



Clinical trial results:

A Multicenter, Randomized, Controlled, Open-label Study to Evaluate the Cognitive Development Effects and Safety, and Pharmacokinetics of Adjunctive Rufinamide Treatment in Pediatric Subjects 1 to Less Than 4 years of Age with Inadequately Controlled Lennox-Gastaut Syndrome Summary

EudraCT number	2010-023505-36
Trial protocol	FR IT GR Outside EU/EEA
Global end of trial date	02 November 2015

Results information

Result version number	v3 (current)
This version publication date	28 July 2019
First version publication date	16 June 2016
Version creation reason	<ul style="list-style-type: none">• Correction of full data set Modifications done in end-point description and baseline section.

Trial information

Trial identification

Sponsor protocol code	E2080-G000-303
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01405053
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Eisai
Sponsor organisation address	155 Tice Boulevard, Woodcliff Lake, United States, 07677
Public contact	Eisai Call Center, Eisai Inc., 888 422-4743, EUMedInfo@eisai.net
Scientific contact	Eisai Call Center, Eisai Inc., 888 422-4743, EUMedInfo@eisai.net

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000709-PIP01-09
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	02 November 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	02 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effect of 2 drug regimens consisting of either rufinamide or any other approved antiepileptic drug (AED) of the investigator's choice as an add-on to the subject's existing regimen of 1-3 AEDs on the overall safety and tolerability of rufinamide in subjects aged 1 to less than 4 years of age with inadequately controlled Lennox-Gastaut Syndrome (LGS). To characterize the age group specific pharmacokinetics of rufinamide in a pediatric population, 1 to less than 4 years of age, with inadequately controlled LGS, using the population approach. To evaluate the effect of rufinamide as adjunctive treatment on the cognitive development and behavioral effects in a pediatric population, 1 to less than 4 years of age, with inadequately controlled LGS.

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 Conference 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 Conference on Harmonisation 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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 June 2011
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	Poland: 9
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Greece: 4
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Canada: 1

Country: Number of subjects enrolled	United States: 16
Worldwide total number of subjects	37
EEA total number of subjects	20

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)	13
Children (2-11 years)	24
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:

Subjects took part in the study at 19 investigative sites in the United States, Canada, France, Greece, Italy, and Poland from 16 June 2011 to 02 November 2015.

Pre-assignment

Screening details:

A total of 43 subjects were screened, out of which 37 subjects were randomized and treated in the study.

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	Rufinamide

Arm description:

Subjects received rufinamide oral suspension as an add-on therapy to the subject's existing regimen of 1 to 3 AEDs. Subjects underwent a 2 week Titration Period during which rufinamide dose was increased from 10 milligram per kilogram per day (mg/kg/day) in increments of 10 mg/kg/day every 3 days to 40 mg/kg/day and thereafter in increments of 5 mg/kg/day to the target maintenance dose of 45 mg/kg/day (all daily treatments were to be administered in 2 equally divided doses). Rufinamide dose reached at the end of the Titration period were to be maintained the same throughout the 104-week Maintenance Period. At the end of Maintenance Period, rufinamide dose should be tapered (as needed) over a period of 2 weeks.

Arm type	Active comparator
Investigational medicinal product name	Rufinamide
Investigational medicinal product code	E2080
Other name	Inovelon, Banzel
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Rufinamide up to 45 mg/kg/day was administered in 2 divided doses as an oral suspension (40 mg/mL).

Arm title	Any Other Approved Antiepileptic Drug (AED)
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Arm description:

Subjects received any other approved AED of the investigator's choice, dosed according to the investigator's usual practice, added to the subject's existing regimen of 1 to 3 AEDs. At the end of Maintenance Period, the AED comparator would be discontinued according to the investigator's usual practice.

Arm type	Active comparator
Investigational medicinal product name	Lamotrigine
Investigational medicinal product code	
Other name	Lamictal
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dosed according to the investigator's usual practice.

Investigational medicinal product name	Clobazam
Investigational medicinal product code	
Other name	Onfi

Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Dosed according to the investigator's usual practice.	
Investigational medicinal product name	Topiramate
Investigational medicinal product code	
Other name	Trokendi XR
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
Dosed according to the investigator's usual practice.	
Investigational medicinal product name	Phenobarbital
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Dosed according to the investigator's usual practice.	
Investigational medicinal product name	Valproic acid
Investigational medicinal product code	
Other name	Depakene, Stavzor
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
Dosed according to the investigator's usual practice.	
Investigational medicinal product name	Zonisamide
Investigational medicinal product code	
Other name	Zonegran
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
Dosed according to the investigator's usual practice.	

Number of subjects in period 1	Rufinamide	Any Other Approved Antiepileptic Drug (AED)
Started	25	12
Completed	15	4
Not completed	10	8
Consent withdrawn by subject	3	4
Adverse event, non-fatal	3	-
Not specified	-	1
Subject's choice	2	1
Inadequate therapeutic effect	2	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups

Reporting group title	Rufinamide
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Reporting group description:

Subjects received rufinamide oral suspension as an add-on therapy to the subject's existing regimen of 1 to 3 AEDs. Subjects underwent a 2 week Titration Period during which rufinamide dose was increased from 10 milligram per kilogram per day (mg/kg/day) in increments of 10 mg/kg/day every 3 days to 40 mg/kg/day and thereafter in increments of 5 mg/kg/day to the target maintenance dose of 45 mg/kg/day (all daily treatments were to be administered in 2 equally divided doses). Rufinamide dose reached at the end of the Titration period were to be maintained the same throughout the 104-week Maintenance Period. At the end of Maintenance Period, rufinamide dose should be tapered (as needed) over a period of 2 weeks.

Reporting group title	Any Other Approved Antiepileptic Drug (AED)
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Reporting group description:

Subjects received any other approved AED of the investigator's choice, dosed according to the investigator's usual practice, added to the subject's existing regimen of 1 to 3 AEDs. At the end of Maintenance Period, the AED comparator would be discontinued according to the investigator's usual practice.

Reporting group values	Rufinamide	Any Other Approved Antiepileptic Drug (AED)	Total
Number of subjects	25	12	37
Age categorical Units: Subjects			

Age continuous Units: months arithmetic mean standard deviation	28.3 ± 9.99	29.8 ± 9.85	-
Gender categorical Units: Subjects			
Female	11	2	13
Male	14	10	24

End points

End points reporting groups

Reporting group title	Rufinamide
Reporting group description: Subjects received rufinamide oral suspension as an add-on therapy to the subject's existing regimen of 1 to 3 AEDs. Subjects underwent a 2 week Titration Period during which rufinamide dose was increased from 10 milligram per kilogram per day (mg/kg/day) in increments of 10 mg/kg/day every 3 days to 40 mg/kg/day and thereafter in increments of 5 mg/kg/day to the target maintenance dose of 45 mg/kg/day (all daily treatments were to be administered in 2 equally divided doses). Rufinamide dose reached at the end of the Titration period were to be maintained the same throughout the 104-week Maintenance Period. At the end of Maintenance Period, rufinamide dose should be tapered (as needed) over a period of 2 weeks.	
Reporting group title	Any Other Approved Antiepileptic Drug (AED)
Reporting group description: Subjects received any other approved AED of the investigator's choice, dosed according to the investigator's usual practice, added to the subject's existing regimen of 1 to 3 AEDs. At the end of Maintenance Period, the AED comparator would be discontinued according to the investigator's usual practice.	

Primary: Child Behavior Checklist (CBCL) Total Problem T-scores at the End of 2-year Treatment Period

End point title	Child Behavior Checklist (CBCL) Total Problem T-scores at the End of 2-year Treatment Period
End point description: CBCL:99-item questionnaire measures specific behavioral problems/developmental delays, answered by parent/legal guardian/caregiver. Items rated on 3-point scale (0=Not True, 1=Somewhat/Sometimes True, 2=Very True/Often True). 99 items were combined to yield scores for 8 problem area scales (emotionally reactive, anxious/depressed, somatic complaints, withdrawn, sleep, attention, aggressive behavior, and other problems) and 3 summary scores (internalizing, externalizing, and total problems). Total Problem score: sum of all problem areas plus 1 additional item, range from 0 to 198. Total raw scores are converted to t-scores with mean of 50 and standard deviation (SD) of 10. T-scores were standardized test scores that indicate same degree of elevation in problems relative to normative sample of peers. Higher scores = more problems. Full analysis set (FAS): randomised subjects who received rufinamide/any other approved add-on AED of investigator's choice, had baseline and at least 1 postdose cognition measurement.	
End point type	Primary
End point timeframe: End of Treatment Period (up to approximately Week 106)	

End point values	Rufinamide	Any Other Approved Antiepileptic Drug (AED)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	4		
Units: score on a scale				
arithmetic mean (standard deviation)	55.7 (± 15.81)	54.8 (± 4.5)		

Statistical analyses

Statistical analysis title	CBCL Total Problems Score
Statistical analysis description:	
The primary statistical model for comparing the 2 treatment groups was an analysis of covariance (ANCOVA) mixed model for repeated measures with baseline score, age, and sex as covariates, and treatment, week, and treatment by week interaction as factors.	
Comparison groups	Any Other Approved Antiepileptic Drug (AED) v Rufinamide
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6928 ^[1]
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	2.601
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.5
upper limit	15.7
Variability estimate	Standard error of the mean
Dispersion value	6.558

Notes:

[1] - P-value is based on ANCOVA Least Square (LE) mean analysis for Week 106 of the study.

Primary: Change From Baseline in CBCL Total Problem T-Scores at End of 2-year Treatment Period

End point title	Change From Baseline in CBCL Total Problem T-Scores at End of 2-year Treatment Period ^[2]
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End point description:

CBCL:99-item questionnaire measures specific behavioral problems/developmental delays, answered by parent/legal guardian/caregiver. Items rated on 3-point scale (0=Not True, 1=Somewhat/Sometimes True, 2=Very True/Often True). 99 items were combined to yield scores for 8 problem area scales (emotionally reactive, anxious/depressed, somatic complaints, withdrawn, sleep, attention, aggressive behavior, and other problems) and 3 summary scores (internalizing, externalizing, and total problems). Total Problem score: sum of all problem areas plus 1 additional item, range from 0 to 198. Total raw scores are converted to t-scores with mean of 50 and SD of 10. T-scores were standardized test scores that indicate same degree of elevation in problems relative to normative sample of peers. Higher scores = more problems. FAS: randomised subjects who received rufinamide/any other approved add-on AED of investigator's choice, had baseline and at least 1 postdose cognition measurement. 'n': subjects evaluable at given time period.

End point type	Primary
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End point timeframe:

Baseline and End of Treatment Period (up to approximately Week 106)

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: Only descriptive data was planned to be analysed for this endpoint.

End point values	Rufinamide	Any Other Approved Antiepileptic Drug (AED)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	9		
Units: score on a scale				

arithmetic mean (standard deviation)				
Baseline (n = 24, 8)	56.6 (± 11.27)	62.8 (± 13.07)		
Change at Week 106 (n = 15, 3)	-0.3 (± 15.72)	-6.7 (± 0.58)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time to Withdrawal From Treatment Due to an Adverse Event or Lack of Efficacy

End point title	Time to Withdrawal From Treatment Due to an Adverse Event or Lack of Efficacy
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End point description:

Withdrawal from either rufinamide or other AED was due to the occurrence of an adverse event or for lack of efficacy. Data was obtained till Week 106 and was extrapolated using Kaplan-Meier method to determine the overall survival time (in weeks) to withdrawal from treatment (excluding taper) due to an adverse event or lack efficacy. The FAS for other efficacy variable had randomized subjects who received rufinamide or any other add-on AED of the investigator's choice and had a baseline efficacy assessment and at least 1 postbaseline efficacy assessment. Subjects who were evaluable at a given time point were included for this assessment. Lower and upper limits of 95% Confidence Interval could not be calculated since insufficient number of subjects had withdrawal from treatment due to adverse event or lack of efficacy, therefore we added -9999.0 and 99999 as space-fillers.

End point type	Other pre-specified
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End point timeframe:

Baseline up to the End of the Treatment Period (up to approximately Week 106)

End point values	Rufinamide	Any Other Approved Antiepileptic Drug (AED)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	2		
Units: weeks				
median (confidence interval 95%)	142 (-9999 to 99999)	28 (17.7 to 99999)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percent Change in Total Seizure Frequency Per 28 Days

End point title	Percent Change in Total Seizure Frequency Per 28 Days
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End point description:

The frequency per 28 days was defined as (S/D)*28 where, S was equal to the sum of the seizures reported in the subject seizure diary during the specified time interval and D was equal to the number of days with non-missing data in the subject seizure diary for the specified study phase. The number of seizures was assessed and recorded by the subject's parent(s)/caregiver(s) in the subject seizure diary. Analysis was performed on the FAS for other efficacy variable included randomized subjects who received rufinamide or any other add-on AED of the investigator's choice and had a baseline efficacy

assessment and at least 1 post baseline efficacy assessment. The FAS for other efficacy variable had randomized subjects who received rufinamide or any other add-on AED of the investigator's choice and had a baseline efficacy assessment and at least 1 postbaseline efficacy assessment, at given time period.

End point type	Other pre-specified
End point timeframe:	
Baseline up to End of the Treatment Period (up to approximately Week 106)	

End point values	Rufinamide	Any Other Approved Antiepileptic Drug (AED)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	8		
Units: percent change in seizure frequency				
median (full range (min-max))	-7.05 (-79.2 to 3644.1)	-20.15 (-83.3 to 143.1)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percent Change in Seizure Frequency by Individual Seizure Type Per 28 Days

End point title	Percent Change in Seizure Frequency by Individual Seizure Type Per 28 Days
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End point description:

The frequency per 28 days was defined as $(S/D)*28$ where, S was equal to the sum of the seizures reported in the subject seizure diary during the specified time interval and D was equal to the number of days with non-missing data in the subject seizure diary for the specified study phase. The number of seizures was assessed and recorded by the subject's parent(s)/caregiver(s) in the subject seizure diary. The FAS for other efficacy variable had randomized subjects who received rufinamide or any other add-on AED of the investigator's choice and had a baseline efficacy assessment and at least 1 postbaseline efficacy assessment. Here "n" were subjects evaluable at given time period.

End point type	Other pre-specified
End point timeframe:	
Baseline up to End of Treatment Period (up to approximately Week 106)	

End point values	Rufinamide	Any Other Approved Antiepileptic Drug (AED)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	9		
Units: percent change in seizure frequency				
median (full range (min-max))				

Partial seizures (n=12, 2)	-39.8 (-100 to 52281.9)	-57.65 (-98.1 to -17.2)		
Absence seizures (n=11, 5)	-23.6 (-100 to 86.8)	-49.7 (-98.9 to 1846.7)		
Atypical absence seizures (n=14, 4)	-70.95 (-100 to 16825.4)	4.9 (-90.9 to 1189.7)		
Myoclonic seizures (n=13, 4)	-24.6 (-73.3 to 11462.4)	-27.9 (-60.9 to 130.2)		
Clonic seizures (n=6, 2)	-60.85 (-100 to 140.4)	-48.35 (-54.2 to -42.5)		
Tonic-atonic seizures (n=17, 4)	-35.2 (-100 to 1250.6)	-31.8 (-81.9 to -4)		
Primary generalized tonic-clonic seizures (n=7, 1)	-97.8 (-100 to 37.6)	-96.6 (-96.6 to -96.6)		
Other seizures (n=10, 3)	-90.65 (-100 to 183.8)	-100 (-100 to 54.0)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Incidence of Worsening of Seizures

End point title	Incidence of Worsening of Seizures
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End point description:

Worsening of seizures was summarized by the incidence of subjects with doubling in total seizure frequency, doubling in frequency of major seizures (generalized tonic-clonic, drop attacks), or occurrence of new seizure type during each successive 3 to 4 month visit interval of the Maintenance Period relative to baseline. Analysis was performed on the FAS for other efficacy variable included randomized subjects who received rufinamide or any other add-on AED of the investigator's choice and had a baseline efficacy assessment and at least 1 post baseline efficacy assessment.

End point type	Other pre-specified
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End point timeframe:

Baseline up to End of Treatment Period (up to approximately Week 106)

End point values	Rufinamide	Any Other Approved Antiepileptic Drug (AED)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	9		
Units: subjects				
number (not applicable)				
Doubling in total seizure frequency	4	1		
Doubling in frequency of major seizures	5	1		
Occurrence of a new seizure type	0	0		

Statistical analyses

Other pre-specified: Change From Baseline in CBCL Sub Scores at Week 106

End point title	Change From Baseline in CBCL Sub Scores at Week 106
End point description:	
CBCL:99-item questionnaire. Item rated on 3-point scale(0=Not True and 2=Very/Often True).99 items were combined to give scores for 8 problem area scales,1 for each 8 syndrome(emotionally reactive, anxious/depressed, somatic, withdrawn, sleep, attention, aggressive behavior, and other problems) were calculated, range:0(normal)to 16(clinical behavior) and 3 summary scores (internalizing, externalizing, total problems).3 summary scores reported scaled to T-scores. Total Problem score was sum of all problem areas +1 additional item, from 0 to 198. Total raw score converted to t-scores with mean of 50 and SD of 10. T-scores: standardized test scores that indicate same degree of elevation in problems relative to normative sample of peers. Higher scores=more problems. FAS: randomised subjects who received rufinamide/any other approved add-on AED of investigator's choice, had baseline efficacy and at least 1 postbaseline efficacy assessment. 'n': subjects evaluable at given time period.	
End point type	Other pre-specified
End point timeframe:	
Baseline and Week 106	

End point values	Rufinamide	Any Other Approved Antiepileptic Drug (AED)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	9		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline: Total emotional reactive scores (n=24,8)	59.0 (± 8.13)	60.9 (± 8.64)		
Week 106: Total emotional reactive scores (n=15,3)	-1.1 (± 9.30)	-1.3 (± 6.11)		
Baseline: Total anxious/depression scores (n=24,8)	56.4 (± 7.48)	54.6 (± 6.67)		
Week 106: Total anxious/depression scores (n=15,3)	0.5 (± 8.87)	0.7 (± 1.15)		
Baseline: Total somatic complaints scores (n=24,8)	59.4 (± 8.13)	54.9 (± 4.70)		
Week 106: Total somatic complaints scores (n=15,3)	0.1 (± 11.24)	-1.7 (± 2.89)		
Baseline: Total withdrawn scores (n=24,8)	71.5 (± 11.2)	72.1 (± 11.03)		
Week 106: Total withdrawn scores (n=15,3)	-2.2 (± 13.22)	-7.0 (± 9.54)		
Baseline: Total sleep problems scores (n=24,8)	57.8 (± 10.72)	62.4 (± 8.57)		
Week 106: Total sleep problem scores (n=15,3)	-1.9 (± 12.30)	-5.7 (± 7.57)		
Baseline: Total attention problems scores (n=24,8)	59.3 (± 9.17)	65.9 (± 10.72)		
Week 106: Total attention problems scores (n=15,3)	-1.1 (± 4.65)	-7.7 (± 2.52)		
Baseline: Total aggressive behavior scores(n=24,8)	52.5 (± 5.01)	58.6 (± 12.07)		
Week106: Total aggressive behavior scores (n=15,3)	3.2 (± 6.26)	-0.3 (± 2.89)		
Baseline: Total internalizing scores (n=24,8)	61.6 (± 10.78)	60.6 (± 9.71)		

Week 106: Total internalizing scores (n=15,3)	-1.5 (± 13.73)	-2.7 (± 1.53)		
Baseline: Total externalizing scores (n=24,8)	47.5 (± 11.22)	58.1 (± 15.92)		
Week 106: Total externalizing scores (n=15,3)	4.7 (± 10.07)	-3.7 (± 3.51)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Language Development Survey (LDS) Scores During Maintenance Period

End point title	Change From Baseline in Language Development Survey (LDS) Scores During Maintenance Period
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End point description:

LDS:caregiver-administered survey with 8-item questionnaire and vocabulary list of 310 words organized within 14 semantic categories. List had high frequency words, less common words, and lexical chunks. Average LDS score, calculated by dividing total number of words across all valid phrases by number of phrases with greater than(>)0words; for subjects with no words, average was 0. This value was compared to standardized chart to obtain percentile rating.LDS yield 2 scores: average phrase length (number of words/phrase) and number of endorsed vocabulary words.LDS phrase length, categorized into delay (less than or equal to[<=]20th percentile); no delay(>20th percentile). LDS vocabulary, categorized into delay(<=15th percentile);no delay(>15th percentile). Both raw scores were used to provide 2normative scores based on child's age in months. Higher score means better language development. Analysis was done on FAS for other efficacy variable."n":subjects evaluable at given time period.

End point type	Other pre-specified
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End point timeframe:

Baseline, Weeks 24, 56, 88, and 106

End point values	Rufinamide	Any Other Approved Antiepileptic Drug (AED)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	9		
Units: words				
arithmetic mean (standard deviation)				
Baseline: LDS average phrase length (n=24,9)	0.3 (± 0.87)	0 (± 0.00)		
Change at Week24:LDS average phrase length(n=23,8)	0.2 (± 1.11)	0.7 (± 1.28)		
Change at Week56:LDS average phrase length(n=21,7)	0.1 (± 1.02)	0.0 (± 0.00)		
Change at Week88:LDS average phrase length(n=18,4)	0.1 (± 1.03)	0.0 (± 0.00)		
Change atWeek106:LDS average phrase length(n=16,4)	0.4 (± 1.12)	0.0 (± 0.00)		
Baseline: LDS Vocabulary Score (n=24,9)	10.4 (± 37.72)	0.6 (± 1.67)		
Change at Week 24: LDS Vocabulary Score (n=23,8)	7.1 (± 21.55)	4.8 (± 8.22)		

Change at Week 56: LDS Vocabulary Score (n=21,7)	17.9 (± 39.24)	-0.40 (± 2.15)		
Change at Week 88: LDS Vocabulary Score (n=18,4)	25.4 (± 49.87)	0.0 (± 0.00)		
Change at Week 106: LDS Vocabulary Score (n=16,4)	39.6 (± 75.62)	1.0 (± 2.00)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Total Score of Quality of Life in Childhood Epilepsy (QoLCE) Scale

End point title	Change From Baseline in Total Score of Quality of Life in Childhood Epilepsy (QoLCE) Scale
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End point description:

QoLCE: 76-item questionnaire designed specifically to measure quality of life in children with epilepsy. QoLCE consists of 16 quality of life subscales (14 multi-item and 2 single item). Each subscale had number of items/questions with responses as excellent, very good, good, fair, and poor. They were changed to 1, 2, 3, 4, and 5 as per instructions. Then changed on scale of 100, where 1 is equal to (=) 0, 2=25, 3=50, 4=75, and 5=100. Items corresponding to each subscale were marked and their mean score was score of that subscale. Form was completed by parent or caregiver who interacted with the child on consistent, daily basis and took 20 to 30 minutes to complete. The higher the score, better the child's quality of life. FAS for other efficacy variable had randomized subjects who received rufinamide or any other add-on AED of investigator's choice and had baseline efficacy assessment and at least 1 postbaseline efficacy assessment. Here "n" were subjects evaluable at given time period.

End point type	Other pre-specified
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End point timeframe:

Baseline and Week 106

End point values	Rufinamide	Any Other Approved Antiepileptic Drug (AED)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	9		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline (n =24, 9)	50.4 (± 10.05)	49.6 (± 7.88)		
Change at Week 106 (n=15, 4)	-1.3 (± 8.49)	1.5 (± 1.00)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change From Baseline in Sub-scores in QoLCE

End point title	Change From Baseline in Sub-scores in QoLCE
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End point description:

The QoLCE was a 76-item questionnaire designed specifically to measure quality of life in children with

epilepsy. QOLCE consists of 16 quality of life subscales (14 multi-item and 2 single item). Each subscales had number of items or questions with responses as excellent, very good, good, fair, and poor. They were changed to 1, 2, 3, 4, and 5 as per instructions. Then changed on a scale of 100, where 1=0, 2=25, 3=50, 4=75, and 5=100. Items corresponding to each subscale were marked and there mean score was score of that subscale. The form was completed by a parent or caregiver who interacted with the child on a consistent, daily basis and took about 20 to 30 minutes to complete. The higher the score, the better the child's quality of life. FAS: randomized subjects who received rufinamide or any other add-on AED of the investigator's choice and had a baseline efficacy assessment and at least 1 postbaseline efficacy assessment. Here "n" were subjects evaluable at given time period.

End point type	Other pre-specified
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End point timeframe:

Baseline and Week 106

End point values	Rufinamide	Any Other Approved Antiepileptic Drug (AED)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	9		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline: Physical restriction (n=24,9)	50.1 (± 10.33)	49.9 (± 8.23)		
Change at Week 106: Physical restriction (n=15,4)	-1.0 (± 7.51)	-6.8 (± 7.32)		
Baseline: Energy/Fatigue (n=24,9)	51.6 (± 10.48)	44.3 (± 4.55)		
Change at Week 106: Energy/Fatigue (n=15,4)	-3.1 (± 12.22)	2.8 (± 4.11)		
Baseline: Attention/Concentration (n=24,9)	49.9 (± 10.14)	51.1 (± 9.05)		
Change at Week 106: Attention/Concentration (n=15,4)	-2.1 (± 7.31)	2.5 (± 6.24)		
Baseline: Memory (n=24,9)	50.2 (± 9.54)	52.6 (± 6.57)		
Change at Week 106: Memory (n=15,4)	-0.5 (± 12.18)	0.5 (± 1.00)		
Baseline: Language (n=24,9)	49.8 (± 10.42)	53.1 (± 4.43)		
Change at Week 106: Language (n=15,4)	-0.5 (± 9.63)	-0.5 (± 11.56)		
Baseline: Other cognitive (n=24,9)	48.6 (± 10.32)	53.1 (± 7.54)		
Change at Week 106: Other cognitive (n=15,4)	0.3 (± 6.19)	-1.0 (± 4.00)		
Baseline: Depression (n=24,9)	51.2 (± 9.27)	45.3 (± 10.59)		
Change at Week 106: Depression (n=15,4)	-2.6 (± 11.64)	2.3 (± 8.62)		
Baseline: Anxiety (n=24,9)	50.1 (± 10.27)	48.5 (± 12.29)		
Change at Week 106: Anxiety (n=15,4)	-0.1 (± 12.12)	1.3 (± 6.90)		
Baseline: Control/Helplessness (n=24,9)	50.7 (± 9.31)	47.8 (± 12.27)		
Change at Week 106: Control/Helplessness (n=15,4)	0.2 (± 10.90)	3.0 (± 11.52)		
Baseline: Self-esteem (n=24,9)	50.1 (± 10.18)	50.5 (± 10.98)		
Change at Week 106: Self-esteem (n=15,4)	-1.3 (± 9.48)	-6.0 (± 8.08)		
Baseline: Social interactions (n=24,9)	49.9 (± 10.56)	50.5 (± 8.48)		
Change at Week 106: Social interactions (n=15,4)	-1.5 (± 11.64)	4.0 (± 5.89)		
Baseline: Social activities (n=24,9)	50.5 (± 10.50)	46.6 (± 3.96)		

Change at Week 106: Social activities (n=15,4)	0.9 (± 11.30)	3.5 (± 3.70)		
Baseline: Stigma (n=24,9)	48.9 (± 11.06)	50.7 (± 8.07)		
Change at Week 106: Stigma (n=15,4)	-0.1 (± 12.67)	4.5 (± 10.25)		
Baseline: Behavior (n=24,9)	51.4 (± 10.39)	45.8 (± 9.33)		
Change at Week 106: Behavior (n=15,4)	0.2 (± 5.92)	7.3 (± 6.55)		
Baseline: General-health (n=24,9)	50.5 (± 10.02)	49.0 (± 8.40)		
Change at Week 106: General health (n=15,4)	-1.3 (± 10.98)	-2.0 (± 10.86)		
Baseline: Quality-of-life (n=24,9)	49.5 (± 9.71)	50.7 (± 9.98)		
Change at Week 106: Quality-of-life (n=15,4)	1.1 (± 9.46)	3.3 (± 12.28)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Visit 1 up to 30 days after the last study visit, or until resolution, whichever came first (up to approximately Week 106)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.0
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Reporting groups

Reporting group title	Rufinamide
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Reporting group description:

Subjects received rufinamide 10 milligram per kilogram per day (mg/kg/day), oral suspension, followed by 10 mg/kg/day increments every 3 days to 40 mg/kg/day, and then increased by 5mg/kg/day to the target maintenance level of 45 mg/kg/day (in 2 divided doses) from Week 0 (Baseline) to Week 1 in Titration Period, further followed by, rufinamide 45 mg/kg/day, oral suspension, from Week 2 to Week 106 in Maintenance Period. Rufinamide was administered as an add-on to the subject's existing regimen of 1-3 antiepileptic drugs (AEDs). During the Taper Period, only subjects who received rufinamide were discontinued gradually over a period of 2 weeks, as deemed necessary by the investigator.

Reporting group title	Any other approved antiepileptic drug (AED)
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Reporting group description:

Subjects received any other approved AED of the investigator's choice, dosed according to the investigator's usual practice, added to the subject's existing regimen of 1 to 3 AEDs.

Serious adverse events	Rufinamide	Any other approved antiepileptic drug (AED)	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 25 (40.00%)	5 / 12 (41.67%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Joint dislocation			
subjects affected / exposed	0 / 25 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Generalized tonic-clonic seizure			
subjects affected / exposed	1 / 25 (4.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			

subjects affected / exposed	0 / 25 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 25 (4.00%)	3 / 12 (25.00%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	2 / 25 (8.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Blindness			
subjects affected / exposed	1 / 25 (4.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration			
subjects affected / exposed	1 / 25 (4.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	2 / 25 (8.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 25 (4.00%)	0 / 12 (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			
Muscular weakness			

subjects affected / exposed	0 / 25 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis viral			
subjects affected / exposed	1 / 25 (4.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	1 / 25 (4.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia influenzal			
subjects affected / exposed	1 / 25 (4.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchiolitis			

subjects affected / exposed	1 / 25 (4.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 25 (4.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 25 (4.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 25 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Rufinamide	Any other approved antiepileptic drug (AED)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 25 (84.00%)	10 / 12 (83.33%)	
Investigations			
Blood bicarbonate decreased			
subjects affected / exposed	2 / 25 (8.00%)	1 / 12 (8.33%)	
occurrences (all)	2	1	
Weight decreased			
subjects affected / exposed	2 / 25 (8.00%)	0 / 12 (0.00%)	
occurrences (all)	3	0	
Injury, poisoning and procedural complications			
Lip injury			
subjects affected / exposed	0 / 25 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Post procedural complication			

subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 12 (8.33%) 1	
Postoperative fever subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 12 (8.33%) 1	
Procedural nausea subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 12 (8.33%) 1	
Procedural pain subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 12 (8.33%) 2	
Surgical and medical procedures Strabismus correction subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 12 (8.33%) 1	
Nervous system disorders Circadian rhythm sleep disorder subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 12 (8.33%) 1	
Cognitive disorder subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 12 (8.33%) 1	
Somnolence subjects affected / exposed occurrences (all)	5 / 25 (20.00%) 7	0 / 12 (0.00%) 0	
General disorders and administration site conditions Gait disturbance subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	1 / 12 (8.33%) 1	
Pyrexia subjects affected / exposed occurrences (all)	4 / 25 (16.00%) 6	3 / 12 (25.00%) 5	
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 3	1 / 12 (8.33%) 1	

Diarrhoea			
subjects affected / exposed	4 / 25 (16.00%)	3 / 12 (25.00%)	
occurrences (all)	4	5	
Nausea			
subjects affected / exposed	1 / 25 (4.00%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Vomiting			
subjects affected / exposed	7 / 25 (28.00%)	1 / 12 (8.33%)	
occurrences (all)	10	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 25 (16.00%)	2 / 12 (16.67%)	
occurrences (all)	6	2	
Lower respiratory tract congestion			
subjects affected / exposed	2 / 25 (8.00%)	0 / 12 (0.00%)	
occurrences (all)	4	0	
Nasal Congestion			
subjects affected / exposed	3 / 25 (12.00%)	0 / 12 (0.00%)	
occurrences (all)	4	0	
Respiratory tract congestion			
subjects affected / exposed	1 / 25 (4.00%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Rhinitis allergic			
subjects affected / exposed	2 / 25 (8.00%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Rhinorrhoea			
subjects affected / exposed	1 / 25 (4.00%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Stridor			
subjects affected / exposed	0 / 25 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Upper respiratory tract congestion			
subjects affected / exposed	0 / 25 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			

Dermatitis diaper subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	1 / 12 (8.33%) 1	
Rash subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 4	1 / 12 (8.33%) 2	
Psychiatric disorders Aggression subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 12 (8.33%) 1	
Irritability subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 3	1 / 12 (8.33%) 1	
Sleep disorder subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1	1 / 12 (8.33%) 1	
Infections and infestations Bronchiolitis subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	0 / 12 (0.00%) 0	
Bronchitis subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 6	0 / 12 (0.00%) 0	
Nasopharyngitis subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	1 / 12 (8.33%) 1	
Otitis media subjects affected / exposed occurrences (all)	4 / 25 (16.00%) 7	0 / 12 (0.00%) 0	
Pharyngitis streptococcal subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 12 (8.33%) 1	
Pneumonia subjects affected / exposed occurrences (all)	4 / 25 (16.00%) 6	0 / 12 (0.00%) 0	
Sinusitis			

subjects affected / exposed occurrences (all)	4 / 25 (16.00%) 4	1 / 12 (8.33%) 1	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	7 / 25 (28.00%) 16	4 / 12 (33.33%) 4	
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 12 (8.33%) 1	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 5	1 / 12 (8.33%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 October 2011	Following amendment changes were made: to satisfy health authority requests, added a minimum of 25% of rufinamide-treated subjects will be between 2 and 3 years of age and that every effort will be made to include a younger population (between 1 and 3 years of age); revised exclusion for prior use of rufinamide; added blood volume required; added instructions if screening visit is extended, added duplicate, consecutive electrocardiogram (ECGs) at Visit 2 and Visits 5, 6, and 7 for steady state and maximum observed concentration (C _{max}); baseline ECG prior to dosing and Visits 5, 6, and 7 approximately 4 to 6 hours after drug administration; changed qualified designated reader to central reader and additional clarification for screening ECG; added measurement of head circumference at baseline, Visits 8, 10, 13, and at Follow-up/Final Visit or early discontinuation.
03 April 2013	Reduced from 8 to 4 weeks the minimum required time on AEDs before randomization, and required that AED doses be documented; allowed historical seizure diaries to satisfy inclusion criteria in lieu of seizure diaries that would be compiled during the Screening Period, thus allowing the Screening Period to be shortened to expedite recruitment; changed criterion for interim analysis compilation to allow reporting of data within the time frame requested by regulators, even if fewer than 75 subjects have completed 6 months of treatment; added amylase and lipase samples to list of laboratory tests per United States Food and Drug Administration(FDA) request for subject safety.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported