline- Moderately ill	10	10		
Baseline- Markedly ill	1	4		
Baseline- Severely ill	0	1		
Baseline- Extremely ill	0	0		
Week 11- Very much improved; N=19, 21	6	7		
Week 11- Much improved; N=19, 21	8	7		
Week 11- Minimally improved; N=19, 21	3	5		
Week 11- No change; N= 19, 21	2	2		
Week 11- Minimally worse; N=19, 21	0	0		
Week 11- Much worse; N=19, 21	0	0		
Week 11- Very much worse; N=19, 21	0	0		
Week 28- Very much improved; N=18, 19	5	4		
Week 28- Much improved; N=18, 19	7	8		
Week 28- Minimally improved; N=18, 19	2	3		
Week 28- No change; N=18, 19	4	3		
Week 28- Minimally worse; N=18, 19	0	1		
Week 28- Much worse; N=18, 19	0	0		
Week 28- Very much worse; N=18, 19	0	0		
Week 52- Very much improved; N=14, 12	1	3		
Week 52- Much improved; N=14, 12	7	5		
Week 52- Minimally improved; N=14, 12	4	4		
Week 52- No change; N=14, 12	1	0		
Week 52- Minimally worse; N=14, 12	0	0		
Week 52- Much worse; N=14, 12	1	0		
Week 52- Very much worse; N=14, 12	0	0		
EOT- Very much improved	1	4		
EOT- Much improved	8	9		
EOT- Minimally improved	5	6		
EOT- No change	4	2		
EOT- Minimally worse	0	1		
EOT- Much worse	1	0		
EOT- Very much worse	0	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: The Effect of Demographics on Population PK Parameters: Area Under the Concentration-Time Curve (AUC)

End point title The Effect of Demographics on Population PK Parameters: Area Under the Concentration-Time Curve (AUC)

End point description:

This outcome was not assessed for this study.

End point type Other pre-specified

End point timeframe:

11 weeks

End point values	Cohort (≥ 2 to < 7 Years of Age) - For Core Study	Cohort (≥ 7 to < 12 Years of Age) - For Core Study		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0 ^[3]	0 ^[4]		
Units: ng*hr/mL				
geometric mean (standard deviation)	()	()		

Notes:

[3] - This outcome was not assessed for this study.

[4] - This outcome was not assessed for this study.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: The Effect of Demographics on Population PK Parameters: Cmax

End point title The Effect of Demographics on Population PK Parameters: Cmax

End point description:

This outcome was not assessed in the study.

End point type Other pre-specified

End point timeframe:

11 weeks

End point values	Cohort (≥ 2 to < 7 Years of Age) - For Core Study	Cohort (≥ 7 to < 12 Years of Age) - For Core Study		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0 ^[5]	0 ^[6]		
Units: ng/mL				
geometric mean (standard deviation)	()	()		

Notes:

[5] - This outcome was not assessed for this study.

[6] - This outcome was not assessed for this study.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: The Effect of Demographics on Population PK Parameters: Time to Reach Cmax (Tmax)

End point title	The Effect of Demographics on Population PK Parameters: Time to Reach Cmax (Tmax)
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End point description:

This outcome was not assessed for this study.

End point type	Other pre-specified
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End point timeframe:

11 weeks

End point values	Cohort (≥ 2 to < 7 Years of Age) - For Core Study	Cohort (≥ 7 to < 12 Years of Age) - For Core Study		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0 ^[7]	0 ^[8]		
Units: Hours				
geometric mean (standard deviation)	()	()		

Notes:

[7] - This outcome was not assessed for this study.

[8] - This outcome was not assessed for this study.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: The Effect of the Most Common Concomitant Antiepileptic Drugs (AEDs) on Population PK Parameters: AUC

End point title	The Effect of the Most Common Concomitant Antiepileptic Drugs (AEDs) on Population PK Parameters: AUC
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End point description:

This outcome was not assessed for this study.

End point type	Other pre-specified
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End point timeframe:

11 weeks

End point values	Cohort (≥ 2 to < 7 Years of Age) - For Core Study	Cohort (≥ 7 to < 12 Years of Age) - For Core Study		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0 ^[9]	0 ^[10]		
Units: ng*hr/mL				
geometric mean (standard deviation)	()	()		

Notes:

[9] - This outcome was not assessed for this study.

[10] - This outcome was not assessed for this study.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: The Effect of the Most Common Concomitant AEDs on Population PK Parameters: Maximum Drug Concentration (Cmax)

End point title	The Effect of the Most Common Concomitant AEDs on Population PK Parameters: Maximum Drug Concentration (Cmax)
End point description:	This outcome was not assessed for this study.
End point type	Other pre-specified
End point timeframe:	11 weeks

End point values	Cohort (≥ 2 to < 7 Years of Age) - For Core Study	Cohort (≥ 7 to < 12 Years of Age) - For Core Study		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0 ^[11]	0 ^[12]		
Units: ng/mL				
geometric mean (standard deviation)	()	()		

Notes:

[11] - This outcome was not assessed for this study.

[12] - This outcome was not assessed for this study.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: The Effect of the Most Common Concomitant AEDs on Population PK Parameters: Tmax

End point title	The Effect of the Most Common Concomitant AEDs on Population PK Parameters: Tmax
End point description:	This outcome was not assessed for this study.
End point type	Other pre-specified
End point timeframe:	11 weeks

End point values	Cohort (≥ 2 to < 7 Years of Age) - For Core Study	Cohort (≥ 7 to < 12 Years of Age) - For Core Study		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0 ^[13]	0 ^[14]		
Units: Hours				
geometric mean (standard deviation)	()	()		

Notes:

[13] - This outcome was not assessed for this study.

[14] - This outcome was not assessed for this study.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For each participant, from the first treatment dose till 30 days after the last dose or up to Week 15 for Core Study and Week 56 for the Extension Phase

Adverse event reporting additional description:

Treatment-emergent adverse events (TEAEs) are presented in this section. The Safety Analysis Set included all subjects who took at least 1 dose of perampanel and had at least 1 postdose safety assessment during the Core Study and the Extension Phase.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1
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Reporting groups

Reporting group title	Cohort (≥ 2 to < 7 Years of Age) - For Core Study
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Reporting group description:

During the titration period, participants started at a set daily dose of 0.015 mg/kg perampanel oral suspension, once daily, and had doses up-titrated at 1-week intervals (6 titration steps) to a maximum daily dose of 0.18 mg/kg. During the Maintenance Period, participants continued taking perampanel oral suspension once daily at the dose level they achieved at the end of the Titration Period.

Reporting group title	Cohort (≥ 7 to < 12 Years of Age) - For Core Study
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Reporting group description:

During the titration period, participants started at a set daily dose of 0.015 mg/kg perampanel oral suspension, once daily, and had doses up-titrated at 1-week intervals (6 titration steps) to a maximum daily dose of 0.18 mg/kg. During the Maintenance Period, participants continued taking perampanel oral suspension once daily at the dose level they achieved at the end of the Titration Period.

Reporting group title	Cohort (≥ 2 to < 7 Years of Age) - For Extension Phase
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Reporting group description:

During the extension phase, participants continued taking perampanel oral suspension, once daily, at the dose level achieved at the end of the treatment phase of the core study to a maximum daily dose of 0.18 mg/kg. The maximum total daily dose a participant was allowed was 12 mg perampanel.

Reporting group title	Cohort (≥ 7 to < 12 Years of Age) - For Extension Phase
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Reporting group description:

During the extension phase, participants continued taking perampanel oral suspension, once daily, at the dose level achieved at the end of the treatment phase of the core study to a maximum daily dose of 0.18 mg/kg. The maximum total daily dose a participant was allowed was 12 mg perampanel.

Serious adverse events	Cohort (≥ 2 to < 7 Years of Age) - For Core Study	Cohort (≥ 7 to < 12 Years of Age) - For Core Study	Cohort (≥ 2 to < 7 Years of Age) - For Extension Phase
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 22 (13.64%)	5 / 28 (17.86%)	6 / 19 (31.58%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Anticonvulsant Drug Level Increased			

subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	0 / 19 (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
Congenital, familial and genetic disorders			
Developmental Hip Dysplasia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 28 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 22 (0.00%)	1 / 28 (3.57%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cyanosis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 22 (0.00%)	1 / 28 (3.57%)	2 / 19 (10.53%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status Epilepticus			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	0 / 19 (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
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cyclic Vomiting Syndrome			

subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleural Effusion			
subjects affected / exposed	0 / 22 (0.00%)	1 / 28 (3.57%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory Failure			
subjects affected / exposed	0 / 22 (0.00%)	1 / 28 (3.57%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Abnormal Behaviour			
subjects affected / exposed	0 / 22 (0.00%)	1 / 28 (3.57%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental Status Changes			
subjects affected / exposed	1 / 22 (4.55%)	0 / 28 (0.00%)	2 / 19 (10.53%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Foot Deformity			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	0 / 19 (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
Muscle Contracture			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	0 / 19 (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
Infections and infestations			
Gastroenteritis			

subjects affected / exposed	0 / 22 (0.00%)	1 / 28 (3.57%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mastoiditis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 28 (3.57%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis Externa			
subjects affected / exposed	0 / 22 (0.00%)	1 / 28 (3.57%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis Media Acute			
subjects affected / exposed	0 / 22 (0.00%)	1 / 28 (3.57%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 28 (3.57%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory Syncytial Virus Bronchiolitis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 28 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic Shock			
subjects affected / exposed	0 / 22 (0.00%)	1 / 28 (3.57%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis Media			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypoglycaemia			

subjects affected / exposed	0 / 22 (0.00%)	1 / 28 (3.57%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	0 / 19 (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

Serious adverse events	Cohort (≥ 7 to < 12 Years of Age) - For Extension Phase		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 22 (31.82%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Anticonvulsant Drug Level Increased			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Developmental Hip Dysplasia			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cyanosis			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Convulsion			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
Status Epilepticus			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cyclic Vomiting Syndrome			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pleural Effusion			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory Failure			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Abnormal Behaviour			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Mental Status Changes			

subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Foot Deformity			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Muscle Contracture			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Mastoiditis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Otitis Externa			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Otitis Media Acute			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Respiratory Syncytial Virus Bronchiolitis			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Septic Shock			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Otitis Media			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Cohort (≥ 2 to < 7 Years of Age) - For Core Study	Cohort (≥ 7 to < 12 Years of Age) - For Core Study	Cohort (≥ 2 to < 7 Years of Age) - For Extension Phase
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 22 (100.00%)	25 / 28 (89.29%)	19 / 19 (100.00%)
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
General disorders and administration site conditions			

Fatigue subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 5	8 / 28 (28.57%) 9	1 / 19 (5.26%) 6
Gait Disturbance subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2	1 / 28 (3.57%) 1	2 / 19 (10.53%) 2
Irritability subjects affected / exposed occurrences (all)	3 / 22 (13.64%) 3	5 / 28 (17.86%) 5	3 / 19 (15.79%) 3
Pyrexia subjects affected / exposed occurrences (all)	8 / 22 (36.36%) 10	4 / 28 (14.29%) 4	8 / 19 (42.11%) 10
Immune system disorders Autoimmune Disorder subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 0	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Hypersensitivity subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Reproductive system and breast disorders Vulval Disorder subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	3 / 22 (13.64%) 5	1 / 28 (3.57%) 1	4 / 19 (21.05%) 5
Nasal Congestion subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2	0 / 28 (0.00%) 0	1 / 19 (5.26%) 2
Rhinorrhoea subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2	0 / 28 (0.00%) 0	3 / 19 (15.79%) 3
Asthma subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 28 (0.00%) 0	2 / 19 (10.53%) 2

Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 28 (0.00%) 0	0 / 19 (0.00%) 0
Psychiatric disorders			
Aggression subjects affected / exposed occurrences (all)	3 / 22 (13.64%) 3	1 / 28 (3.57%) 1	5 / 19 (26.32%) 5
Anxiety subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 3	0 / 28 (0.00%) 0	2 / 19 (10.53%) 3
Insomnia subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	2 / 28 (7.14%) 3	1 / 19 (5.26%) 2
Oppositional Defiant Disorder subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2	1 / 28 (3.57%) 1	2 / 19 (10.53%) 2
Tearfulness subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2	0 / 28 (0.00%) 0	2 / 19 (10.53%) 2
Abnormal Behaviour subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Investigations			
Thyroxine Decreased subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	2 / 28 (7.14%) 2	0 / 19 (0.00%) 0
Weight Increased subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	3 / 28 (10.71%) 3	1 / 19 (5.26%) 1
Blood Bicarbonate Decreased subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Blood Sodium Decreased subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Blood Triglycerides Increased			

subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Blood Uric Acid Decreased subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 2	0 / 28 (0.00%) 0	2 / 19 (10.53%) 2
Cardiac Murmur subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 28 (0.00%) 0	1 / 19 (5.26%) 2
Cardiac Murmur Functional subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Globulins Decreased subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Heart Rate Increased subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Tri-Iodothyronine Decreased subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Weight Decreased subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 28 (0.00%) 0	2 / 19 (10.53%) 2
Injury, poisoning and procedural complications			
Fall subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2	1 / 28 (3.57%) 1	2 / 19 (10.53%) 3
Contusion subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Epiphyseal Fracture subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Head Injury			

subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Laceration subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Ligament Sprain subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 28 (3.57%) 2	0 / 19 (0.00%) 0
Congenital, familial and genetic disorders Phimosi subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Cardiac disorders Bradycardia subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Nervous system disorders Ataxia subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	2 / 28 (7.14%) 2	0 / 19 (0.00%) 0
Balance Disorder subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	2 / 28 (7.14%) 2	1 / 19 (5.26%) 1
Dizziness subjects affected / exposed occurrences (all)	3 / 22 (13.64%) 3	2 / 28 (7.14%) 2	3 / 19 (15.79%) 6
Headache subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	2 / 28 (7.14%) 3	2 / 19 (10.53%) 4
Lethargy subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	2 / 28 (7.14%) 2	4 / 19 (21.05%) 4
Psychomotor Hyperactivity subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	2 / 28 (7.14%) 4	0 / 19 (0.00%) 0
Somnolence			

subjects affected / exposed occurrences (all)	4 / 22 (18.18%) 8	3 / 28 (10.71%) 3	3 / 19 (15.79%) 16
Tremor			
subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	2 / 28 (7.14%) 2	0 / 19 (0.00%) 0
Cognitive Disorder			
subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 28 (0.00%) 0	2 / 19 (10.53%) 2
Drooling			
subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Dyskinesia			
subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Hypotonia			
subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Intention Tremor			
subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Sedation			
subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Speech Disorder			
subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Agitation			
subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	1 / 28 (3.57%) 1	1 / 19 (5.26%) 1
Depressed Mood			
subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 28 (3.57%) 1	1 / 19 (5.26%) 1
Disorientation			
subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Echolalia			

subjects affected / exposed	1 / 22 (4.55%)	0 / 28 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Emotional Disorder			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	3
Hallucination			
subjects affected / exposed	1 / 22 (4.55%)	0 / 28 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Mood Altered			
subjects affected / exposed	1 / 22 (4.55%)	1 / 28 (3.57%)	1 / 19 (5.26%)
occurrences (all)	1	1	1
Mood Swings			
subjects affected / exposed	0 / 22 (0.00%)	1 / 28 (3.57%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Sleep Disorder			
subjects affected / exposed	1 / 22 (4.55%)	0 / 28 (0.00%)	2 / 19 (10.53%)
occurrences (all)	1	0	3
Suicidal Ideation			
subjects affected / exposed	0 / 22 (0.00%)	1 / 28 (3.57%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Epistaxis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 28 (3.57%)	2 / 19 (10.53%)
occurrences (all)	0	1	2
Grunting			
subjects affected / exposed	1 / 22 (4.55%)	0 / 28 (0.00%)	1 / 19 (5.26%)
occurrences (all)	2	0	1
Rhinitis Allergic			
subjects affected / exposed	0 / 22 (0.00%)	1 / 28 (3.57%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Neutropenia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	0 / 19 (0.00%)
occurrences (all)	0	0	0

Thrombocytopenia subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 28 (0.00%) 0	2 / 19 (10.53%) 2
Ear and labyrinth disorders Ear Pain subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Eye disorders Conjunctivitis subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 28 (3.57%) 1	1 / 19 (5.26%) 1
Eye Irritation subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Ocular Hyperaemia subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	1 / 28 (3.57%) 1	1 / 19 (5.26%) 1
Photophobia subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Gastrointestinal disorders Abdominal Pain Upper subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	4 / 28 (14.29%) 7	0 / 19 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	3 / 22 (13.64%) 3	5 / 28 (17.86%) 8	4 / 19 (21.05%) 5
Abdominal Pain subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 28 (0.00%) 0	0 / 19 (0.00%) 0
Aphthous Stomatitis subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Constipation subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	1 / 28 (3.57%) 1	1 / 19 (5.26%) 2
Diarrhoea			

subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	1 / 28 (3.57%) 1	3 / 19 (15.79%) 3
Flatulence subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Gingival Recession subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Nausea subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	1 / 28 (3.57%) 1	2 / 19 (10.53%) 2
Oral Mucosal Discolouration subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Skin and subcutaneous tissue disorders			
Dermatitis Contact subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	2 / 28 (7.14%) 2	1 / 19 (5.26%) 1
Eczema subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	1 / 28 (3.57%) 1	1 / 19 (5.26%) 1
Rash subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 28 (0.00%) 0	2 / 19 (10.53%) 2
Skin Disorder subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Urticaria subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 28 (0.00%) 0	2 / 19 (10.53%) 3
Renal and urinary disorders			
Dysuria subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Enuresis			

subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 28 (3.57%) 1	0 / 19 (0.00%) 0
Haematuria subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Proteinuria subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Musculoskeletal and connective tissue disorders			
Myalgia subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Pain In Extremity subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Posture Abnormal subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Infections and infestations			
Ear Infection subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	2 / 28 (7.14%) 2	3 / 19 (15.79%) 3
Otitis Media subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 3	2 / 28 (7.14%) 2	2 / 19 (10.53%) 8
Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	3 / 22 (13.64%) 3	2 / 28 (7.14%) 4	5 / 19 (26.32%) 11
Atypical Pneumonia subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Bronchitis subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 28 (3.57%) 1	0 / 19 (0.00%) 0
Clostridium Difficile Infection			

subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Fungal Skin Infection			
subjects affected / exposed	1 / 22 (4.55%)	0 / 28 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Gastroenteritis Viral			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	1 / 22 (4.55%)	0 / 28 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	2
Lice Infestation			
subjects affected / exposed	1 / 22 (4.55%)	0 / 28 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Nasopharyngitis			
subjects affected / exposed	1 / 22 (4.55%)	1 / 28 (3.57%)	3 / 19 (15.79%)
occurrences (all)	1	2	4
Pharyngitis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 28 (3.57%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Sinusitis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 28 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	2
Tinea Capitis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 28 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Urinary Tract Infection			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	2
Viral Rash			
subjects affected / exposed	0 / 22 (0.00%)	0 / 28 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	1 / 22 (4.55%)	2 / 28 (7.14%)	2 / 19 (10.53%)
occurrences (all)	1	3	3

Increased Appetite subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	3 / 28 (10.71%) 3	1 / 19 (5.26%) 1
Dehydration subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Hypernatraemia subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1
Metabolic Acidosis subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 2	0 / 28 (0.00%) 0	2 / 19 (10.53%) 2
Vitamin D Deficiency subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 28 (0.00%) 0	1 / 19 (5.26%) 1

Non-serious adverse events	Cohort (≥ 7 to < 12 Years of Age) - For Extension Phase		
Total subjects affected by non-serious adverse events subjects affected / exposed	22 / 22 (100.00%)		
Vascular disorders Hypotension subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	6 / 22 (27.27%) 6		
Gait Disturbance subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
Irritability subjects affected / exposed occurrences (all)	5 / 22 (22.73%) 5		
Pyrexia subjects affected / exposed occurrences (all)	7 / 22 (31.82%) 6		

<p>Immune system disorders</p> <p>Autoimmune Disorder</p> <p>subjects affected / exposed</p> <p>0 / 22 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Hypersensitivity</p> <p>subjects affected / exposed</p> <p>0 / 22 (0.00%)</p> <p>occurrences (all)</p> <p>0</p>			
<p>Reproductive system and breast disorders</p> <p>Vulval Disorder</p> <p>subjects affected / exposed</p> <p>0 / 22 (0.00%)</p> <p>occurrences (all)</p> <p>0</p>			
<p>Respiratory, thoracic and mediastinal disorders</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>2 / 22 (9.09%)</p> <p>occurrences (all)</p> <p>2</p> <p>Nasal Congestion</p> <p>subjects affected / exposed</p> <p>0 / 22 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Rhinorrhoea</p> <p>subjects affected / exposed</p> <p>1 / 22 (4.55%)</p> <p>occurrences (all)</p> <p>2</p> <p>Asthma</p> <p>subjects affected / exposed</p> <p>0 / 22 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Oropharyngeal pain</p> <p>subjects affected / exposed</p> <p>2 / 22 (9.09%)</p> <p>occurrences (all)</p> <p>4</p>			
<p>Psychiatric disorders</p> <p>Aggression</p> <p>subjects affected / exposed</p> <p>2 / 22 (9.09%)</p> <p>occurrences (all)</p> <p>3</p> <p>Anxiety</p> <p>subjects affected / exposed</p> <p>0 / 22 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Insomnia</p>			

subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 6		
Oppositional Defiant Disorder subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Tearfulness subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
Abnormal Behaviour subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Investigations			
Thyroxine Decreased subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
Weight Increased subjects affected / exposed occurrences (all)	4 / 22 (18.18%) 4		
Blood Bicarbonate Decreased subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
Blood Sodium Decreased subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
Blood Triglycerides Increased subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
Blood Uric Acid Decreased subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Cardiac Murmur subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
Cardiac Murmur Functional subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		

<p>Globulins Decreased</p> <p>subjects affected / exposed</p> <p>0 / 22 (0.00%)</p> <p>occurrences (all)</p> <p>0</p>			
<p>Heart Rate Increased</p> <p>subjects affected / exposed</p> <p>0 / 22 (0.00%)</p> <p>occurrences (all)</p> <p>0</p>			
<p>Tri-Iodothyronine Decreased</p> <p>subjects affected / exposed</p> <p>0 / 22 (0.00%)</p> <p>occurrences (all)</p> <p>0</p>			
<p>Weight Decreased</p> <p>subjects affected / exposed</p> <p>1 / 22 (4.55%)</p> <p>occurrences (all)</p> <p>1</p>			
<p>Injury, poisoning and procedural complications</p> <p>Fall</p> <p>subjects affected / exposed</p> <p>1 / 22 (4.55%)</p> <p>occurrences (all)</p> <p>2</p> <p>Contusion</p> <p>subjects affected / exposed</p> <p>0 / 22 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Epiphyseal Fracture</p> <p>subjects affected / exposed</p> <p>0 / 22 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Head Injury</p> <p>subjects affected / exposed</p> <p>0 / 22 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Laceration</p> <p>subjects affected / exposed</p> <p>0 / 22 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Ligament Sprain</p> <p>subjects affected / exposed</p> <p>2 / 22 (9.09%)</p> <p>occurrences (all)</p> <p>2</p>			
<p>Congenital, familial and genetic disorders</p> <p>Phimosi</p> <p>subjects affected / exposed</p> <p>0 / 22 (0.00%)</p> <p>occurrences (all)</p> <p>0</p>			
<p>Cardiac disorders</p>			

Bradycardia			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Ataxia			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Balance Disorder			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	4		
Headache			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	5		
Lethargy			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	3		
Psychomotor Hyperactivity			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Somnolence			
subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	6		
Tremor			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Cognitive Disorder			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Drooling			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Dyskinesia			

subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Hypotonia			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Intention Tremor			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Sedation			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Speech Disorder			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Agitation			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Depressed Mood			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Disorientation			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Echolalia			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Emotional Disorder			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Hallucination			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Mood Altered			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences (all)	0		
Mood Swings			

subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
Sleep Disorder subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Suicidal Ideation subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
Epistaxis subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Grunting subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
Rhinitis Allergic subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
Neutropenia subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
Thrombocytopenia subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Ear and labyrinth disorders Ear Pain subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
Eye disorders Conjunctivitis subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Eye Irritation			

subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
Ocular Hyperaemia subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Photophobia subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
Gastrointestinal disorders			
Abdominal Pain Upper subjects affected / exposed occurrences (all)	5 / 22 (22.73%) 10		
Vomiting subjects affected / exposed occurrences (all)	6 / 22 (27.27%) 10		
Abdominal Pain subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
Aphthous Stomatitis subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
Constipation subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Diarrhoea subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 2		
Flatulence subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
Gingival Recession subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
Nausea subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		

Oral Mucosal Discolouration subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
Skin and subcutaneous tissue disorders			
Dermatitis Contact subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
Eczema subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Rash subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 2		
Skin Disorder subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
Urticaria subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
Renal and urinary disorders			
Dysuria subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
Enuresis subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
Haematuria subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
Proteinuria subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
Musculoskeletal and connective tissue disorders			
Myalgia subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		

Pain In Extremity subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
Posture Abnormal subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
Infections and infestations			
Ear Infection subjects affected / exposed occurrences (all)	4 / 22 (18.18%) 4		
Otitis Media subjects affected / exposed occurrences (all)	3 / 22 (13.64%) 7		
Upper Respiratory Tract Infection subjects affected / exposed occurrences (all)	6 / 22 (27.27%) 10		
Atypical Pneumonia subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
Bronchitis subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
Clostridium Difficile Infection subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
Fungal Skin Infection subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
Gastroenteritis Viral subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Influenza subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Lice Infestation			

subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 22 (13.64%) 5		
Pharyngitis subjects affected / exposed occurrences (all)	3 / 22 (13.64%) 3		
Sinusitis subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 2		
Tinea Capitis subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
Urinary Tract Infection subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
Viral Rash subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
Metabolism and nutrition disorders			
Decreased Appetite subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 2		
Increased Appetite subjects affected / exposed occurrences (all)	4 / 22 (18.18%) 4		
Dehydration subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
Hypernatraemia subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
Metabolic Acidosis subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		

Vitamin D Deficiency subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0		
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More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 April 2012	In addition to minor administrative changes, Amendment 01 dated 03 Apr 2012 made the following changes to the protocol: <ul style="list-style-type: none">• Addition of the Palatability Questionnaire• Revised the corrected QT interval to QTcF• Addition of the Clinical Global Impression (CGI) referencing• Deletion of the CGI appendix• Added text regarding the telephone interview At the time of Amendment 01, 9 subjects had been enrolled in the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported