

**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 levetiracetam, 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 levetiracetam, 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 levetiracetam, 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 $\geq 50\%$ reduction in partial-onset seizure (POS) frequency from Baseline

| | |
|-----------------|---|
| End point title | Number of participants with a $\geq 50\%$ reduction in partial-onset seizure (POS) frequency from Baseline ^[1] |
|-----------------|---|

End point description:

The number of participants experiencing a $\geq 50\%$ 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: $28 \times \{[(\text{number of countable partial seizures in Phase}) + (10 \times \text{number of days with innumerable seizures in Phase}) + (\text{number of occurrences of status epilepticus in Phase})] / \text{number of applicable days in the Phase}\}$, 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. $\geq 50\%$ reduction from BL is calculated as $100 \times (28\text{-day partial seizure rate [PSR] for the TP} - 28\text{-day PSR for the BL Phase}) / 28\text{-day PSR for the BL Phase}$.

| | |
|----------------|---------|
| 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 $\geq 25\%$, $\geq 75\%$, or 100% reduction in partial-onset seizure frequency from Baseline

| | |
|-----------------|--|
| End point title | Number of participants with a $\geq 25\%$, $\geq 75\%$, or 100% reduction in partial-onset seizure frequency from Baseline |
|-----------------|--|

End point description:

The number of participants experiencing a $\geq 25\%$, $\geq 75\%$, 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 | | | | |
| $\geq 25\%$ | 27 | 33 | 30 | 37 |
| $\geq 75\%$ | 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: $100 \times (\text{Treatment Phase average} - \text{Baseline Phase average}) / \text{Baseline Phase average}$. 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: $100 \times \text{Treatment Phase average} - \text{Baseline Phase average} / \text{Baseline Phase average}$. 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: $100 \times (\text{Treatment Phase average} - \text{Baseline Phase average}) / \text{Baseline Phase average}$. 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: $100 \times (\text{Treatment Phase average} - \text{Baseline Phase average}) / \text{Baseline Phase average}$. 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 levetiracetam, 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 | | | |
| Total subjects affected by serious adverse events | | RTG flexible dose plus valproic acid | |
| subjects affected / exposed | | 1 / 52 (1.92%) | |

| | | | |
|--|----------------|--|--|
| number of deaths (all causes) number of deaths resulting from adverse events | 0 | | |
| 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 occurrences (all) | 5 / 56 (8.93%) 6 | 7 / 51 (13.73%) 7 | 3 / 44 (6.82%) 4 |
| Eye disorders Diplopia subjects affected / exposed occurrences (all) | 3 / 56 (5.36%) 3 | 0 / 51 (0.00%) 0 | 1 / 44 (2.27%) 1 |
| Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) | 2 / 56 (3.57%) 2 | 4 / 51 (7.84%) 5 | 1 / 44 (2.27%) 1 |
| Psychiatric disorders Confusional state subjects affected / exposed occurrences (all) | 3 / 56 (5.36%) 4 | 0 / 51 (0.00%) 0 | 3 / 44 (6.82%) 3 |
| Renal and urinary disorders Strangury subjects affected / exposed occurrences (all) | 3 / 56 (5.36%) 3 | 0 / 51 (0.00%) 0 | 0 / 44 (0.00%) 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 occurrences (all) | 9 / 52 (17.31%) 10 | | |
| Somnolence subjects affected / exposed occurrences (all) | 17 / 52 (32.69%) 20 | | |
| Disturbance in attention subjects affected / exposed occurrences (all) | 3 / 52 (5.77%) 6 | | |
| Headache subjects affected / exposed occurrences (all) | 2 / 52 (3.85%) 2 | | |
| Memory impairment | | | |

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