Clinical trial results:
An Open-Label, Flexible-Dose Study of Retigabine Immediate Release (IR) as Adjunctive Therapy to Specified Monotherapy Antiepileptic Treatments in Adults with Partial-Onset Seizures.

Summary

EudraCT number	2009-017744-14
Trial protocol	NL DE ES FR BE DK IT BG PL
Global end of trial date	04 December 2012

Results information

Result version number	v1 (current)
This version publication date	28 December 2016
First version publication date	28 December 2016

Trial information

Trial identification

Sponsor protocol code	113905

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 March 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 December 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of retigabine immediate release (IR) as adjunctive therapy to each of the following specified monotherapy AED treatments: carbamazepine/ oxcarbazepine, lamotrigine, levetiracetam or valproic acid in subjects with partial-onset seizures (POS) using a flexible dosing regimen.

Protection of trial subjects:

Not Applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 July 2010
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	Belgium: 1
Country: Number of subjects enrolled	Bulgaria: 39
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Germany: 15
Country: Number of subjects enrolled	Italy: 29
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	Russian Federation: 67
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Thailand: 13
Country: Number of subjects enrolled	Ukraine: 23
Worldwide total number of subjects	203
EEA total number of subjects	100

Notes:

Subjects enrolled per age group

In utero	0

Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	191
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study 113905 was an open-label, multi-center, multi-country study of retigabine using a flexible dosing regimen in adult participants (par.) (>=18 years old) with partial-onset seizures. Since this was an open-label study, hypothesis testing was not performed. The focus of the analysis was on descriptive statistics.

Pre-assignment

Screening details:

Eligible par. must have been taking one of the following antiepileptic drug treatments: carbamazepine/oxcarbazepine, lamotrigine, levetiracetam, or valproic acid and required to have had at least 4 partial seizures during the 8-wk BL Phase and must have been receiving a stable dose of 1 of the prespecified monotherapy antiepileptic drug treatments.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	RTG flexible dose plus C/O

Arm description:

Along with concurrent carbamazepine/oxcarbazepine (C/O), participants initiated treatment with retigabine (RTG) immediate release (IR) at 150 milligrams per day (mg/day) (50 mg thrice a day [TID]) and titrated to 600 mg/day (200 mg/day TID) over a 4-week Titration Phase. This was followed by a 16-week Flexible Dose Evaluation Phase, during which the dose could be increased or decreased on a weekly basis between 50 and 150 mg/day, depending on efficacy and tolerability, with the total dose staying between 300 and 1200 mg/day. Participants who were unable to tolerate a minimum dose of 300 mg/day were discontinued from the study.

Arm type	Experimental
Investigational medicinal product name	GW582892 (Retigabine IR) 50 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

GW582892 50 mg tablets were administered orally to maintain dosage between 300 to 1200 mg/day

Investigational medicinal product name	GW582892 (Retigabine IR) 100 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

GW582892 100 mg tablets were administered orally to maintain dosage between 300 to 1200 mg/day

Investigational medicinal product name	GW582892 (Retigabine IR) 200 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

GW582892 200 mg tablets were administered orally to maintain dosage between 300 to 1200 mg/day

Investigational medicinal product name	GW582892 (Retigabine IR) 300 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

GW582892 300 mg tablets were administered orally to maintain dosage between 300 to 1200 mg/day

Investigational medicinal product name	GW582892 (Retigabine IR) 400 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

GW582892 400 mg tablets were administered orally to maintain dosage between 300 to 1200 mg/day

Arm title	RTG flexible dose plus lamotrigine

Arm description:

Along with concurrent lamotrigine, participants initiated treatment with RTG IR at 150 mg/day (50 mg TID) and titrated to 600 mg/day (200 mg/day TID) over a 4-week Titration Phase. This was followed by a 16-week Flexible Dose Evaluation Phase, during which the dose could be increased or decreased on a weekly basis between 50 and 150 mg/day, depending on efficacy and tolerability, with the total dose staying between 300 and 1200 mg/day. Participants who were unable to tolerate a minimum dose of 300 mg/day were discontinued from the study.

Arm type	Experimental
Investigational medicinal product name	GW582892 (Retigabine IR) 50 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

GW582892 50 mg tablets were administered orally to maintain dosage between 300 to 1200 mg/day

Investigational medicinal product name	GW582892 (Retigabine IR) 100 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

GW582892 100 mg tablets were administered orally to maintain dosage between 300 to 1200 mg/day

Investigational medicinal product name	GW582892 (Retigabine IR) 200 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

GW582892 200 mg tablets were administered orally to maintain dosage between 300 to 1200 mg/day

Investigational medicinal product name	GW582892 (Retigabine IR) 300 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

GW582892 300 mg tablets were administered orally to maintain dosage between 300 to 1200 mg/day

Investigational medicinal product name	GW582892 (Retigabine IR) 400 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

GW582892 400 mg tablets were administered orally to maintain dosage between 300 to 1200 mg/day

Arm title	RTG flexible dose plus levetiracetam

Arm description:

Along with concurrent leveteracetam, participants initiated treatment with RTG IR at 150 mg/day (50 mg TID) and titrated to 600 mg/day (200 mg/day TID) over a 4-week Titration Phase. This was followed by a 16-week Flexible Dose Evaluation Phase, during which the dose could be increased or decreased on a weekly basis between 50 and 150 mg/day, depending on efficacy and tolerability, with the total dose staying between 300 and 1200 mg/day. Participants who were unable to tolerate a minimum dose of 300 mg/day were discontinued from the study.

Arm type	Experimental
Investigational medicinal product name	GW582892 (Retigabine IR) 50 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

GW582892 50 mg tablets were administered orally to maintain dosage between 300 to 1200 mg/day

Investigational medicinal product name	GW582892 (Retigabine IR) 100 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

GW582892 100 mg tablets were administered orally to maintain dosage between 300 to 1200 mg/day

Investigational medicinal product name	GW582892 (Retigabine IR) 200 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

GW582892 200 mg tablets were administered orally to maintain dosage between 300 to 1200 mg/day

Investigational medicinal product name	GW582892 (Retigabine IR) 300 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

GW582892 300 mg tablets were administered orally to maintain dosage between 300 to 1200 mg/day

Investigational medicinal product name	GW582892 (Retigabine IR) 400 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

GW582892 400 mg tablets were administered orally to maintain dosage between 300 to 1200 mg/day

Arm title	RTG flexible dose plus valproic acid

Arm description:

Along with concurrent valproic acid, participants initiated treatment with RTG IR at 150 mg/day (50 mg TID) and titrated to 600 mg/day (200 mg/day TID) over a 4-week Titration Phase. This was followed by a 16-week Flexible Dose Evaluation Phase, during which the dose could be increased or decreased on a weekly basis between 50 and 150 mg/day, depending on efficacy and tolerability, with the total dose staying between 300 and 1200 mg/day. Participants who were unable to tolerate a minimum dose of 300 mg/day were discontinued from the study.

Arm type	Experimental
Investigational medicinal product name	GW582892 (Retigabine IR) 50 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

GW582892 50 mg tablets were administered orally to maintain dosage between 300 to 1200 mg/day

Investigational medicinal product name	GW582892 (Retigabine IR) 100 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

GW582892 100 mg tablets were administered orally to maintain dosage between 300 to 1200 mg/day

Investigational medicinal product name	GW582892 (Retigabine IR) 200 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

GW582892 200 mg tablets were administered orally to maintain dosage between 300 to 1200 mg/day

Investigational medicinal product name	GW582892 (Retigabine IR) 300 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

GW582892 300 mg tablets were administered orally to maintain dosage between 300 to 1200 mg/day

Investigational medicinal product name	GW582892 (Retigabine IR) 400 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

GW582892 400 mg tablets were administered orally to maintain dosage between 300 to 1200 mg/day

Number of subjects in period 1	RTG flexible dose plus C/O	RTG flexible dose plus lamotrigine	RTG flexible dose plus levetiracetam
Started	56	51	44
Completed	38	38	25
Not completed	18	13	19
Consent withdrawn by subject	4	2	4
Physician decision	-	1	1
Adverse event, non-fatal	12	8	11
Lost to follow-up	-	-	1
Lack of efficacy	1	2	2
Protocol deviation	1	-	-

Number of subjects in period 1	RTG flexible dose plus valproic acid
Started	52
Completed	42
Not completed	10
Consent withdrawn by subject	3
Physician decision	-
Adverse event, non-fatal	4
Lost to follow-up	2
Lack of efficacy	1
Protocol deviation	-

Baseline characteristics

Reporting groups	
Reporting group title	RTG flexible dose plus C/O
Reporting group description:	
Along with concurrent carbamazepine/oxcarbazepine (C/O), participants initiated treatment with retigabine (RTG) immediate release (IR) at 150 milligrams per day (mg/day) (50 mg thrice a day [TID]) and titrated to 600 mg/day (200 mg/day TID) over a 4-week Titration Phase. This was followed by a 16-week Flexible Dose Evaluation Phase, during which the dose could be increased or decreased on a weekly basis between 50 and 150 mg/day, depending on efficacy and tolerability, with the total dose staying between 300 and 1200 mg/day. Participants who were unable to tolerate a minimum dose of 300 mg/day were discontinued from the study.	
Reporting group title	RTG flexible dose plus lamotrigine
Reporting group description:	
Along with concurrent lamotrigine, participants initiated treatment with RTG IR at 150 mg/day (50 mg TID) and titrated to 600 mg/day (200 mg/day TID) over a 4-week Titration Phase. This was followed by a 16-week Flexible Dose Evaluation Phase, during which the dose could be increased or decreased on a weekly basis between 50 and 150 mg/day, depending on efficacy and tolerability, with the total dose staying between 300 and 1200 mg/day. Participants who were unable to tolerate a minimum dose of 300 mg/day were discontinued from the study.	
Reporting group title	RTG flexible dose plus levetiracetam
Reporting group description:	
Along with concurrent leveteracetam, participants initiated treatment with RTG IR at 150 mg/day (50 mg TID) and titrated to 600 mg/day (200 mg/day TID) over a 4-week Titration Phase. This was followed by a 16-week Flexible Dose Evaluation Phase, during which the dose could be increased or decreased on a weekly basis between 50 and 150 mg/day, depending on efficacy and tolerability, with the total dose staying between 300 and 1200 mg/day. Participants who were unable to tolerate a minimum dose of 300 mg/day were discontinued from the study.	
Reporting group title	RTG flexible dose plus valproic acid
Reporting group description:	
Along with concurrent valproic acid, participants initiated treatment with RTG IR at 150 mg/day (50 mg TID) and titrated to 600 mg/day (200 mg/day TID) over a 4-week Titration Phase. This was followed by a 16-week Flexible Dose Evaluation Phase, during which the dose could be increased or decreased on a weekly basis between 50 and 150 mg/day, depending on efficacy and tolerability, with the total dose staying between 300 and 1200 mg/day. Participants who were unable to tolerate a minimum dose of 300 mg/day were discontinued from the study.	

Reporting group values	RTG flexible dose plus C/O	RTG flexible dose plus lamotrigine	RTG flexible dose plus levetiracetam
Number of subjects	56	51	44
Age categorical Units: Subjects			
Age continuous			
Baseline (BL) data were collected in members of the Safety Population (Pop), comprised of those participants (par.) who took at least one dose of RTG.			
Units: years			
arithmetic mean	40.6	38.2	37
standard deviation	± 14.99	± 11.91	± 14.94
Gender categorical			
Baseline data were collected in members of the Safety Population, comprised of those participants who took at least one dose of RTG.			
Units: Subjects			
Female	33	26	25
Male	23	25	19

Race/Ethnicity, Customized			
Baseline data were collected in members of the Safety Population, comprised of those participants who took at least one dose of RTG.			
Units: Subjects			
Asian - Central/South Asian Heritage	1	1	0
Asian - South East Asian Heritage	0	5	5
White - White/Caucasian/European	55	45	39

Reporting group values	RTG flexible dose plus valproic acid	Total	
Number of subjects	52	203	
Age categorical			
Units: Subjects			

Age continuous			
Baseline (BL) data were collected in members of the Safety Population (Pop), comprised of those participants (par.) who took at least one dose of RTG.			
Units: years			
arithmetic mean	40.3		
standard deviation	± 14.05	-	
Gender categorical			
Baseline data were collected in members of the Safety Population, comprised of those participants who took at least one dose of RTG.			
Units: Subjects			
Female	26	110	
Male	26	93	
Race/Ethnicity, Customized			
Baseline data were collected in members of the Safety Population, comprised of those participants who took at least one dose of RTG.			
Units: Subjects			
Asian - Central/South Asian Heritage	0	2	
Asian - South East Asian Heritage	3	13	
White - White/Caucasian/European	49	188	

End points

End points reporting groups

Reporting group title	RTG flexible dose plus C/O

Reporting group description:

Along with concurrent carbamazepine/oxcarbazepine (C/O), participants initiated treatment with retigabine (RTG) immediate release (IR) at 150 milligrams per day (mg/day) (50 mg thrice a day [TID]) and titrated to 600 mg/day (200 mg/day TID) over a 4-week Titration Phase. This was followed by a 16-week Flexible Dose Evaluation Phase, during which the dose could be increased or decreased on a weekly basis between 50 and 150 mg/day, depending on efficacy and tolerability, with the total dose staying between 300 and 1200 mg/day. Participants who were unable to tolerate a minimum dose of 300 mg/day were discontinued from the study.

Reporting group title	RTG flexible dose plus lamotrigine

Reporting group description:

Along with concurrent lamotrigine, participants initiated treatment with RTG IR at 150 mg/day (50 mg TID) and titrated to 600 mg/day (200 mg/day TID) over a 4-week Titration Phase. This was followed by a 16-week Flexible Dose Evaluation Phase, during which the dose could be increased or decreased on a weekly basis between 50 and 150 mg/day, depending on efficacy and tolerability, with the total dose staying between 300 and 1200 mg/day. Participants who were unable to tolerate a minimum dose of 300 mg/day were discontinued from the study.

Reporting group title	RTG flexible dose plus levetiracetam

Reporting group description:

Along with concurrent leveteracetam, participants initiated treatment with RTG IR at 150 mg/day (50 mg TID) and titrated to 600 mg/day (200 mg/day TID) over a 4-week Titration Phase. This was followed by a 16-week Flexible Dose Evaluation Phase, during which the dose could be increased or decreased on a weekly basis between 50 and 150 mg/day, depending on efficacy and tolerability, with the total dose staying between 300 and 1200 mg/day. Participants who were unable to tolerate a minimum dose of 300 mg/day were discontinued from the study.

Reporting group title	RTG flexible dose plus valproic acid

Reporting group description:

Along with concurrent valproic acid, participants initiated treatment with RTG IR at 150 mg/day (50 mg TID) and titrated to 600 mg/day (200 mg/day TID) over a 4-week Titration Phase. This was followed by a 16-week Flexible Dose Evaluation Phase, during which the dose could be increased or decreased on a weekly basis between 50 and 150 mg/day, depending on efficacy and tolerability, with the total dose staying between 300 and 1200 mg/day. Participants who were unable to tolerate a minimum dose of 300 mg/day were discontinued from the study.

Primary: Number of participants with a >=50% reduction in partial-onset seizure (POS) frequency from Baseline

End point title	Number of participants with a >=50% reduction in partial-onset seizure (POS) frequency from Baseline[1]

End point description:

The number of participants experiencing a >=50% reduction from Baseline (BL) in POS frequency during the Treatment Phase (TP) (i.e., Titration Phase and Flexible Dose Evaluation [FDE] Phase) was measured. A POS has its onset in a limited area on one side of the brain. POSs may remain limited or may spread to involve both sides of the brain. For both the Baseline Phase and the TP, seizure frequency was calculated as a 28-day rate using the following formula: 28 x {[(number of countable partial seizures in Phase) + (10 x number of days with innumerable seizures in Phase) + (number of occurrences of status epilepticus in Phase)] / number of applicable days in the Phase}, where all days in the Phase are considered applicable (including days with 0 seizures), except for days on which the participant failed to complete the Seizure Diary. >= 50% reduction from BL is calculated as 100 x (28-day partial seizure rate [PSR] for the TP - 28-day PSR for the BL Phase) / 28-day PSR for the BL Phase.

End point type	Primary

End point timeframe:

From Baseline through Week 20 (Day 140)/Early Withdrawal

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Since this was an open-label study, hypothesis testing was not performed. The focus of the analysis was on descriptive statistics.

End point values	RTG flexible dose plus C/O	RTG flexible dose plus lamotrigine	RTG flexible dose plus levetiracetam	RTG flexible dose plus valproic acid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	55[2]	50[3]	44[4]	51[5]
Units: participants	22	16	22	29

Notes:

[2] - Intent-To-Treat (ITT) Pop: par. in the Safety Pop who provided at >= 1 post-BL efficacy assessment
[3] - ITT Population

[4] - ITT Population

[5] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated reduction or increase from Baseline in partial-onset seizure frequency

End point title	Number of participants with the indicated reduction or increase from Baseline in partial-onset seizure frequency

End point description:

Participants were assessed for the percent change from Baseline in seizure frequency; changes were categorized as Any Decrease (>0 to 25%, 25 to <50%, 50 to 75%, >75 to 100%) or No Change or Any Increase (>25%, 0 to 25%). A partial-onset seizure is a seizure that has its onset in a limited area on one side of the brain. Partial-onset seizures may remain limited or may spread to involve both sides of the brain.

End point type	Secondary

End point timeframe:

From Baseline through Week 20 (Day 140)/Early Withdrawal

End point values	RTG flexible dose plus C/O	RTG flexible dose plus lamotrigine	RTG flexible dose plus levetiracetam	RTG flexible dose plus valproic acid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	55[6]	50[7]	44[8]	51[9]
Units: participants				
Any decrease	43	43	36	44
>0 to <25% decrease	16	10	6	7
25 to <50% decrease	5	17	8	8
50 to 75% decrease	10	8	14	17
>75 to 100% decrease	12	8	8	12
No change or any increase	12	7	8	7
>25% increase	10	4	5	6
0 to 25% increase	2	3	3	1

Notes:

[6] - ITT Population

[7] - ITT Population

[8] - ITT Population

[9] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with a >=25%, >=75%, or 100% reduction in partial-onset seizure frequency from Baseline

End point title	Number of participants with a >=25%, >=75%, or 100% reduction in partial-onset seizure frequency from Baseline

End point description:

The number of participants experiencing a >=25%, >=75%, and 100% reduction from Baseline in partial-onset seizure frequency during the Treatment Phase (TP) (i.e., Titration Phase and Flexible Dose Evaluation [FDE] Phase) was measured. A partial-onset seizure is a seizure that has its onset in a limited area on one side of the brain. Partial-onset seizures may remain limited or may spread to involve both sides of the brain.

End point type	Secondary

End point timeframe:

From Baseline through Week 20 (Day 140)/Early Withdrawal

End point values	RTG flexible dose plus C/O	RTG flexible dose plus lamotrigine	RTG flexible dose plus levetiracetam	RTG flexible dose plus valproic acid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	55[10]	50[11]	44[12]	51[13]
Units: participants				
>=25%	27	33	30	37
>=75%	12	8	8	12
100%	0	2	1	2

Notes:

[10] - ITT Population

[11] - ITT Population

[12] - ITT Population

[13] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from Baseline in partial-onset seizure frequency

End point title	Percent change from Baseline in partial-onset seizure frequency

End point description:

Percent change from Baseline was calculated as the difference in the partial-onset seizure frequency (Treatment Phase minus the Baseline Phase) divided by the Baseline Phase frequency, multiplied by 100. Negative values indicate reductions from Baseline. A partial-onset seizure is a seizure that has its onset in a limited area on one side of the brain. Partial-onset seizures may remain limited or may spread to involve both sides of the brain.

End point type	Secondary

End point timeframe:

From Baseline through Week 20 (Day 140)/Early Withdrawal

End point values	RTG flexible dose plus C/O	RTG flexible dose plus lamotrigine	RTG flexible dose plus levetiracetam	RTG flexible dose plus valproic acid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	55[14]	50[15]	44[16]	51[17]
Units: percent change				
arithmetic mean (standard deviation)	-24.6 (± 55.25)	-27.8 (± 59.97)	-28.7 (± 80.27)	-27.1 (± 102.1)

Notes:

[14] - ITT Population

[15] - ITT Population

[16] - ITT Population

[17] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Functional Status Diary (FSD): Percent change from Baseline in epilepsy-related worry

End point title	Functional Status Diary (FSD): Percent change from Baseline in epilepsy-related worry

End point description:

Participants were asked the following question daily: "How would you rate your epilepsy-related worry over the last 24 hours?" The original possible responses were 0-10, with 0="No worry" and 10="Worst worry imaginable." However, in the summarization, "1" was added to each participant's daily response, changing the possible values to 1-11, so that there would be no possibility of the percent change from Baseline being undefined. Baseline and Treatment Phase averages were calculated for each participant. The denominators for these by-phase averages were the number of non-missing days for each variable and phase. The by-phase averages were used as follows in the calculation of percent change from Baseline for each participant: 100 x Treatment Phase average – Baseline Phase average) / Baseline Phase average. A negative percent change from Baseline indicates a reduction from Baseline.

End point type	Secondary

End point timeframe:

Baseline through Week 20/Early Withdrawal

End point values	RTG flexible dose plus C/O	RTG flexible dose plus lamotrigine	RTG flexible dose plus levetiracetam	RTG flexible dose plus valproic acid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	55[18]	50[19]	39[20]	48[21]
Units: Percent change				
arithmetic mean (standard deviation)	0.8 (± 45.6)	-7.5 (± 29.53)	-9.1 (± 36.76)	-2 (± 73.16)

Notes:

[18] - ITT Population

[19] - ITT Population

[20] - ITT Population

[21] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Functional Status Diary (FSD): Percent change from Baseline in epilepsy-related limitation of ability to do what you needed to

End point title	Functional Status Diary (FSD): Percent change from Baseline in epilepsy-related limitation of ability to do what you needed to

End point description:

Participants were asked the following question daily: "How would you rate the extent to which epilepsy limited your ability to do what you needed to do over the last 24 hours?" The original possible responses were 0-10, with 0="Not at all limited" and 10="Unable to do anything I needed to." However, in the summarization, "1" was added to each participant's daily response, changing the possible values to 1-11, so that there would be no possibility of the percent change from Baseline being undefined. Baseline and Treatment Phase averages were calculated for each participant. The denominators for these by-phase averages were the number of non-missing days for each variable and phase. The by-phase averages were used as follows in the calculation of percent change from Baseline for each participant: 100 x Treatment Phase average – Baseline Phase average) / Baseline Phase average. A negative percent change from Baseline indicates a reduction from Baseline.

End point type	Secondary

End point timeframe:

Baseline through Week 20/Early Withdrawal

End point values	RTG flexible dose plus C/O	RTG flexible dose plus lamotrigine	RTG flexible dose plus levetiracetam	RTG flexible dose plus valproic acid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	55[22]	50[23]	40[24]	48[25]
Units: Percent change				
arithmetic mean (standard deviation)	10.2 (± 83.8)	-7.7 (± 25.24)	2.5 (± 30.97)	10.6 (± 98.84)

Notes:

[22] - ITT Population

[23] - ITT Population

[24] - ITT Population

[25] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Functional Status Diary (FSD): Percent change from Baseline in epilepsy-related limitation of ability to do what you wanted to

End point title	Functional Status Diary (FSD): Percent change from Baseline in epilepsy-related limitation of ability to do what you wanted to

End point description:

Participants were asked the following question daily: "How would you rate the extent to which epilepsy limited your ability to do what you wanted to do over the last 24 hours?" The original possible responses

were 0-10, with 0="Not at all limited" and 10="Unable to do anything I wanted to." However, in the summarization, "1" was added to each participant's daily response, changing the possible values to 1-11, so that there would be no possibility of the percent change from Baseline being undefined. Baseline and Treatment Phase averages were calculated for each participant. The denominators for these by-phase averages were the number of non-missing days for each variable and phase. The by-phase averages were used as follows in the calculation of percent change from Baseline for each participant: 100 x Treatment Phase average – Baseline Phase average) / Baseline Phase average. A negative percent change from Baseline indicates a reduction from Baseline.

End point type	Secondary

End point timeframe:

Baseline through Week 20/Early Withdrawal

End point values	RTG flexible dose plus C/O	RTG flexible dose plus lamotrigine	RTG flexible dose plus levetiracetam	RTG flexible dose plus valproic acid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	55[26]	50[27]	39[28]	48[29]
Units: Percent change				
arithmetic mean (standard deviation)	6.3 (± 83.07)	-5 (± 25.72)	3.2 (± 36.94)	7.1 (± 97.31)

Notes:

[26] - ITT Population

[27] - ITT Population

[28] - ITT Population

[29] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from Baseline in functional status: percentage of days with no missed work or school time

End point title	Percent change from Baseline in functional status: percentage of days with no missed work or school time

End point description:

Participants were asked the following question daily: "Did you miss any time from work or school in the last 24 hours due to epilepsy?" Possible responses were Yes, No, and NA=Not Applicable (no planned work or school in the last 24 hours). The variable summarized is the percentage of days with no missed work or school. Baseline and Treatment Phase averages were calculated for each participant. The denominators for these by-phase averages were the number of non-missing days for each variable and phase. The by-phase averages were used as follows in the calculation of percent change from Baseline for each participant: 100 x Treatment Phase average – Baseline Phase average) / Baseline Phase average. A positive percent change from Baseline indicates a reduction from Baseline in missed work or school.

End point type	Secondary

End point timeframe:

Baseline through Week 20/Early Withdrawal

End point values	RTG flexible dose plus C/O	RTG flexible dose plus lamotrigine	RTG flexible dose plus levetiracetam	RTG flexible dose plus valproic acid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	34[30]	39[31]	31[32]	29[33]
Units: Percent change				
arithmetic mean (standard deviation)	53.5 (± 295.57)	4.9 (± 9.37)	3.7 (± 29.33)	4.5 (± 11.71)

Notes:

[30] - ITT Population

[31] - ITT Population

[32] - ITT Population

[33] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Short Form 36 Health Survey, version 2 (SF-36v2) domain scores at Week 20/Early Withdrawal

End point title	Change from Baseline in the Short Form 36 Health Survey, version 2 (SF-36v2) domain scores at Week 20/Early Withdrawal

End point description:

The SF-36v2 health survey is a self-administered, generic, 36-item questionnaire designed to measure 8 domains of functional health status and well-being: physical functioning, role-physical, bodily pain, general health perceptions, vitality, social functioning, role-emotional, and mental health. Each domain is scored from 0 (poorer health) to 100 (better health). Change from Baseline was calculated as the post-Baseline score minus the Baseline score. Positive changes from Baseline indicate improvement.

End point type	Secondary

End point timeframe:

Baseline through Week 20/Early Withdrawal

End point values	RTG flexible dose plus C/O	RTG flexible dose plus lamotrigine	RTG flexible dose plus levetiracetam	RTG flexible dose plus valproic acid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53[34]	46[35]	38[36]	46[37]
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Physical Functioning	-0.54 (± 5.461)	0.89 (± 6.665)	-0.7 (± 4.974)	0.46 (± 5.465)
Role-Physical	-1.31 (± 9.563)	1.04 (± 9.366)	0.31 (± 10.958)	1.87 (± 7.644)
Bodily Pain	0.92 (± 10.315)	0.62 (± 10.925)	1.28 (± 8.571)	2.81 (± 11.198)
General Health	-0.35 (± 7.303)	2.55 (± 7.24)	0.68 (± 6.342)	2.45 (± 7.749)
Vitality	-2.94 (± 10.657)	0.52 (± 9.722)	0.47 (± 6.838)	1.56 (± 8.318)
Social Functioning	-1.83 (± 12.022)	0.58 (± 11.063)	1.84 (± 9.787)	2.1 (± 10.107)
Role-Emotional	-1.43 (± 13.224)	1.07 (± 10.991)	2.19 (± 9.258)	4.36 (± 12.719)

Mental Health	-2.04 (± 10.51)	0.72 (± 9.48)	2.48 (± 8.685)	3.31 (± 10.636)

Notes:

[34] - ITT Population

[35] - ITT Population

[36] - ITT Population

[37] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the SF-36v2 Physical Component Summary Score at Week 20/Early Withdrawal

End point title	Change from Baseline in the SF-36v2 Physical Component Summary Score at Week 20/Early Withdrawal

End point description:

The SF-36 v2 Health Survey is a self-administered, generic, 36-item questionnaire designed to measure 8 domains of functional health status and well-being: physical functioning, role-physical, bodily pain, general health perceptions, vitality, social functioning, role-emotional, and mental health. Each domain is scored from 0 (poorer health) to 100 (better health).The physical component summary (PCS) score is a summary score representing overall physical health, which is derived from the 8 domains. As with the domains, PCS scores range from 0 to 100; higher scores represent better health. Change from Baseline was calculated as the post-Baseline score minus the Baseline score. Positive changes from Baseline indicate improvement.

End point type	Secondary

End point timeframe:

Baseline through Week 20/Early Withdrawal

End point values	RTG flexible dose plus C/O	RTG flexible dose plus lamotrigine	RTG flexible dose plus levetiracetam	RTG flexible dose plus valproic acid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53[38]	46[39]	38[40]	46[41]
Units: Scores on a scale				
arithmetic mean (standard deviation)	0.17 (± 5.202)	1.22 (± 6.218)	-0.58 (± 5.648)	0.82 (± 4.525)

Notes:

[38] - ITT Population

[39] - ITT Population

[40] - ITT Population

[41] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the SF-36v2 Mental Component Summary Score at Week 20/Early Withdrawal

End point title	Change from Baseline in the SF-36v2 Mental Component Summary Score at Week 20/Early Withdrawal

End point description:

The SF-36 v2 Health Survey is a self-administered, generic, 36-item questionnaire designed to measure 8 domains of functional health status and well-being: physical functioning, role-physical, bodily pain,

general health perceptions, vitality, social functioning, role-emotional, and mental health. Each domain is scored from 0 (poorer health) to 100 (better health).The mental component summary (MCS) score is a summary score representing overall mental health, which is derived from the 8 domains. As with the domains, MCS scores range from 0 to 100; higher scores represent better health. Change from Baseline was calculated as the post-Baseline score minus the Baseline score. Positive changes from Baseline indicate improvement.

End point type	Secondary

End point timeframe:

Baseline through Week 20/Early Withdrawal

End point values	RTG flexible dose plus C/O	RTG flexible dose plus lamotrigine	RTG flexible dose plus levetiracetam	RTG flexible dose plus valproic acid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53[42]	46[43]	38[44]	46[45]
Units: Scores on a scale				
arithmetic mean (standard deviation)	-2.59 (± 12.359)	0.66 (± 10.149)	2.75 (± 8.851)	3.79 (± 10.206)

Notes:

[42] - ITT Population

[43] - ITT Population

[44] - ITT Population

[45] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated response for the epilepsy-related worry component of the Patient Global Impression of Change (PGI-C) Score

End point title	Number of participants with the indicated response for the epilepsy-related worry component of the Patient Global Impression of Change (PGI-C) Score

End point description:

The PGI-C questionnaire was to be completed by the participant. Participants were asked the following question: Compared to before you started this study, how would you rate your current epilepsy-related worry: Much better, Moderately better, A little better, Unchanged, A little worse, Moderately worse, Much worse?

End point type	Secondary

End point timeframe:

Baseline through Week 20/Early Withdrawal

End point values	RTG flexible dose plus C/O	RTG flexible dose plus lamotrigine	RTG flexible dose plus levetiracetam	RTG flexible dose plus valproic acid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53[46]	46[47]	40[48]	46[49]
Units: participants				
Much better	7	9	4	11
Moderately better	11	16	15	16
A little better	13	6	4	11

Unchanged	16	11	13	6
A little worse	5	2	4	0
Moderately worse	0	1	0	0
Much worse	1	1	0	2

Notes:

[46] - ITT Population

[47] - ITT Population

[48] - ITT Population

[49] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the PGI-C Score: Epilepsy-related worry

End point title	Change from Baseline in the PGI-C Score: Epilepsy-related worry

End point description:

The PGI-C questionnaire was to be completed by the participant. Participants were asked the following question: Compared to before you started this study, how would you rate your current epilepsy-related worry: Much better, Moderately better, A little better, Unchanged, A little worse, Moderately worse, Much worse? Rating scores are integers from 1 to 7, with 1=Much better and 7=Much worse.

End point type	Secondary

End point timeframe:

Baseline through Week 20/Early Withdrawal

End point values	RTG flexible dose plus C/O	RTG flexible dose plus lamotrigine	RTG flexible dose plus levetiracetam	RTG flexible dose plus valproic acid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53[50]	46[51]	40[52]	46[53]
Units: Scores on a scale				
arithmetic mean (standard deviation)	3.1 (± 1.32)	2.7 (± 1.44)	3 (± 1.24)	2.5 (± 1.38)

Notes:

[50] - ITT Population

[51] - ITT Population

[52] - ITT Population

[53] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated response for the current ability to do the things you need to do component of the PGI-C Score

End point title	Number of participants with the indicated response for the current ability to do the things you need to do component of the PGI-C Score

End point description:

The PGI-C questionnaire was to be completed by the participant. Participants were asked the following question: Compared to before you started this study, how would you rate your current ability to do the things you need to do: Much better, Moderately better, A little better, Unchanged, A little worse, Moderately worse, Much worse?

End point type	Secondary

End point timeframe:

Baseline through Week 20/Early Withdrawal

End point values	RTG flexible dose plus C/O	RTG flexible dose plus lamotrigine	RTG flexible dose plus levetiracetam	RTG flexible dose plus valproic acid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53[54]	46[55]	40[56]	46[57]
Units: participants				
Much better	5	9	6	10
Moderately better	13	11	9	14
A little better	10	6	6	9
Unchanged	19	17	17	11
A little worse	2	3	1	1
Moderately worse	2	0	0	0
Much worse	2	0	1	1

Notes:

[54] - ITT Population

[55] - ITT Population

[56] - ITT Population

[57] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the PGI-C Score: Current ability to do the things you need to do

End point title	Change from Baseline in the PGI-C Score: Current ability to do the things you need to do

End point description:

The PGI-C questionnaire was to be completed by the participant. Participants were asked the following question: Compared to before you started this study, how would you rate your current ability to do the things you need to do: Much better, Moderately better, A little better, Unchanged, A little worse, Moderately worse, Much worse? Rating scores are integers from 1 to 7, with 1=Much better and 7=Much worse.

End point type	Secondary

End point timeframe:

Baseline through Week 20/Early Withdrawal

End point values	RTG flexible dose plus C/O	RTG flexible dose plus lamotrigine	RTG flexible dose plus levetiracetam	RTG flexible dose plus valproic acid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53[58]	46[59]	40[60]	46[61]
Units: Scores on a scale				
arithmetic mean (standard deviation)	3.3 (± 1.43)	2.9 (± 1.29)	3.1 (± 1.34)	2.6 (± 1.32)

Notes:

[58] - ITT Population

[59] - ITT Population

[60] - ITT Population

[61] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated response for the current ability to do the things you want to do component of the PGI-C Score

End point title	Number of participants with the indicated response for the current ability to do the things you want to do component of the PGI-C Score

End point description:

The PGI-C questionnaire was to be completed by the participant. Participants were asked the following question: Compared to before you started this study, how would you rate your current ability to do the things you want to do: Much better, Moderately better, A little better, Unchanged, A little worse, Moderately worse, Much worse.

End point type	Secondary

End point timeframe:

Baseline through Week 20/Early Withdrawal

End point values	RTG flexible dose plus C/O	RTG flexible dose plus lamotrigine	RTG flexible dose plus levetiracetam	RTG flexible dose plus valproic acid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53[62]	46[63]	40[64]	46[65]
Units: participants				
Much better	2	8	4	11
Moderately better	13	13	12	16
A little better	11	4	6	9
Unchanged	20	20	17	8
A little worse	3	1	1	1
Moderately worse	3	0	0	0
Much worse	1	0	0	1

Notes:

[62] - ITT Population

[63] - ITT Population

[64] - ITT Population

[65] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the PGI-C Score: Current ability to do the things you want to do

End point title	Change from Baseline in the PGI-C Score: Current ability to do the things you want to do

End point description:

The PGI-C questionnaire was to be completed by the participant. Participants were asked the following question: Compared to before you started this study, how would you rate your current ability to do the things you want to do: Much better, Moderately better, A little better, Unchanged, A little worse, Moderately worse, Much worse? Rating scores are integers from 1 to 7, with 1=Much better and 7=Much worse.

End point type	Secondary

End point timeframe:

Baseline through Week 20/Early Withdrawal

End point values	RTG flexible dose plus C/O	RTG flexible dose plus lamotrigine	RTG flexible dose plus levetiracetam	RTG flexible dose plus valproic acid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53[66]	46[67]	40[68]	46[69]
Units: Scores on a scale				
arithmetic mean (standard deviation)	3.4 (± 1.29)	2.8 (± 1.23)	3 (± 1.12)	2.5 (± 1.3)

Notes:

[66] - ITT Population

[67] - ITT Population

[68] - ITT Population

[69] - ITT Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (SAEs) and non-serious AEs were collected from the start of study medication through the end of the Follow-up Phase (up to Week 33). SAEs considered to be related to study participation were also to be collected prior to treatment.

Adverse event reporting additional description:

SAEs and non-serious AEs were collected in members of the Safety Population, comprised of all participants who took at least one dose of investigational product.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	RTG flexible dose plus C/O

Reporting group description:

Along with concurrent carbamazepine/oxcarbazepine (C/O), participants initiated treatment with retigabine (RTG) immediate release (IR) at 150 milligrams per day (mg/day) (50 mg thrice a day [TID]) and titrated to 600 mg/day (200 mg/day TID) over a 4-week Titration Phase. This was followed by a 16-week Flexible Dose Evaluation Phase, during which the dose could be increased or decreased on a weekly basis between 50 and 150 mg/day, depending on efficacy and tolerability, with the total dose staying between 300 and 1200 mg/day. Participants who were unable to tolerate a minimum dose of 300 mg/day were discontinued from the study.

Reporting group title	RTG flexible dose plus lamotrigine

Reporting group description:

Along with concurrent lamotrigine, participants initiated treatment with RTG IR at 150 mg/day (50 mg TID) and titrated to 600 mg/day (200 mg/day TID) over a 4-week Titration Phase. This was followed by a 16-week Flexible Dose Evaluation Phase, during which the dose could be increased or decreased on a weekly basis between 50 and 150 mg/day, depending on efficacy and tolerability, with the total dose staying between 300 and 1200 mg/day. Participants who were unable to tolerate a minimum dose of 300 mg/day were discontinued from the study.

Reporting group title	RTG flexible dose plus levetiracetam

Reporting group description:

Along with concurrent leveteracetam, participants initiated treatment with RTG IR at 150 mg/day (50 mg TID) and titrated to 600 mg/day (200 mg/day TID) over a 4-week Titration Phase. This was followed by a 16-week Flexible Dose Evaluation Phase, during which the dose could be increased or decreased on a weekly basis between 50 and 150 mg/day, depending on efficacy and tolerability, with the total dose staying between 300 and 1200 mg/day. Participants who were unable to tolerate a minimum dose of 300 mg/day were discontinued from the study.

Reporting group title	RTG flexible dose plus valproic acid

Reporting group description:

Along with concurrent valproic acid, participants initiated treatment with RTG IR at 150 mg/day (50 mg TID) and titrated to 600 mg/day (200 mg/day TID) over a 4-week Titration Phase. This was followed by a 16-week Flexible Dose Evaluation Phase, during which the dose could be increased or decreased on a weekly basis between 50 and 150 mg/day, depending on efficacy and tolerability, with the total dose staying between 300 and 1200 mg/day. Participants who were unable to tolerate a minimum dose of 300 mg/day were discontinued from the study.

Serious adverse events	RTG flexible dose plus C/O	RTG flexible dose plus lamotrigine	RTG flexible dose plus levetiracetam
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 56 (0.00%)	4 / 51 (7.84%)	4 / 44 (9.09%)
number of deaths (all causes)	0	0	0

number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	0 / 56 (0.00%)	1 / 51 (1.96%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 56 (0.00%)	1 / 51 (1.96%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrioventricular block second degree			
subjects affected / exposed	0 / 56 (0.00%)	0 / 51 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 56 (0.00%)	1 / 51 (1.96%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Convulsion			
subjects affected / exposed	0 / 56 (0.00%)	1 / 51 (1.96%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 56 (0.00%)	1 / 51 (1.96%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 56 (0.00%)	0 / 51 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Grand mal convulsion			

subjects affected / exposed	0 / 56 (0.00%)	0 / 51 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 56 (0.00%)	1 / 51 (1.96%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial seizures			
subjects affected / exposed	0 / 56 (0.00%)	1 / 51 (1.96%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial seizures with secondary generalization			
subjects affected / exposed	0 / 56 (0.00%)	1 / 51 (1.96%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vestibular disorder			
subjects affected / exposed	0 / 56 (0.00%)	0 / 51 (0.00%)	0 / 44 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 56 (0.00%)	0 / 51 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc disorder			
subjects affected / exposed	0 / 56 (0.00%)	0 / 51 (0.00%)	1 / 44 (2.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	RTG flexible dose plus valproic acid		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 52 (1.92%)		

number of deaths (all causes)	0			
number of deaths resulting from adverse events				
Injury, poisoning and procedural complications				
Femoral neck fracture				
subjects affected / exposed	0 / 52 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Hypertensive crisis				
subjects affected / exposed	0 / 52 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Atrioventricular block second degree				
subjects affected / exposed	0 / 52 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebrovascular accident				
subjects affected / exposed	0 / 52 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Convulsion				
subjects affected / exposed	0 / 52 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	0 / 52 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	0 / 52 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Grand mal convulsion				

subjects affected / exposed	0 / 52 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	0 / 52 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Partial seizures				
subjects affected / exposed	0 / 52 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Partial seizures with secondary generalization				
subjects affected / exposed	0 / 52 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				
Vestibular disorder				
subjects affected / exposed	1 / 52 (1.92%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Vomiting				
subjects affected / exposed	0 / 52 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Intervertebral disc disorder				
subjects affected / exposed	0 / 52 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	RTG flexible dose plus C/O	RTG flexible dose plus lamotrigine	RTG flexible dose plus levetiracetam
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 56 (69.64%)	33 / 51 (64.71%)	23 / 44 (52.27%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	15 / 56 (26.79%)	15 / 51 (29.41%)	14 / 44 (31.82%)
occurrences (all)	32	20	20
Somnolence			
subjects affected / exposed	11 / 56 (19.64%)	8 / 51 (15.69%)	7 / 44 (15.91%)
occurrences (all)	12	9	7
Disturbance in attention			
subjects affected / exposed	3 / 56 (5.36%)	3 / 51 (5.88%)	0 / 44 (0.00%)
occurrences (all)	3	3	0
Headache			
subjects affected / exposed	1 / 56 (1.79%)	4 / 51 (7.84%)	2 / 44 (4.55%)
occurrences (all)	1	4	2
Memory impairment			
subjects affected / exposed	4 / 56 (7.14%)	1 / 51 (1.96%)	1 / 44 (2.27%)
occurrences (all)	5	1	1
Speech disorder			
subjects affected / exposed	2 / 56 (3.57%)	4 / 51 (7.84%)	2 / 44 (4.55%)
occurrences (all)	2	5	2
Convulsion			
subjects affected / exposed	1 / 56 (1.79%)	1 / 51 (1.96%)	1 / 44 (2.27%)
occurrences (all)	1	1	1
Ataxia			
subjects affected / exposed	3 / 56 (5.36%)	0 / 51 (0.00%)	0 / 44 (0.00%)
occurrences (all)	5	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	6 / 56 (10.71%)	5 / 51 (9.80%)	5 / 44 (11.36%)
occurrences (all)	6	6	5
Asthenia			
subjects affected / exposed	1 / 56 (1.79%)	2 / 51 (3.92%)	5 / 44 (11.36%)
occurrences (all)	2	2	6
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	5 / 56 (8.93%)	7 / 51 (13.73%)	3 / 44 (6.82%)
occurrences (all)	6	7	4
Eye disorders			
Diplopia			
subjects affected / exposed	3 / 56 (5.36%)	0 / 51 (0.00%)	1 / 44 (2.27%)
occurrences (all)	3	0	1
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 56 (3.57%)	4 / 51 (7.84%)	1 / 44 (2.27%)
occurrences (all)	2	5	1
Psychiatric disorders			
Confusional state			
subjects affected / exposed	3 / 56 (5.36%)	0 / 51 (0.00%)	3 / 44 (6.82%)
occurrences (all)	4	0	3
Renal and urinary disorders			
Strangury			
subjects affected / exposed	3 / 56 (5.36%)	0 / 51 (0.00%)	0 / 44 (0.00%)
occurrences (all)	3	0	0

Non-serious adverse events	RTG flexible dose plus valproic acid		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 52 (59.62%)		
Nervous system disorders			
Dizziness			
subjects affected / exposed	9 / 52 (17.31%)		
occurrences (all)	10		
Somnolence			
subjects affected / exposed	17 / 52 (32.69%)		
occurrences (all)	20		
Disturbance in attention			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	6		
Headache			
subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Memory impairment			

subjects affected / exposed	2 / 52 (3.85%)		
occurrences (all)	2		
Speech disorder			
subjects affected / exposed	0 / 52 (0.00%)		
occurrences (all)	0		
Convulsion			
subjects affected / exposed	3 / 52 (5.77%)		
occurrences (all)	3		
Ataxia			
subjects affected / exposed	0 / 52 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Asthenia			
subjects affected / exposed	4 / 52 (7.69%)		
occurrences (all)	6		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	4 / 52 (7.69%)		
occurrences (all)	4		
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 52 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 52 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 52 (1.92%)		
occurrences (all)	1		
Renal and urinary disorders			

Strangury subjects affected / exposed occurrences (all)	0 / 52 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 May 2010	Addition of Health Outcome Assessments; PGI-C and SF-36v2, Clarification on timings of inclusion criteria no. 2, no. 4 and exclusion criteria no. 7, no. 8 and no. 11. Also ECG was added to Visit 5 (Week 12) and magnesium was added to blood chemistry analysis.
05 April 2011	Sponsor Information page including primary and back-up medical monitor details. To clarify end of study treatment and entry into the Open-Label, Extension study, Baseline seizure collection period, concurrent AED use, Visit 8 assessments, exclusion no. 1-Clarify history of generalized epilepsy, and benzodiazepine use during the Baseline phase. Withdrawal criteria amended to include increase in QTc >60 msec from Baseline. To amend visit windows from ±3 to ±5 days to provide greater flexibility for scheduling subjects appointments. Added procedures/assessments to be performed from end of the Titration Phase through to the Taper/Follow-Up Phase including assessments which needs to be performed prior to the scheduled final visit (Visit 7) in order to assess eligibility for the extension study, RTG113413. Re-estimation of sample size and AED subgroup targets and typos and punctuations were corrected.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported