Clinical trial results:
A Randomized, Active-controlled, Open-label, Flexible-dose Study to Assess the Safety and Tolerability of Topiramate as Monotherapy Compared With Levetiracetam as Monotherapy in Pediatric Subjects With New or Recent-onset Epilepsy

Summary

EudraCT number	2012-001552-19
Trial protocol	AT IT HU BE DE GB FR PL
Global end of trial date	30 April 2020

Results information

Result version number	v2 (current)
This version publication date	14 May 2021
First version publication date	14 November 2020
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	TOPMATEPY4067

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02201251
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Research & Development, LLC
Sponsor organisation address	920 Route 202 NJ, Raritan, United States,
Public contact	Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 June 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 April 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the effects of topiramate monotherapy compared with levetiracetam another standard antiepileptic drug (AED), as monotherapy for new-onset or recent-onset epilepsy (seizure disorder) on pediatric growth and maturation, bone mineralization, and kidney stone formation in children aged 2 to 15 years.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. Safety evaluations included monitoring of adverse events (AEs), vital sign measurements, electrocardiogram (ECG), clinical laboratory parameters, dual-energy X-ray absorptiometry (DEXA) scan, renal ultrasound, biochemical bone markers, hand/wrist x-ray, Tanner staging, cognitive, developmental, and behavioral assessments, and physical examinations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 April 2015
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	Austria: 2
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Hungary: 9
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Philippines: 3
Country: Number of subjects enrolled	Poland: 16
Country: Number of subjects enrolled	Russian Federation: 6
Country: Number of subjects enrolled	Taiwan: 17
Country: Number of subjects enrolled	United States: 2
Worldwide total number of subjects	63
EEA total number of subjects	34

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)	47
Adolescents (12-17 years)	16
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:

A total of 114 subjects were screened. Out of 114 screened subjects, 63 subjects (topiramate group: 28 subjects, levetiracetam group: 35 subjects) were randomized in the study and received at least 1 dose of study drug.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Topiramate

Arm description:

Subjects received topiramate weight-based sprinkle capsule and tablet, as tolerated (not to exceed 350 milligrams per day [mg/day] for subjects 2 to less than [<] 10 years of age, and not to exceed 400 mg/day for subjects 10 to 15 years of age), twice daily (BID) for up to 1 year during open-label treatment phase. Subjects were to either continue on commercially available topiramate or were tapered off of study drug over a period of up to 2 weeks during post-treatment phase of 30 days.

Arm type	Experimental
Investigational medicinal product name	Topiramate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Capsule
Routes of administration	Oral use

Dosage and administration details:

Topiramate BID for up to 1 year during open-label treatment phase was administered.

Arm title	Levetiracetam

Arm description:

Subjects received levetiracetam weight-based tablet or oral solution, as tolerated (not to exceed 60 milligrams per kilogram per day [mg/kg/day] for subjects 2 to 15 years of age). The daily dosage was increased every 2 weeks by increments of 20 mg/kg/day to the recommended daily dosage of 60 mg/kg/day. The maximum recommended daily dosage was 3000 mg (1500 mg BID) for up to 1 year during open-label treatment phase. Subjects were to either continue on commercially available levetiracetam or were tapered off of study drug over a period of up to 2 weeks during post-treatment phase of 30 days.

Arm type	Active comparator
Investigational medicinal product name	Levetiracetam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution, Tablet
Routes of administration	Oral use

Dosage and administration details:

Levetiracetam every 2 weeks by increments of 20 mg/kg/day to the recommended daily dosage for up to 1 year during open-label treatment phase was administered.

Number of subjects in period 1	Topiramate	Levetiracetam
Started	28	35
Completed	24	32
Not completed	4	3
Consent withdrawn by subject	2	1
Adverse event, non-fatal	1	1
Noncompliance with study drug	-	1
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Topiramate
Reporting group description:	
Subjects received topiramate weight-based sprinkle capsule and tablet, as tolerated (not to exceed 350 milligrams per day [mg/day] for subjects 2 to less than [<] 10 years of age, and not to exceed 400 mg/day for subjects 10 to 15 years of age), twice daily (BID) for up to 1 year during open-label treatment phase. Subjects were to either continue on commercially available topiramate or were tapered off of study drug over a period of up to 2 weeks during post-treatment phase of 30 days.	
Reporting group title	Levetiracetam
Reporting group description:	
Subjects received levetiracetam weight-based tablet or oral solution, as tolerated (not to exceed 60 milligrams per kilogram per day [mg/kg/day] for subjects 2 to 15 years of age). The daily dosage was increased every 2 weeks by increments of 20 mg/kg/day to the recommended daily dosage of 60 mg/kg/day. The maximum recommended daily dosage was 3000 mg (1500 mg BID) for up to 1 year during open-label treatment phase. Subjects were to either continue on commercially available levetiracetam or were tapered off of study drug over a period of up to 2 weeks during post-treatment phase of 30 days.	

Reporting group values	Topiramate	Levetiracetam	Total
Number of subjects	28	35	63
Title for AgeCategorical Units: subjects			
Children (2-11 years)	20	27	47
Adolescents (12-17 years)	8	8	16
Adults (18-64 years)	0	0	0
From 65 to 84 years	0	0	0
85 years and over	0	0	0
Title for AgeContinuous Units: years			
arithmetic mean	9.9	9.3	
standard deviation	± 2.76	± 3.29	-
Title for Gender Units: subjects			
Female	16	18	34
Male	12	17	29

End points

End points reporting groups

Reporting group title	Topiramate

Reporting group description:

Subjects received topiramate weight-based sprinkle capsule and tablet, as tolerated (not to exceed 350 milligrams per day [mg/day] for subjects 2 to less than [<] 10 years of age, and not to exceed 400 mg/day for subjects 10 to 15 years of age), twice daily (BID) for up to 1 year during open-label treatment phase. Subjects were to either continue on commercially available topiramate or were tapered off of study drug over a period of up to 2 weeks during post-treatment phase of 30 days.

Reporting group title	Levetiracetam

Reporting group description:

Subjects received levetiracetam weight-based tablet or oral solution, as tolerated (not to exceed 60 milligrams per kilogram per day [mg/kg/day] for subjects 2 to 15 years of age). The daily dosage was increased every 2 weeks by increments of 20 mg/kg/day to the recommended daily dosage of 60 mg/kg/day. The maximum recommended daily dosage was 3000 mg (1500 mg BID) for up to 1 year during open-label treatment phase. Subjects were to either continue on commercially available levetiracetam or were tapered off of study drug over a period of up to 2 weeks during post-treatment phase of 30 days.

Primary: Change From Baseline in Weight Z-score at Month 1

End point title	Change From Baseline in Weight Z-score at Month 1[1]

End point description:

The Z-Score indicates how many standard deviations (SD) a subject was from the population normal values. The body weight z-scores were designed to take into account the amount of weight gain that was expected due to normal growth in children and adolescents. Body weight data were converted to Z-scores using the Statistical Analysis System (SAS) programs provided by the Centers for Disease Control (CDC) for the calculation of the 2000 CDC growth charts. The mean (SD) change in Z scores from baseline by visit for the total safety population for all age cohorts combined were presented. The safety analysis set included all randomized subjects who received at least 1 dose of study drug. Here, N (Number of Subjects Analyzed) signifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline, Month 1

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 inferential statistical analyses was planned to report for the primary end point.

End point values	Topiramate	Levetiracetam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	34		
Units: Z-score				
arithmetic mean (standard deviation)	-0.112 (± 0.1220)	-0.014 (± 0.1244)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Weight Z-score at Month 3

End point title	Change From Baseline in Weight Z-score at Month 3[2]

End point description:

The Z-Score indicates how many SD a subject was from the population normal values. The body weight z-scores were designed to take into account the amount of weight gain that was expected due to normal growth in children and adolescents. Body weight data were converted to Z-scores using the SAS programs provided by the CDC for the calculation of the 2000 CDC growth charts. The mean (SD) change in Z scores from baseline by visit for the total safety population for all age cohorts combined were presented. The safety analysis set included all randomized subjects who received at least 1 dose of study drug. Here, N (Number of Subjects Analyzed) signifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline, Month 3

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 inferential statistical analyses was planned to report for the primary end point.

End point values	Topiramate	Levetiracetam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	34		
Units: Z-score				
arithmetic mean (standard deviation)	-0.201 (± 0.2094)	-0.027 (± 0.1802)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Weight Z-score at Month 6

End point title	Change From Baseline in Weight Z-score at Month 6[3]

End point description:

The Z-Score indicates how many SD a subject was from the population normal values. The body weight z-scores were designed to take into account the amount of weight gain that was expected due to normal growth in children and adolescents. Body weight data were converted to Z-scores using the SAS programs provided by the CDC for the calculation of the 2000 CDC growth charts. The mean (SD) change in Z scores from baseline by visit for the total safety population for all age cohorts combined were presented. The safety analysis set included all randomized subjects who received at least 1 dose of study drug. Here, N (Number of Subjects Analyzed) signifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline, Month 6

Notes:

[3] - 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 inferential statistical analyses was planned to report for the primary end point.

End point values	Topiramate	Levetiracetam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	33		
Units: Z-score				
arithmetic mean (standard deviation)	-0.319 (± 0.2496)	-0.070 (± 0.2304)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Weight Z-score at Month 9

End point title	Change From Baseline in Weight Z-score at Month 9[4]

End point description:

The Z-Score indicates how many SD a subject was from the population normal values. The body weight z-scores were designed to take into account the amount of weight gain that was expected due to normal growth in children and adolescents. Body weight data were converted to Z-scores using the SAS programs provided by the CDC for the calculation of the 2000 CDC growth charts. The mean (SD) change in Z scores from baseline by visit for the total safety population for all age cohorts combined were presented. The safety analysis set included all randomized subjects who received at least 1 dose of study drug. Here, N (Number of Subjects Analyzed) signifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline, Month 9

Notes:

[4] - 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 inferential statistical analyses was planned to report for the primary end point.

End point values	Topiramate	Levetiracetam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	32		
Units: Z-score				
arithmetic mean (standard deviation)	-0.326 (± 0.3235)	-0.110 (± 0.3584)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Weight Z-score at Month 12

End point title	Change From Baseline in Weight Z-score at Month 12[5]

End point description:

The Z-Score indicates how many SD a subject was from the population normal values. The body weight z-scores were designed to take into account the amount of weight gain that was expected due to normal growth in children and adolescents. Body weight data were converted to Z-scores using the SAS programs provided by the CDC for the calculation of the 2000 CDC growth charts. The mean (SD) change in Z scores from baseline by visit for the total safety population for all age cohorts combined were presented. The safety analysis set included all randomized subjects who received at least 1 dose of

study drug. Here, N (Number of Subjects Analyzed) signifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline, Month 12

Notes:

[5] - 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 inferential statistical analyses was planned to report for the primary end point.

End point values	Topiramate	Levetiracetam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	32		
Units: Z-score				
arithmetic mean (standard deviation)	-0.351 (± 0.3905)	-0.065 (± 0.3026)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Height Z-score at Month 1

End point title	Change From Baseline in Height Z-score at Month 1[6]

End point description:

Z-Score was a statistical measure to evaluate how a single data point compares to a standard. It described whether a mean was above or below the standard and how unusual the measurement is with range from minus (-) 3 to plus (+) 3; 0 equal to (=) same mean, greater than (>) 0 a greater mean, and less than (<) 0 a lesser mean than the standard. Growth parameters were compared to a standard defined by CDC growth charts. The mean (SD) change in Z scores from baseline by visit for the total safety population for all age cohorts combined were presented. The safety analysis set included all randomized subjects who received at least 1 dose of study drug. Here, N (Number of Subjects Analyzed) signifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline, Month 1

Notes:

[6] - 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 inferential statistical analyses was planned to report for the primary end point.

End point values	Topiramate	Levetiracetam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	33		
Units: Z-score				
arithmetic mean (standard deviation)	0.004 (± 0.0870)	-0.015 (± 0.1017)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Height Z-score at Month 3

End point title	Change From Baseline in Height Z-score at Month 3[7]

End point description:

Z-Score was a statistical measure to evaluate how a single data point compares to a standard. It described whether a mean was above or below the standard and how unusual the measurement is with range from -3 to +3; 0 =same mean, >0 a greater mean, and <0 a lesser mean than the standard. Growth parameters were compared to a standard defined by CDC growth charts. The mean (SD) change in Z scores from baseline by visit for the total safety population for all age cohorts combined were presented. The safety analysis set included all randomized subjects who received at least 1 dose of study drug. Here, N (Number of Subjects Analyzed) signifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline, Month 3

Notes:

[7] - 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 inferential statistical analyses was planned to report for the primary end point.

End point values	Topiramate	Levetiracetam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	34		
Units: Z-score				
arithmetic mean (standard deviation)	-0.036 (± 0.1452)	0.017 (± 0.1631)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Height Z-score at Month 6

End point title	Change From Baseline in Height Z-score at Month 6[8]

End point description:

Z-Score was a statistical measure to evaluate how a single data point compares to a standard. It described whether a mean was above or below the standard and how unusual the measurement is with range from -3 to +3; 0 =same mean, >0 a greater mean, and <0 a lesser mean than the standard. Growth parameters were compared to a standard defined by CDC growth charts. The mean (SD) change in Z scores from baseline by visit for the total safety population for all age cohorts combined were presented. The safety analysis set included all randomized subjects who received at least 1 dose of study drug. Here, N (Number of Subjects Analyzed) signifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline, Month 6

Notes:

[8] - 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 inferential statistical analyses was planned to report for the primary end point.

End point values	Topiramate	Levetiracetam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	33		
Units: Z-score				
arithmetic mean (standard deviation)	-0.008 (± 0.1753)	0.077 (± 0.2670)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Height Z-score at Month 9

End point title	Change From Baseline in Height Z-score at Month 9[9]

End point description:

Z-Score was a statistical measure to evaluate how a single data point compares to a standard. It described whether a mean was above or below the standard and how unusual the measurement is with range from -3 to +3; 0 =same mean, >0 a greater mean, and <0 a lesser mean than the standard. Growth parameters were compared to a standard defined by CDC growth charts. The mean (SD) change in Z scores from baseline by visit for the total safety population for all age cohorts combined were presented. The safety analysis set included all randomized subjects who received at least 1 dose of study drug. Here, N (Number of Subjects Analyzed) signifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline, Month 9

Notes:

[9] - 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 inferential statistical analyses was planned to report for the primary end point.

End point values	Topiramate	Levetiracetam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	32		
Units: Z-score				
arithmetic mean (standard deviation)	-0.059 (± 0.2337)	0.086 (± 0.2929)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Height Z-score at Month 12

End point title	Change From Baseline in Height Z-score at Month 12[10]

End point description:

Z-Score was a statistical measure to evaluate how a single data point compares to a standard. It described whether a mean was above or below the standard and how unusual the measurement is with range from -3 to +3; 0 =same mean, >0 a greater mean, and <0 a lesser mean than the standard. Growth parameters were compared to a standard defined by CDC growth charts. The mean (SD) change in Z scores from baseline by visit for the total safety population for all age cohorts combined were presented. The safety analysis set included all randomized subjects who received at least 1 dose of

study drug. Here, N (Number of Subjects Analyzed) signifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline, Month 12

Notes:

[10] - 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 inferential statistical analyses was planned to report for the primary end point.

End point values	Topiramate	Levetiracetam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	32		
Units: Z-score				
arithmetic mean (standard deviation)	-0.057 (± 0.2734)	0.088 (± 0.3315)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Bone Mineral Density (BMD) Z-score at Month 6

End point title	Change from Baseline in Bone Mineral Density (BMD) Z-score at Month 6[11]

End point description:

The BMD was measured by dual energy X-ray absorptiometry (DEXA) for the posterior-anterior lumbar spine (L1_L4) and total body less head area. The Z-Score is the number of standard deviations a subject's BMD differs from the average BMD of their age, sex and ethnicity. Positive scores indicate BMD above the mean; positive values are "best values" and negative values are "worst values". Positive changes from baseline indicated an improvement in condition. The safety analysis set included all randomized subjects who received at least 1 dose of study drug. Here, n (number analyzed) signifies number of subjects evaluable for this endpoint for specified category.

End point type	Primary

End point timeframe:

Baseline, Month 6

Notes:

[11] - 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 inferential statistical analyses was planned to report for the primary end point.

End point values	Topiramate	Levetiracetam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	35		
Units: Z-score				
arithmetic mean (standard deviation)				
Lumbar spine (n= 24, 32)	-0.181 (± 0.2590)	0.035 (± 0.2606)		
Total body less head (n=25, 30)	-0.180 (± 0.2647)	0.102 (± 0.2574)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in BMD Z-score at Month 12

End point title	Change from Baseline in BMD Z-score at Month 12[12]

End point description:

The BMD was measured by DEXA for the posterior-anterior lumbar spine (L1_L4) and total body less head area. The Z-Score is the number of standard deviations a subject's BMD differs from the average BMD of their age, sex and ethnicity. Positive scores indicate BMD above the mean; positive values are "best values" and negative values are "worst values". Positive changes from baseline indicated an improvement in condition. The safety analysis set included all randomized subjects who received at least 1 dose of study drug. Here, n (number analyzed) signifies number of subjects evaluable for this endpoint for specified category.

End point type	Primary

End point timeframe:

Baseline, Month 12

Notes:

[12] - 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 inferential statistical analyses was planned to report for the primary end point.

End point values	Topiramate	Levetiracetam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	35		
Units: Z-score				
arithmetic mean (standard deviation)				
Lumbar spine (n= 23, 30)	-0.346 (± 0.3461)	0.084 (± 0.3552)		
Total body less head (n=24, 28)	-0.367 (± 0.3170)	0.054 (± 0.3766)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Bone Mineral Content (BMC)-Z Score at Month 6

End point title	Change From Baseline in Bone Mineral Content (BMC)-Z Score at Month 6[13]

End point description:

The BMC is an estimate of the amount of mineral (such as calcium) in the bone, which was assessed by DEXA scan for the posterior-anterior lumbar spine (L1_L4) and total body less head area. Positive changes from baseline indicated an improvement in condition. The safety analysis set included all randomized subjects who received at least 1 dose of study drug. Here, n (number analyzed) signifies number of subjects evaluable for this endpoint for specified category.

End point type	Primary

End point timeframe:

Baseline, Month 6

Notes:

[13] - 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 inferential statistical analyses was planned to report for the primary end point.

End point values	Topiramate	Levetiracetam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	35		
Units: Z-score				
arithmetic mean (standard deviation)				
Lumbar spine (n= 14, 19)	-0.141 (± 0.2155)	0.075 (± 0.2806)		
Total body less head (n=15, 19)	-0.242 (± 0.2516)	0.151 (± 0.2154)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in BMC-Z Score at Month 12

End point title	Change From Baseline in BMC-Z Score at Month 12[14]

End point description:

The BMC is an estimate of the amount of mineral (such as calcium) in the bone, which was assessed by DEXA scan for the posterior-anterior lumbar spine (L1_L4) and total body less head area. Positive changes from baseline indicated an improvement in condition. The safety analysis set included all randomized subjects who received at least 1 dose of study drug. Here, n (number analyzed) signifies number of subjects evaluable for this endpoint for specified category.

End point type	Primary

End point timeframe:

Baseline, Month 12

Notes:

[14] - 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 inferential statistical analyses was planned to report for the primary end point.

End point values	Topiramate	Levetiracetam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	35		
Units: Z-score				
arithmetic mean (standard deviation)				
Lumbar spine (n= 14, 18)	-0.274 (± 0.3123)	0.124 (± 0.3584)		
Total body less head (n=15, 18)	-0.266 (± 0.6800)	0.017 (± 0.2533)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Treatment-emergent Adverse Events (TEAE)

End point title	Number of Subjects with Treatment-emergent Adverse Events (TEAE)

End point description:

An adverse event (AE) is any untoward medical occurrence in a subject who received study drug without

regard to possibility of causal relationship. TEAE are defined as AEs with onset during the treatment period or that are a consequence of a pre-existing condition that has worsened since baseline. Safety analysis set included all randomized subjects who received at least 1 dose of study treatment.

End point type	Secondary

End point timeframe:

Up to 1 year

End point values	Topiramate	Levetiracetam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	35		
Units: Subjects	25	29		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Kidney Stones

End point title	Percentage of Subjects with Kidney Stones

End point description:

Percentage of subjects with kidney stones were reported.

End point type	Secondary

End point timeframe:

Up to 1 year

End point values	Topiramate	Levetiracetam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	35		
Units: Percentage of Subject				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Day 390

Adverse event reporting additional description:

The safety analysis set included all randomized subjects who received at least 1 dose of study drug.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Levetiracetam

Reporting group description:

Subjects received levetiracetam weight-based tablet or oral solution, as tolerated (not to exceed 60 milligrams per kilogram per day [mg/kg/day] for subjects 2 to 15 years of age). The daily dosage was increased every 2 weeks by increments of 20 mg/kg/day to the recommended daily dosage of 60 mg/kg/day. The maximum recommended daily dosage was 3000 mg (1500 mg BID) for up to 1 year during open-label treatment phase. Subjects were to either continue on commercially available levetiracetam or were tapered off of study drug over a period of up to 2 weeks during post-treatment phase of 30 days.

Reporting group title	Topiramate

Reporting group description:

Subjects received topiramate weight-based sprinkle capsule and tablet, as tolerated (not to exceed 350 milligrams per day [mg/day] for subjects 2 to less than [<] 10 years of age, and not to exceed 400 mg/day for subjects 10 to 15 years of age), twice daily (BID) for up to 1 year during open-label treatment phase. Subjects were to either continue on commercially available topiramate or were tapered off of study drug over a period of up to 2 weeks during post-treatment phase of 30 days.

Serious adverse events	Levetiracetam	Topiramate	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 35 (14.29%)	0 / 28 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Skull Fracture			
subjects affected / exposed	1 / 35 (2.86%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 35 (2.86%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Generalised Tonic-Clonic Seizure			
subjects affected / exposed	1 / 35 (2.86%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 35 (2.86%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Myositis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Levetiracetam	Topiramate	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 35 (74.29%)	24 / 28 (85.71%)	
Nervous system disorders			
Disturbance in Attention			
subjects affected / exposed	0 / 35 (0.00%)	4 / 28 (14.29%)	
occurrences (all)	0	4	
Headache			
subjects affected / exposed	9 / 35 (25.71%)	3 / 28 (10.71%)	
occurrences (all)	25	3	
Memory Impairment			
subjects affected / exposed	2 / 35 (5.71%)	0 / 28 (0.00%)	
occurrences (all)	2	0	
Psychomotor Hyperactivity			
subjects affected / exposed	2 / 35 (5.71%)	1 / 28 (3.57%)	
occurrences (all)	2	1	
Somnolence			
subjects affected / exposed	3 / 35 (8.57%)	2 / 28 (7.14%)	
occurrences (all)	4	2	

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 35 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	2	
Pyrexia			
subjects affected / exposed	3 / 35 (8.57%)	3 / 28 (10.71%)	
occurrences (all)	9	3	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 35 (5.71%)	1 / 28 (3.57%)	
occurrences (all)	6	4	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	1 / 35 (2.86%)	2 / 28 (7.14%)	
occurrences (all)	1	4	
Abdominal Pain Upper			
subjects affected / exposed	2 / 35 (5.71%)	4 / 28 (14.29%)	
occurrences (all)	11	8	
Diarrhoea			
subjects affected / exposed	4 / 35 (11.43%)	1 / 28 (3.57%)	
occurrences (all)	4	1	
Nausea			
subjects affected / exposed	2 / 35 (5.71%)	0 / 28 (0.00%)	
occurrences (all)	4	0	
Vomiting			
subjects affected / exposed	5 / 35 (14.29%)	2 / 28 (7.14%)	
occurrences (all)	8	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 35 (5.71%)	1 / 28 (3.57%)	
occurrences (all)	2	1	
Epistaxis			
subjects affected / exposed	2 / 35 (5.71%)	2 / 28 (7.14%)	
occurrences (all)	3	2	
Oropharyngeal Pain			

subjects affected / exposed	3 / 35 (8.57%)	4 / 28 (14.29%)	
occurrences (all)	5	5	
Rhinitis Allergic			
subjects affected / exposed	0 / 35 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	2	
Psychiatric disorders			
Attention Deficit/Hyperactivity Disorder			
subjects affected / exposed	0 / 35 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	2	
Irritability			
subjects affected / exposed	5 / 35 (14.29%)	0 / 28 (0.00%)	
occurrences (all)	5	0	
Nervousness			
subjects affected / exposed	2 / 35 (5.71%)	0 / 28 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 35 (2.86%)	3 / 28 (10.71%)	
occurrences (all)	1	13	
Influenza			
subjects affected / exposed	1 / 35 (2.86%)	2 / 28 (7.14%)	
occurrences (all)	1	2	
Nasopharyngitis			
subjects affected / exposed	7 / 35 (20.00%)	7 / 28 (25.00%)	
occurrences (all)	14	15	
Pharyngitis			
subjects affected / exposed	0 / 35 (0.00%)	3 / 28 (10.71%)	
occurrences (all)	0	4	
Respiratory Tract Infection Viral			
subjects affected / exposed	3 / 35 (8.57%)	1 / 28 (3.57%)	
occurrences (all)	5	1	
Rhinitis			
subjects affected / exposed	3 / 35 (8.57%)	2 / 28 (7.14%)	
occurrences (all)	3	2	
Sinusitis			

subjects affected / exposed	1 / 35 (2.86%)	3 / 28 (10.71%)	
occurrences (all)	1	4	
Tonsillitis			
subjects affected / exposed	1 / 35 (2.86%)	3 / 28 (10.71%)	
occurrences (all)	1	3	
Upper Respiratory Tract Infection			
subjects affected / exposed	7 / 35 (20.00%)	11 / 28 (39.29%)	
occurrences (all)	16	22	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	1 / 35 (2.86%)	4 / 28 (14.29%)	
occurrences (all)	1	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 March 2014	The overall reason for the amendment is to clarify exclusion and withdrawal criteria for subjects with a history of or significant risk of suicidal or violent behavior.
24 August 2017	The overall objective of this amendment is to improve a slower than expected study enrollment. At the current rate of subject randomization, the previously agreed upon milestone for the study completion will not be met.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Enrollment stopped early due to futility; but all enrolled subjects completed trial except 7 subjects(reasons in subject disposition). Also, no exposure to topiramate in 2-5 years age cohort. Hence no conclusions made due to absence of comparability.

Notes: