



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	v1
This version publication date	16 June 2016
First version publication date	16 June 2016

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	100 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 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 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.
- 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	01 April 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)	25
Children (2-11 years)	12
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:

A total of 43 participants were consented and screened; 6 were screen failures (4 failed to meet inclusion or exclusion criteria, 1 withdrew consent, and 1 was excluded for other reasons) and 37 were randomized into the study (25 randomized to rufinamide and 12 to any other antiepileptic drug (AED)).

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:

During the Titration Period, rufinamide was administered at 10 mg/kg/day (administered in 2 equally divided doses) and increased at 10 mg/kg/day increments every 3 days to 40 mg/kg/day, then increased by 5 mg/kg/day to the target maintenance level of 45 mg/kg/day. In case of tolerability issues, the drug could be titrated more slowly or titrated to a lower dose at the investigator's discretion. Only participants on rufinamide participated in the Taper Period and only those that completed the Taper Period at the end of the study had a Final or Follow-up Visit. Participants that discontinued rufinamide early were tapered (if deemed necessary by the investigator) before starting add-on AED. Add-on AEDs were titrated according to the investigator's usual practice.

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 antiepileptic drugs (AEDs)
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Arm description:

Any approved AED of the investigator's choice, dosed according to the investigator's usual practice, added to the participant's existing regimen of 1 to 3 AEDs. Add-on AEDs were titrated 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 antiepileptic drugs (AEDs)
Started	25	12
Completed	15	4
Not completed	10	8
Consent withdrawn by subject	3	4
Participant choice	2	-
Adverse event, non-fatal	3	-
Not specified	-	1
Participant's choice	-	1
Inadequate therapeutic effect	2	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups

Reporting group title	Rufinamide
Reporting group description:	
During the Titration Period, rufinamide was administered at 10 mg/kg/day (administered in 2 equally divided doses) and increased at 10 mg/kg/day increments every 3 days to 40 mg/kg/day, then increased by 5 mg/kg/day to the target maintenance level of 45 mg/kg/day. In case of tolerability issues, the drug could be titrated more slowly or titrated to a lower dose at the investigator's discretion. Only participants on rufinamide participated in the Taper Period and only those that completed the Taper Period at the end of the study had a Final or Follow-up Visit. Participants that discontinued rufinamide early were tapered (if deemed necessary by the investigator) before starting add-on AED. Add-on AEDs were titrated according to the investigator's usual practice.	
Reporting group title	Any other antiepileptic drugs (AEDs)
Reporting group description:	
Any approved AED of the investigator's choice, dosed according to the investigator's usual practice, added to the participant's existing regimen of 1 to 3 AEDs. Add-on AEDs were titrated according to the investigator's usual practice.	

Reporting group values	Rufinamide	Any other antiepileptic drugs (AEDs)	Total
Number of subjects	25	12	37
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: months			
arithmetic mean	28.3	29.8	
standard deviation	± 9.99	± 9.83	-
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: During the Titration Period, rufinamide was administered at 10 mg/kg/day (administered in 2 equally divided doses) and increased at 10 mg/kg/day increments every 3 days to 40 mg/kg/day, then increased by 5 mg/kg/day to the target maintenance level of 45 mg/kg/day. In case of tolerability issues, the drug could be titrated more slowly or titrated to a lower dose at the investigator's discretion. Only participants on rufinamide participated in the Taper Period and only those that completed the Taper Period at the end of the study had a Final or Follow-up Visit. Participants that discontinued rufinamide early were tapered (if deemed necessary by the investigator) before starting add-on AED. Add-on AEDs were titrated according to the investigator's usual practice.	
Reporting group title	Any other antiepileptic drugs (AEDs)
Reporting group description: Any approved AED of the investigator's choice, dosed according to the investigator's usual practice, added to the participant's existing regimen of 1 to 3 AEDs. Add-on AEDs were titrated according to the investigator's usual practice.	

Primary: Child Behavior Checklist (CBCL) Total Problems T-Scores at the end of the 2-Year Treatment Period and Change from Baseline

End point title	Child Behavior Checklist (CBCL) Total Problems T-Scores at the end of the 2-Year Treatment Period and Change from Baseline
End point description: The CBCL is a 99-item survey completed by a parent/legal guardian or suitable caregiver (referred to as the rater) of the participant and provided T-scores for all problem area scales and the summary scores to identify behavioral problems or developmental delays. Items were rated using a 3-point scale (0=Not True, 1=Somewhat/Sometimes True, 2=Very True/ Often True) to indicate how often or typical the behavior was. The 99 items were combined to yield scores for 8 problem area scales (emotionally reactive, anxious/depressed, somatic complaints, withdrawn, sleep problems, attention problems, aggressive behavior, and other problems) and 3 summary scores (internalizing, externalizing, and total problems). The Total Problem score was the sum of all the problem areas plus 1 additional item. The T-scores were standardized test scores that indicate the same degree of elevation in problems on each of the scales relative to the normative sample of peers. High scores indicate more problems.	
End point type	Primary
End point timeframe: Baseline and End of Treatment Period (Week 106)	

End point values	Rufinamide	Any other antiepileptic drugs (AEDs)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24 ^[1]	9 ^[2]		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Total T-Score	55.7 (± 15.81)	54.8 (± 4.5)		
Change from baseline T-Score	-0.3 (± 15.72)	-6.7 (± 0.58)		

Notes:

[1] - n = 15

[2] - n = 4, 3

Statistical analyses

Statistical analysis title	CBCL Total Problems Score
Statistical analysis description:	
The primary statistical model for comparing the 2 treatment groups was ANCOVA mixed model for repeated measures with baseline score, age, and sex as covariates, and treatment, week, and treatment by week interaction as factors. Statistical analysis for the Actual and Change from Baseline (Week 0) data presented for the primary efficacy endpoint was not calculated.	
Comparison groups	Rufinamide v Any other antiepileptic drugs (AEDs)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6928 ^[3]
Method	ANCOVA

Notes:

[3] - P-value is based on ANCOVA Least Square (LE) mean analysis for Week 106 of the study. LS mean (SE): Rufinamide = 56.346 (2.720) and Any other AED = 53.746 (5.953).

Other pre-specified: Shift from Baseline to Week 106 in Child Behavior Checklist (CBCL) Subscores

End point title	Shift from Baseline to Week 106 in Child Behavior Checklist (CBCL) Subscores
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End point description:

The CBCL 1.5 – 5 is a 99-item survey designed to record the problem behaviors of preschoolers. Each item describes a specific behavior and the rater (parent or caretaker) is asked to rate its frequency on a three-point Likert scale ((0=Not True, 1=Somewhat/Sometimes True, 2=Very True/ Often True) to indicate how often or typical the behavior was. The scoring gives a summary profile of 8 problem area scales (emotionally reactive, anxious/depressed, somatic complaints, withdrawn, sleep problems, attention problems, aggressive behavior, and other problems) and 3 summary scores (internalizing, externalizing, and total problems). A T-score of 63 and above for summary scales and of 70 and above for syndrome and DSM-oriented scales, are generally considered clinically significant; values between 60 and 63 for summary scales or between 65 and 70 for syndrome and DSM-oriented scales, identify the borderline clinical range; values under 60 or under 65 are considered not-clinical.

End point type	Other pre-specified
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End point timeframe:

Baseline to End of Treatment Period (Week 106)

End point values	Rufinamide	Any other antiepileptic drugs (AEDs)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	9		
Units: Percentage of participants				
number (not applicable)				
Total emotional reactive scores (n = 15, 3)	100	100		
Total anxious/depression scores (n = 15, 3)	100	100		
Total withdrawn scores (n = 15, 3)	100	100		
Total sleep problem scores (n = 15, 3)	100	100		
Total attention problems scores (n = 15, 3)	100	100		
Total aggressive behavior scores (n = 15, 3)	100	100		
Total internalizing scores (n = 15, 3)	100	100		

Total externalizing scores (n = 15, 3)	100	100		
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Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percent Change in Seizure Frequency by Individual Seizure Type per 28 Days Relative to Baseline

End point title	Percent Change in Seizure Frequency by Individual Seizure Type per 28 Days Relative to Baseline
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End point description:

The frequency per 28 days was defined as (S/D)*28 where, S is equal to the sum of the seizures reported in the Participant Diary during the specified time interval and D is equal to the number of days with non-missing data in the Participant Seizure diary for the specified study phase. The number of seizures was assessed and recorded by the participant's parent(s)/caregiver(s) in the participant seizure diary. The participant's parent(s)/caregiver(s) were trained by the investigator in how to recognize, classify, and complete the diary. The multiple cohorts of participants included participants treated with rufinamide or other AED for at least 1, 2, 4, 6, 10, 14, 18, 22, and 26.5 months.

End point type	Other pre-specified
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End point timeframe:

Baseline to End of Treatment Period (Week 106)

End point values	Rufinamide	Any other antiepileptic drugs (AEDs)		
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)		

Statistical analyses

Statistical analysis title	Partial seizures
Statistical analysis description: The median difference and the 95% confidence interval were based on the Hodges-Lehmann method.	
Comparison groups	Any other antiepileptic drugs (AEDs) v Rufinamide
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9011
Method	Wilcoxon sum rank test
Parameter estimate	Median difference (final values)
Point estimate	-19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-52380
upper limit	82.8

Statistical analysis title	Absence seizures
Statistical analysis description: The median difference and the 95% confidence interval were based on the Hodges-Lehmann method.	
Comparison groups	Any other antiepileptic drugs (AEDs) v Rufinamide
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7427
Method	Wilcoxon rank sum test
Parameter estimate	Median difference (final values)
Point estimate	-23.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-75.3
upper limit	1822.5

Statistical analysis title	Atypical absence seizures
Statistical analysis description: The median difference and the 95% confidence interval were based on the Hodges-Lehmann method.	
Comparison groups	Any other antiepileptic drugs (AEDs) v Rufinamide
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.367
Method	Wilcoxon rank sum test
Parameter estimate	Median difference (final values)
Point estimate	50.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-139.2
upper limit	1190.5

Statistical analysis title	Myoclonic seizures
Statistical analysis description: The median difference and the 95% confidence interval were based on the Hodges-Lehmann method.	
Comparison groups	Any other antiepileptic drugs (AEDs) v Rufinamide
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9563
Method	Wilcoxon rank sum test
Parameter estimate	Median difference (final values)
Point estimate	4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-93.8
upper limit	146

Statistical analysis title	Clonic seizures
Statistical analysis description: The median difference and the 95% confidence interval were based on the Hodges-Lehmann method.	
Comparison groups	Any other antiepileptic drugs (AEDs) v Rufinamide
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Wilcoxon rank sum test
Parameter estimate	Median difference (final values)
Point estimate	12.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-194.6
upper limit	57.5

Statistical analysis title	Tonic-Atonic Seizures
Statistical analysis description: The median difference and the 95% confidence interval were based on the Hodges-Lehmann method.	
Comparison groups	Any other antiepileptic drugs (AEDs) v Rufinamide

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7524
Method	Wilcoxon rank sum test
Parameter estimate	Median difference (final values)
Point estimate	4.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-57.3
upper limit	56.1

Statistical analysis title	Primary generalized tonic clonic seizures
Statistical analysis description: The median difference and the 95% confidence interval were based on the Hodges-Lehmann method.	
Comparison groups	Any other antiepileptic drugs (AEDs) v Rufinamide
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Wilcoxon rank sum test
Parameter estimate	Median difference (final values)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-134.2
upper limit	3.4

Statistical analysis title	Other seizures
Statistical analysis description: The median difference and the 95% confidence interval were based on the Hodges-Lehmann method.	
Comparison groups	Any other antiepileptic drugs (AEDs) v Rufinamide
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4266
Method	Wilcoxon rank sum test
Parameter estimate	Median difference (final values)
Point estimate	-2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-237.8
upper limit	46

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

End point title	Overall 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 is equal to the sum of the seizures reported in the Participant Diary during the specified time interval and D is equal to the number of days with non-missing data in the Participant Seizure diary for the specified study phase. The number of seizures was assessed and recorded by the participant's parent(s)/caregiver(s) in the participant seizure diary. The participant's parent(s)/caregiver(s) were trained by the investigator in how to recognize, classify, and complete the diary. The multiple cohorts of participants included participants treated with rufinamide or other AED for at least 1, 2, 4, 6, 10, 14, 18, 22, and 26.5 months.

End point type	Other pre-specified
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End point timeframe:

Baseline to End of the Treatment Period (Week 106)

End point values	Rufinamide	Any other antiepileptic drugs (AEDs)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	9		
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: Incidence of Worsening of Seizures Any Time

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

Worsening of seizures was defined as the doubling in total seizure frequency or 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. Cohorts included participants treated with rufinamide or other-AED for at least 1, 2, 4, 6, 10, 14, 18, 22, and 26.5 months. The number of seizures was assessed and recorded by the participant's parent(s)/caregiver(s) in the participant seizure diary. The participant's parent(s)/caregiver(s) were trained by the investigator in how to recognize, classify, and complete the diary. Sample sizes were small so these results should be interpreted with caution.

End point type	Other pre-specified
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End point timeframe:

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

End point values	Rufinamide	Any other antiepileptic drugs (AEDs)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	9		
Units: Percentage of participants				
number (not applicable)				
Doubling in total seizure frequency	16.7	11.1		
Doubling in frequency of major seizures	20.8	11.1		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean Change From Baseline in Language Development Survey (LDS) Average Phrase Length Score During the Maintenance Period

End point title	Mean Change From Baseline in Language Development Survey (LDS) Average Phrase Length Score During the Maintenance Period
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End point description:

The LDS was a parent-administered survey that measured a child's expressive vocabulary and beginning word combinations. It included 310 words organized within 14 semantic categories (e.g., toys, body parts, food, animals, people). The list contained high frequency words (e.g., "more"), less common words (e.g., "hamburger"), and lexical chunks (e.g., "all gone", "night, night", "Sesame Street"). The parent was asked to indicate words on the list that the child spontaneously produced but were also allowed to add additional words spoken by the child. The average LDS score was calculated by dividing the total number of words across all valid phrases by the number of phrases with greater than 0 words; for participants with no words, the average is 0. This value is compared to a standardized chart to obtain a percentile rating. Greater than 20th percentile suggests no delayed phrase development while less than or equal to 20th percentile suggests delayed phrase development.

End point type	Other pre-specified
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End point timeframe:

Baseline to Week 24, Baseline to Week 56, Baseline to Week 88, and Baseline to Week 106 (End of the Treatment Period)

End point values	Rufinamide	Any other antiepileptic drugs (AEDs)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	9		
Units: Average phrase length				
arithmetic mean (standard deviation)				
Week 24 (n = 23, 8)	0.2 (± 1.11)	0.7 (± 1.28)		
Week 56 (n= 21, 7)	0.1 (± 1.02)	0 (± 0)		
Week 88 (n = 18, 4)	0.1 (± 1.03)	0 (± 0)		
Week 106 (n = 16, 4)	0.4 (± 1.12)	0 (± 0)		

Statistical analyses

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

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

The LDS was a parent-administered survey that measured a child's expressive vocabulary and beginning word combinations. It included 310 words organized within 14 semantic categories (e.g., toys, body parts, food, animals, people). The list contained high frequency words (e.g., "more"), less common words (e.g., "hamburger"), and lexical chunks (e.g., "all gone", "night, night", "Sesame Street"). The parent was asked to indicate words on the list that the child spontaneously produced but were also allowed to add additional words spoken by the child. The LDS vocabulary score was calculated by counting the number of vocabulary words endorsed (including non-English words and words added by the respondent) up to a maximum of 315 words. This value was compared to a standardized chart to obtain a percentile rating. The LDS vocabulary score can be categorized into delayed vocabulary development (≤ 15 th percentile) or no delayed vocabulary development (> 15 th percentile).

End point type	Other pre-specified
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End point timeframe:

Baseline to Week 24, Baseline to Week 56, Baseline to Week 88, and Baseline to Week 106 (End of the Treatment Period)

End point values	Rufinamide	Any other antiepileptic drugs (AEDs)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	9		
Units: Number of words				
arithmetic mean (standard deviation)				
Week 24 (n = 23, 8)	7.1 (\pm 21.55)	4.8 (\pm 8.22)		
Week 56 (n = 21, 7)	17.9 (\pm 39.24)	-0.4 (\pm 2.15)		
Week 88 (n = 18, 4)	25.4 (\pm 49.87)	0 (\pm 0)		
Week 106 (n = 16, 4)	39.6 (\pm 75.62)	1 (\pm 2)		

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:

The QoLCE was a 76-item questionnaire designed specifically to measure quality of life in children with epilepsy. It contained 16 subscales covering seven domains of life function: physical activities, social activities, cognition, emotional well-being, behavior, general health, and general quality of life. 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 items were combined into 13 scales and 3 of the items were used to represent an overall score in 3 separate areas. The full score was 100. The higher the score, the better the child's quality of life.

End point type	Other pre-specified
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End point timeframe:

Baseline to the End of the Treatment Period

End point values	Rufinamide	Any other antiepileptic drugs (AEDs)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	9		
Units: Scores on a scale				
arithmetic mean (standard deviation)	-0.3 (± 7.87)	1.4 (± 1.81)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean Change from Baseline in Sub-scores in Quality of Life In Childhood Epilepsy (QoLCE) at End of Treatment Period

End point title	Mean Change from Baseline in Sub-scores in Quality of Life In Childhood Epilepsy (QoLCE) at End of Treatment Period
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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. It contained 16 subscales covering seven domains of life function: Physical activities, social activities, cognition, emotional well-being, behavior, general health, and general quality of life. 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 items were combined into 13 scales and 3 of the items were used to represent an overall score in 3 separate areas. The full score was 100. The higher the score, the better the child's quality of life.

End point type	Other pre-specified
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End point timeframe:

Baseline to End of Treatment Period (Week 106)

End point values	Rufinamide	Any other antiepileptic drugs (AEDs)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	9		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Physical restriction	-0.3 (± 7.82)	-2.8 (± 8)		
Energy/Fatigue	-3 (± 11.29)	1.4 (± 3.17)		
Attention/Concentration	-0.5 (± 10.97)	0.4 (± 5.46)		
Memory	-0.9 (± 10.46)	0.4 (± 0.88)		
Language	0.8 (± 10.11)	-0.4 (± 7.16)		
Other cognitive	0.8 (± 8.34)	0.1 (± 4.62)		
Depression	-1.1 (± 10.34)	1.6 (± 5.8)		
Anxiety	0.1 (± 10.75)	-0.2 (± 12.17)		
Control/Helplessness	0.9 (± 10.1)	3.3 (± 8.61)		

Self-esteem	-0.1 (± 9.86)	0.6 (± 9.06)		
Social interactions	-0.7 (± 10.26)	2.9 (± 5.18)		
Social activities	-0.2 (± 11.07)	6.2 (± 6.85)		
Stigma	1.1 (± 11.77)	2.2 (± 7.1)		
Behavior	0.5 (± 5.9)	1.6 (± 7.67)		
General health	0.8 (± 9.92)	-3.7 (± 9.6)		
Quality-of-life	2.6 (± 9.24)	-0.4 (± 11.93)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Overall Survival-Time to Withdrawal from Rufinamide or Other Antiepileptic Drug (AED) (Excluding Taper)

End point title	Overall Survival-Time to Withdrawal from Rufinamide or Other Antiepileptic Drug (AED) (Excluding Taper)
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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. Kaplan-Meier estimation was used to determine the overall survival time (in weeks) to withdrawal from treatment (excluding taper) due to an adverse event or lack efficacy. The 95% confidence interval was not calculated for these data points, therefore we added 99999.0 and -9999.0 as space-fillers.

End point type	Other pre-specified
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End point timeframe:

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

End point values	Rufinamide	Any other antiepileptic drugs (AEDs)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	9		
Units: Weeks				
median (confidence interval 95%)	142 (-9999 to 99999)	28 (17.7 to 99999)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were collected from Visit 1 through 30 days after the last study visit, or until resolution, whichever came first. All serious AEs were followed to resolution, or stabilization if resolution was unlikely. Approximately 108 weeks.

Adverse event reporting additional description:

Only treatment-emergent AEs (TEAEs) and serious TEAEs were reported. TEAEs were defined as an AE that had an onset date, or a worsening in severity from baseline (pretreatment), on or after the first dose of study drug and up to 7 days following study drug discontinuation. AEs were graded on a 3-point scale (mild, moderate, severe).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Rufinamide
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Reporting group description:

During the Titration Period, rufinamide was administered at 10 mg/kg/day (administered in 2 equally divided doses) and increased at 10 mg/kg/day increments every 3 days to 40 mg/kg/day, then increased by 5 mg/kg/day to the target maintenance level of 45 mg/kg/day. In case of tolerability issues, the drug could be titrated more slowly or titrated to a lower dose at the investigator's discretion. Only participants on rufinamide participated in the Taper Period and only those that completed the Taper Period at the end of the study had a Final or Follow-up Visit. Participants that discontinued rufinamide early were tapered (if deemed necessary by the investigator) before starting add-on AED. Add-on AEDs were titrated according to the investigator's usual practice.

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

Any approved AED of the investigator's choice, dosed according to the investigator's usual practice, added to the participant's existing regimen of 1 to 3 AEDs. Add-on AEDs were titrated according to the investigator's usual practice.

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

subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	1 / 12 (8.33%) 2	
Skin and subcutaneous tissue disorders			
Dermatitis Diaper			
subjects affected / exposed	1 / 25 (4.00%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Rash			
subjects affected / exposed	2 / 25 (8.00%)	1 / 12 (8.33%)	
occurrences (all)	4	2	
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 25 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Irritability			
subjects affected / exposed	3 / 25 (12.00%)	1 / 12 (8.33%)	
occurrences (all)	3	1	
Sleep Disorder			
subjects affected / exposed	1 / 25 (4.00%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	2 / 25 (8.00%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Bronchitis			
subjects affected / exposed	3 / 25 (12.00%)	0 / 12 (0.00%)	
occurrences (all)	6	0	
Nasopharyngitis			
subjects affected / exposed	2 / 25 (8.00%)	1 / 12 (8.33%)	
occurrences (all)	2	1	
Otitis Media			
subjects affected / exposed	4 / 25 (16.00%)	0 / 12 (0.00%)	
occurrences (all)	7	0	
Pharyngitis Streptococcal			
subjects affected / exposed	0 / 25 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	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
24 November 2010	<ul style="list-style-type: none">• 21 Mar 2011, v2.0 (revision): corrected EudraCT number from 2010-23505-36 to 2010-023505-36• 13 Apr 2011, v3.0 (revision): typographical errors for section references corrected• 26 Oct 2011, v4.0 (Amendment 01): 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 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 patients have completed 6 months of treatment; added amylase and lipase samples to list of laboratory tests per FDA request for subject safety.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported