



Clinical trial results:

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety and Tolerability of RWJ-333369 as Adjunctive Therapy in Subjects with Partial Onset Seizures Followed by an Open-Label Extension Study

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2006-003839-68 |
| Trial protocol | FI SE DE CZ |
| Global end of trial date | 05 October 2010 |

Results information

| | |
|--------------------------------|--|
| Result version number | v2 (current) |
| This version publication date | 02 June 2016 |
| First version publication date | 03 August 2015 |
| Version creation reason | <ul style="list-style-type: none">Correction of full data setReview of data |

Trial information

Trial identification

| | |
|-----------------------|----------------------|
| Sponsor protocol code | 333369-EPY-3001/3004 |
|-----------------------|----------------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00425282 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Janssen-Cilag International N.V. |
| Sponsor organisation address | Turnhoutseweg 30, 2340 Beerse, Belgium, |
| Public contact | Janssen-Cilag International N.V., Janssen-Cilag International N.V., ClinicalTrialsEU@its.jnj.com |
| Scientific contact | Janssen-Cilag International N.V., Janssen-Cilag International N.V., ClinicalTrialsEU@its.jnj.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 05 October 2010 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 05 October 2010 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to determine the efficacy, safety, and tolerability of carisbamate (CRS) 200 and 400 milligram per day (mg/d) as adjunctive treatment of partial onset seizures (POS).

Protection of trial subjects:

Safety was monitored by means of Data Safety Monitoring Board (DSMB). Safety was evaluated by examining the incidence and severity of adverse events, evaluation of clinical laboratory tests (hematology, serum chemistry, serum lipid profile and urinalysis), vital signs, 12-lead electrocardiogram (ECGs), physical and neurological examination, and assessment of physician withdrawal checklist.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 12 February 2007 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Argentina: 39 |
| Country: Number of subjects enrolled | Australia: 21 |
| Country: Number of subjects enrolled | China: 53 |
| Country: Number of subjects enrolled | Croatia: 11 |
| Country: Number of subjects enrolled | Czech Republic: 48 |
| Country: Number of subjects enrolled | Finland: 19 |
| Country: Number of subjects enrolled | Germany: 22 |
| Country: Number of subjects enrolled | India: 75 |
| Country: Number of subjects enrolled | Malaysia: 9 |
| Country: Number of subjects enrolled | Korea, Republic of: 64 |
| Country: Number of subjects enrolled | Russian Federation: 105 |
| Country: Number of subjects enrolled | Sweden: 14 |
| Country: Number of subjects enrolled | United States: 85 |
| Worldwide total number of subjects | 565 |
| EEA total number of subjects | 114 |

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) | 23 |
| Adults (18-64 years) | 532 |
| From 65 to 84 years | 10 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects who successfully completed the 8-week prospective baseline period and experienced at least 6 simple partial motor, complex partial, or secondarily generalized seizures per 56 days, with no seizure-free period of more than 3 weeks during the baseline period, were allowed to enter into the double blind treatment phase.

Period 1

| | |
|------------------------------|--|
| Period 1 title | Double-blind Phase (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Carer, Assessor |

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo |

Arm description:

Subjects received placebo orally from Day 1 and remained on placebo for the next 12 weeks.

| | |
|--|----------|
| Arm type | other |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received placebo orally for 12 weeks.

| | |
|------------------|----------------|
| Arm title | CRS 200 mg/day |
|------------------|----------------|

Arm description:

Subjects received their randomly assigned dosage, CRS 200 mg/day orally beginning on Day 1, and remained on that dosage for the next 12 weeks.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Carisbamate |
| Investigational medicinal product code | |
| Other name | (S)-2-O-carbamoyl-1-O-chlorophenyl-ethanol |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received CRS 200 mg/day orally for 12 weeks.

| | |
|------------------|----------------|
| Arm title | CRS 400 mg/day |
|------------------|----------------|

Arm description:

Subjects received their randomly assigned dosage, CRS 400 mg/day orally beginning on Day 1, and remained on that dosage for the next 12 weeks.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|--|
| Investigational medicinal product name | Carisbamate |
| Investigational medicinal product code | |
| Other name | (S)-2-O-carbamoyl-1-O-chlorophenyl-ethanol |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received CRS 400 mg/day orally for 12 weeks.

| Number of subjects in period 1 | Placebo | CRS 200 mg/day | CRS 400 mg/day |
|---------------------------------------|---------|----------------|----------------|
| Started | 186 | 187 | 192 |
| Completed | 171 | 176 | 180 |
| Not completed | 15 | 11 | 12 |
| Consent withdrawn by subject | 3 | 5 | 2 |
| Adverse event, non-fatal | 7 | 1 | 7 |
| Other | 2 | 1 | - |
| Pregnancy | 1 | - | 1 |
| Adverse event, serious non-fatal | - | 1 | 2 |
| Lost to follow-up | - | 1 | - |
| Protocol deviation | 2 | 2 | - |

Baseline characteristics

Reporting groups

| | |
|--|----------------|
| Reporting group title | Placebo |
| Reporting group description: | |
| Subjects received placebo orally from Day 1 and remained on placebo for the next 12 weeks. | |
| Reporting group title | CRS 200 mg/day |
| Reporting group description: | |
| Subjects received their randomly assigned dosage, CRS 200 mg/day orally beginning on Day 1, and remained on that dosage for the next 12 weeks. | |
| Reporting group title | CRS 400 mg/day |
| Reporting group description: | |
| Subjects received their randomly assigned dosage, CRS 400 mg/day orally beginning on Day 1, and remained on that dosage for the next 12 weeks. | |

| Reporting group values | Placebo | CRS 200 mg/day | CRS 400 mg/day |
|---|---------|----------------|----------------|
| Number of subjects | 186 | 187 | 192 |
| Title for AgeCategorical Units: subjects | | | |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 7 | 6 | 10 |
| Adults (18-64 years) | 175 | 177 | 180 |
| From 65 to 84 years | 4 | 4 | 2 |
| 85 years and over | 0 | 0 | 0 |
| Title for AgeContinuous Units: Years | | | |
| arithmetic mean | 36 | 35.1 | 34.8 |
| standard deviation | ± 13.06 | ± 12.11 | ± 12.89 |
| Title for Gender Units: subjects | | | |
| Female | 99 | 95 | 86 |
| Male | 87 | 92 | 106 |

| Reporting group values | Total | | |
|---|-------|--|--|
| Number of subjects | 565 | | |
| Title for AgeCategorical Units: subjects | | | |
| Children (2-11 years) | 0 | | |
| Adolescents (12-17 years) | 23 | | |
| Adults (18-64 years) | 532 | | |
| From 65 to 84 years | 10 | | |
| 85 years and over | 0 | | |
| Title for AgeContinuous Units: Years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Title for Gender Units: subjects | | | |
| Female | 280 | | |

| | | | |
|------|-----|--|--|
| Male | 285 | | |
|------|-----|--|--|

End points

End points reporting groups

| | |
|--|----------------|
| Reporting group title | Placebo |
| Reporting group description: Subjects received placebo orally from Day 1 and remained on placebo for the next 12 weeks. | |
| Reporting group title | CRS 200 mg/day |
| Reporting group description: Subjects received their randomly assigned dosage, CRS 200 mg/day orally beginning on Day 1, and remained on that dosage for the next 12 weeks. | |
| Reporting group title | CRS 400 mg/day |
| Reporting group description: Subjects received their randomly assigned dosage, CRS 400 mg/day orally beginning on Day 1, and remained on that dosage for the next 12 weeks. | |

Primary: Percent Reduction From Baseline to Double Blind Phase in Partial Onset Seizure Frequency

| | |
|---|--|
| End point title | Percent Reduction From Baseline to Double Blind Phase in Partial Onset Seizure Frequency |
| End point description: The intent-to-treat (ITT) population included all randomized subjects who had completed the seizure diary during both the baseline period and the double-blind phase. | |
| End point type | Primary |
| End point timeframe: Baseline up to Day 85 | |

| End point values | Placebo | CRS 200 mg/day | CRS 400 mg/day | |
|-------------------------------|----------------------|---------------------|---------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 183 ^[1] | 187 | 191 ^[2] | |
| Units: percent reduction | | | | |
| median (full range (min-max)) | 15.21 (-1300 to 100) | 16.44 (-190 to 100) | 27.27 (-262 to 100) | |

Notes:

[1] - Here 'N' signifies number of subjects analysed for this endpoint.

[2] - Here 'N' signifies number of subjects analysed for this endpoint.

Statistical analyses

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Placebo v CRS 200 mg/day |
| Number of subjects included in analysis | 370 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.678 |
| Method | Wilcoxon rank sum test |

| | |
|---|--------------------------|
| Statistical analysis title | Statistical Analysis 2 |
| Comparison groups | Placebo v CRS 400 mg/day |
| Number of subjects included in analysis | 374 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.009 |
| Method | Wilcoxon rank sum test |

Secondary: Change from Baseline to the End of Double Blind Treatment Phase in the Seizure Severity Questionnaire (SSQ) Recovery Phase Composite Score (RPCS)

| | |
|-----------------|---|
| End point title | Change from Baseline to the End of Double Blind Treatment Phase in the Seizure Severity Questionnaire (SSQ) Recovery Phase Composite Score (RPCS) |
|-----------------|---|

End point description:

The SSQ is a 10-item questionnaire designed to track seizure severity signs and is formatted as a structured interview. It is organized into 3 components: the Warning, Activity-movement, and Recovery (cognitive, emotional, and physical) aspects of seizures. Questions review duration, severity, bothersomeness, and overall ratings, and the most bothersome aspect of seizures. Lower scores represent better function. The ITT population included all randomized subjects who had completed the seizure diary during both the baseline period and the double-blind phase.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to Day 85

| End point values | Placebo | CRS 200 mg/day | CRS 400 mg/day | |
|--------------------------------------|--------------------|--------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 182 ^[3] | 185 ^[4] | 189 ^[5] | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 43 (n= 172, 177, 181) | -0.6 (± 1.73) | -0.5 (± 1.76) | -0.6 (± 1.81) | |
| Day 85 (n= 170, 173, 178) | -0.7 (± 1.86) | -0.6 (± 1.62) | -0.5 (± 1.81) | |
| Endpoint (n= 182, 184, 189) | -0.7 (± 1.83) | -0.5 (± 1.59) | -0.4 (± 1.84) | |

Notes:

[3] - Here 'N' signifies number of subjects analysed for this endpoint.

[4] - Here 'N' signifies number of subjects analysed for this endpoint.

[5] - Here 'N' signifies number of subjects analysed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Double Blind End Point in SSQ Scores

| | |
|-----------------|--|
| End point title | Change From Baseline to Double Blind End Point in SSQ Scores |
|-----------------|--|

End point description:

The SSQ is a 10-item questionnaire designed to track seizure severity signs and is formatted as a structured interview. It is organized into 3 components: the Warning, Activity-movement, and Recovery (cognitive, emotional, and physical) aspects of seizures. Questions review duration, severity, bothersomeness, and overall ratings, and the most bothersome aspect of seizures. Lower scores represent better function. The intent-to-treat (ITT) population included all randomized subjects who had completed the seizure diary during both the baseline period and the double-blind phase.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to Day 85

| End point values | Placebo | CRS 200 mg/day | CRS 400 mg/day | |
|--------------------------------------|--------------------|--------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 175 ^[6] | 174 ^[7] | 180 ^[8] | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 3.7 (± 1.26) | 3.7 (± 1.21) | 3.8 (± 1.26) | |
| End Point | -0.6 (± 1.5) | -0.6 (± 1.28) | -0.5 (± 1.38) | |

Notes:

[6] - Here 'N' signifies number of subjects analysed for this endpoint.

[7] - Here 'N' signifies number of subjects analysed for this endpoint.

[8] - Here 'N' signifies number of subjects analysed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to End of study

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 10.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | PLACEBO |
|-----------------------|---------|

Reporting group description:

Placebo

| | |
|-----------------------|-----------|
| Reporting group title | CRS 400mg |
|-----------------------|-----------|

Reporting group description:

CARISBAMATE 400 mg per day

| | |
|-----------------------|-----------|
| Reporting group title | CRS 200mg |
|-----------------------|-----------|

Reporting group description:

CARISBAMATE 200 mg per day

| Serious adverse events | PLACEBO | CRS 400mg | CRS 200mg |
|---|-----------------|-----------------|------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 8 / 186 (4.30%) | 5 / 192 (2.60%) | 10 / 187 (5.35%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Injury, poisoning and procedural complications | | | |
| Ankle Fracture | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | 0 / 192 (0.00%) | 1 / 187 (0.53%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Facial Bones Fracture | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | 0 / 192 (0.00%) | 0 / 187 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Joint Dislocation | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | 0 / 192 (0.00%) | 1 / 187 (0.53%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower Limb Fracture | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 186 (0.00%) | 1 / 192 (0.52%) | 0 / 187 (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 |
| Rib Fracture | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | 0 / 192 (0.00%) | 0 / 187 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin Injury | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | 1 / 192 (0.52%) | 0 / 187 (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 |
| Skin Laceration | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | 0 / 192 (0.00%) | 1 / 187 (0.53%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Traumatic Brain Injury | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | 0 / 192 (0.00%) | 0 / 187 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Epilepsy | | | |
| subjects affected / exposed | 2 / 186 (1.08%) | 1 / 192 (0.52%) | 3 / 187 (1.60%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Grand Mal Convulsion | | | |
| subjects affected / exposed | 2 / 186 (1.08%) | 0 / 192 (0.00%) | 0 / 187 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Status Epilepticus | | | |
| subjects affected / exposed | 3 / 186 (1.61%) | 1 / 192 (0.52%) | 0 / 187 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |

| | | | | |
|--|---|-----------------|-----------------|-----------------|
| Asthenia | subjects affected / exposed | 0 / 186 (0.00%) | 0 / 192 (0.00%) | 1 / 187 (0.53%) |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| | | | | |
| Ear and labyrinth disorders | | | | |
| Vertigo | subjects affected / exposed | 0 / 186 (0.00%) | 0 / 192 (0.00%) | 1 / 187 (0.53%) |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| | | | | |
| Gastrointestinal disorders | | | | |
| Abdominal Distension | subjects affected / exposed | 0 / 186 (0.00%) | 0 / 192 (0.00%) | 1 / 187 (0.53%) |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| | | | | |
| Dyspepsia | subjects affected / exposed | 0 / 186 (0.00%) | 0 / 192 (0.00%) | 1 / 187 (0.53%) |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| | | | | |
| Skin and subcutaneous tissue disorders | | | | |
| Rash Generalised | subjects affected / exposed | 0 / 186 (0.00%) | 1 / 192 (0.52%) | 0 / 187 (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 |
| | | | | |
| Psychiatric disorders | | | | |
| Psychotic Disorder | subjects affected / exposed | 0 / 186 (0.00%) | 1 / 192 (0.52%) | 1 / 187 (0.53%) |
| | occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| | | | | |
| Renal and urinary disorders | | | | |
| Urinary Retention | subjects affected / exposed | 0 / 186 (0.00%) | 0 / 192 (0.00%) | 1 / 187 (0.53%) |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| | | | | |
| Infections and infestations | | | | |
| Bronchitis | subjects affected / exposed | | | |
| | occurrences causally related to treatment / all | | | |
| | deaths causally related to treatment / all | | | |
| | | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 186 (0.54%) | 0 / 192 (0.00%) | 0 / 187 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia Necrotising | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | 0 / 192 (0.00%) | 1 / 187 (0.53%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary Tract Infection | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | 0 / 192 (0.00%) | 1 / 187 (0.53%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | 0 / 192 (0.00%) | 1 / 187 (0.53%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 1 %

| Non-serious adverse events | PLACEBO | CRS 400mg | CRS 200mg |
|---|-------------------|--------------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 81 / 186 (43.55%) | 101 / 192 (52.60%) | 81 / 187 (43.32%) |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | 0 / 192 (0.00%) | 2 / 187 (1.07%) |
| occurrences (all) | 0 | 0 | 2 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | 3 / 192 (1.56%) | 2 / 187 (1.07%) |
| occurrences (all) | 2 | 6 | 2 |
| Chest Pain | | | |
| subjects affected / exposed | 2 / 186 (1.08%) | 0 / 192 (0.00%) | 3 / 187 (1.60%) |
| occurrences (all) | 2 | 0 | 3 |
| Fatigue | | | |

| | | | |
|--|------------------------|------------------------|----------------------|
| subjects affected / exposed occurrences (all) | 12 / 186 (6.45%) 13 | 13 / 192 (6.77%) 13 | 7 / 187 (3.74%) 8 |
| Pyrexia subjects affected / exposed occurrences (all) | 1 / 186 (0.54%) 1 | 3 / 192 (1.56%) 4 | 2 / 187 (1.07%) 2 |
| Irritability subjects affected / exposed occurrences (all) | 1 / 186 (0.54%) 2 | 4 / 192 (2.08%) 5 | 4 / 187 (2.14%) 5 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough subjects affected / exposed occurrences (all) | 1 / 186 (0.54%) 1 | 1 / 192 (0.52%) 1 | 2 / 187 (1.07%) 3 |
| Dyspnoea subjects affected / exposed occurrences (all) | 1 / 186 (0.54%) 2 | 2 / 192 (1.04%) 2 | 2 / 187 (1.07%) 2 |
| Nasal Congestion subjects affected / exposed occurrences (all) | 2 / 186 (1.08%) 2 | 0 / 192 (0.00%) 0 | 3 / 187 (1.60%) 3 |
| Pharyngolaryngeal Pain subjects affected / exposed occurrences (all) | 1 / 186 (0.54%) 2 | 4 / 192 (2.08%) 4 | 1 / 187 (0.53%) 1 |
| Psychiatric disorders | | | |
| Anxiety subjects affected / exposed occurrences (all) | 1 / 186 (0.54%) 2 | 2 / 192 (1.04%) 2 | 3 / 187 (1.60%) 3 |
| Bradyphrenia subjects affected / exposed occurrences (all) | 0 / 186 (0.00%) 0 | 2 / 192 (1.04%) 2 | 0 / 187 (0.00%) 0 |
| Confusional State subjects affected / exposed occurrences (all) | 1 / 186 (0.54%) 1 | 2 / 192 (1.04%) 2 | 1 / 187 (0.53%) 1 |
| Depressed Mood subjects affected / exposed occurrences (all) | 0 / 186 (0.00%) 0 | 2 / 192 (1.04%) 2 | 0 / 187 (0.00%) 0 |
| Depression | | | |

| | | | |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 2 / 186 (1.08%) 2 | 2 / 192 (1.04%) 2 | 0 / 187 (0.00%) 0 |
| Insomnia subjects affected / exposed occurrences (all) | 4 / 186 (2.15%) 5 | 6 / 192 (3.13%) 6 | 4 / 187 (2.14%) 6 |
| Nervousness subjects affected / exposed occurrences (all) | 2 / 186 (1.08%) 2 | 1 / 192 (0.52%) 1 | 0 / 187 (0.00%) 0 |
| Injury, poisoning and procedural complications | | | |
| Contusion subjects affected / exposed occurrences (all) | 2 / 186 (1.08%) 2 | 3 / 192 (1.56%) 3 | 7 / 187 (3.74%) 8 |
| Excoriation subjects affected / exposed occurrences (all) | 1 / 186 (0.54%) 1 | 1 / 192 (0.52%) 1 | 2 / 187 (1.07%) 3 |
| Head Injury subjects affected / exposed occurrences (all) | 3 / 186 (1.61%) 3 | 1 / 192 (0.52%) 1 | 0 / 187 (0.00%) 0 |
| Skin Laceration subjects affected / exposed occurrences (all) | 0 / 186 (0.00%) 0 | 1 / 192 (0.52%) 1 | 2 / 187 (1.07%) 3 |
| Thermal Burn subjects affected / exposed occurrences (all) | 2 / 186 (1.08%) 2 | 0 / 192 (0.00%) 0 | 1 / 187 (0.53%) 1 |
| Tongue Injury subjects affected / exposed occurrences (all) | 2 / 186 (1.08%) 3 | 0 / 192 (0.00%) 0 | 0 / 187 (0.00%) 0 |
| Nervous system disorders | | | |
| Coordination Abnormal subjects affected / exposed occurrences (all) | 1 / 186 (0.54%) 2 | 3 / 192 (1.56%) 3 | 1 / 187 (0.53%) 1 |
| Disturbance in Attention subjects affected / exposed occurrences (all) | 1 / 186 (0.54%) 3 | 3 / 192 (1.56%) 3 | 2 / 187 (1.07%) 2 |
| Dizziness | | | |

| | | | |
|--------------------------------------|-------------------|-------------------|-------------------|
| subjects affected / exposed | 13 / 186 (6.99%) | 23 / 192 (11.98%) | 7 / 187 (3.74%) |
| occurrences (all) | 19 | 35 | 8 |
| Epilepsy | | | |
| subjects affected / exposed | 4 / 186 (2.15%) | 2 / 192 (1.04%) | 1 / 187 (0.53%) |
| occurrences (all) | 5 | 2 | 1 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | 4 / 192 (2.08%) | 1 / 187 (0.53%) |
| occurrences (all) | 0 | 4 | 1 |
| Headache | | | |
| subjects affected / exposed | 27 / 186 (14.52%) | 27 / 192 (14.06%) | 25 / 187 (13.37%) |
| occurrences (all) | 58 | 53 | 50 |
| Memory Impairment | | | |
| subjects affected / exposed | 2 / 186 (1.08%) | 1 / 192 (0.52%) | 1 / 187 (0.53%) |
| occurrences (all) | 2 | 1 | 0 |
| Migraine | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | 2 / 192 (1.04%) | 0 / 187 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Paraesthesia | | | |
| subjects affected / exposed | 7 / 186 (3.76%) | 3 / 192 (1.56%) | 2 / 187 (1.07%) |
| occurrences (all) | 9 | 3 | 2 |
| Psychomotor Hyperactivity | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | 2 / 192 (1.04%) | 0 / 187 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Somnolence | | | |
| subjects affected / exposed | 2 / 186 (1.08%) | 10 / 192 (5.21%) | 8 / 187 (4.28%) |
| occurrences (all) | 2 | 11 | 8 |
| Tremor | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | 1 / 192 (0.52%) | 2 / 187 (1.07%) |
| occurrences (all) | 2 | 1 | 4 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 186 (0.00%) | 0 / 192 (0.00%) | 2 / 187 (1.07%) |
| occurrences (all) | 0 | 0 | 2 |
| Ear and labyrinth disorders | | | |
| Tinnitus | | | |

| | | | |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 2 / 186 (1.08%) 2 | 1 / 192 (0.52%) 1 | 0 / 187 (0.00%) 0 |
| Vertigo subjects affected / exposed occurrences (all) | 3 / 186 (1.61%) 5 | 3 / 192 (1.56%) 3 | 0 / 187 (0.00%) 0 |
| Eye disorders | | | |
| Conjunctival Haemorrhage subjects affected / exposed occurrences (all) | 1 / 186 (0.54%) 1 | 2 / 192 (1.04%) 2 | 0 / 187 (0.00%) 0 |
| Conjunctivitis subjects affected / exposed occurrences (all) | 2 / 186 (1.08%) 2 | 0 / 192 (0.00%) 0 | 0 / 187 (0.00%) 0 |
| Diplopia subjects affected / exposed occurrences (all) | 0 / 186 (0.00%) 0 | 0 / 192 (0.00%) 0 | 2 / 187 (1.07%) 2 |
| Vision Blurred subjects affected / exposed occurrences (all) | 1 / 186 (0.54%) 1 | 4 / 192 (2.08%) 5 | 2 / 187 (1.07%) 5 |
| Gastrointestinal disorders | | | |
| Abdominal Pain Upper subjects affected / exposed occurrences (all) | 4 / 186 (2.15%) 4 | 1 / 192 (0.52%) 1 | 2 / 187 (1.07%) 2 |
| Constipation subjects affected / exposed occurrences (all) | 1 / 186 (0.54%) 1 | 3 / 192 (1.56%) 3 | 3 / 187 (1.60%) 3 |
| Dry Mouth subjects affected / exposed occurrences (all) | 0 / 186 (0.00%) 0 | 1 / 192 (0.52%) 1 | 2 / 187 (1.07%) 2 |
| Diarrhoea subjects affected / exposed occurrences (all) | 4 / 186 (2.15%) 9 | 5 / 192 (2.60%) 5 | 7 / 187 (3.74%) 8 |
| Dyspepsia subjects affected / exposed occurrences (all) | 3 / 186 (1.61%) 4 | 3 / 192 (1.56%) 4 | 0 / 187 (0.00%) 0 |
| Gastritis | | | |

| | | | |
|---|------------------------|----------------------|------------------------|
| subjects affected / exposed occurrences (all) | 2 / 186 (1.08%) 2 | 2 / 192 (1.04%) 6 | 0 / 187 (0.00%) 0 |
| Mouth Ulceration subjects affected / exposed occurrences (all) | 1 / 186 (0.54%) 1 | 2 / 192 (1.04%) 4 | 1 / 187 (0.53%) 1 |
| Nausea subjects affected / exposed occurrences (all) | 11 / 186 (5.91%) 15 | 6 / 192 (3.13%) 8 | 10 / 187 (5.35%) 12 |
| Toothache subjects affected / exposed occurrences (all) | 0 / 186 (0.00%) 0 | 1 / 192 (0.52%) 1 | 3 / 187 (1.60%) 3 |
| Vomiting subjects affected / exposed occurrences (all) | 7 / 186 (3.76%) 9 | 2 / 192 (1.04%) 2 | 3 / 187 (1.60%) 3 |
| Skin and subcutaneous tissue disorders Dermatitis Allergic subjects affected / exposed occurrences (all) | 0 / 186 (0.00%) 0 | 2 / 192 (1.04%) 2 | 0 / 187 (0.00%) 0 |
| Eczema subjects affected / exposed occurrences (all) | 0 / 186 (0.00%) 0 | 2 / 192 (1.04%) 2 | 0 / 187 (0.00%) 0 |
| Rash subjects affected / exposed occurrences (all) | 1 / 186 (0.54%) 1 | 0 / 192 (0.00%) 0 | 3 / 187 (1.60%) 3 |
| Renal and urinary disorders Pollakiuria subjects affected / exposed occurrences (all) | 0 / 186 (0.00%) 0 | 2 / 192 (1.04%) 2 | 1 / 187 (0.53%) 1 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 1 / 186 (0.54%) 1 | 3 / 192 (1.56%) 3 | 0 / 187 (0.00%) 0 |
| Back Pain subjects affected / exposed occurrences (all) | 2 / 186 (1.08%) 3 | 2 / 192 (1.04%) 2 | 1 / 187 (0.53%) 1 |
| Myalgia | | | |

| | | | |
|---|----------------------|-----------------------|-----------------------|
| subjects affected / exposed occurrences (all) | 3 / 186 (1.61%) 3 | 1 / 192 (0.52%) 1 | 3 / 187 (1.60%) 3 |
| Musculoskeletal Pain subjects affected / exposed occurrences (all) | 2 / 186 (1.08%) 2 | 1 / 192 (0.52%) 1 | 1 / 187 (0.53%) 1 |
| Pain in Extremity subjects affected / exposed occurrences (all) | 4 / 186 (2.15%) 4 | 3 / 192 (1.56%) 3 | 2 / 187 (1.07%) 2 |
| Infections and infestations | | | |
| Bronchitis subjects affected / exposed occurrences (all) | 2 / 186 (1.08%) 2 | 1 / 192 (0.52%) 3 | 0 / 187 (0.00%) 0 |
| Influenza subjects affected / exposed occurrences (all) | 3 / 186 (1.61%) 5 | 4 / 192 (2.08%) 5 | 4 / 187 (2.14%) 4 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 9 / 186 (4.84%) 9 | 6 / 192 (3.13%) 7 | 6 / 187 (3.21%) 6 |
| Respiratory Tract Infection Viral subjects affected / exposed occurrences (all) | 0 / 186 (0.00%) 0 | 0 / 192 (0.00%) 0 | 3 / 187 (1.60%) 3 |
| Sinusitis subjects affected / exposed occurrences (all) | 0 / 186 (0.00%) 0 | 3 / 192 (1.56%) 3 | 0 / 187 (0.00%) 0 |
| Upper Respiratory Tract Infection subjects affected / exposed occurrences (all) | 5 / 186 (2.69%) 7 | 8 / 192 (4.17%) 10 | 9 / 187 (4.81%) 10 |
| Viral Infection subjects affected / exposed occurrences (all) | 0 / 186 (0.00%) 0 | 3 / 192 (1.56%) 3 | 0 / 187 (0.00%) 0 |
| Urinary Tract Infection subjects affected / exposed occurrences (all) | 3 / 186 (1.61%) 3 | 2 / 192 (1.04%) 2 | 2 / 187 (1.07%) 2 |
| Metabolism and nutrition disorders | | | |
| Decreased Appetite | | | |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 186 (1.08%) | 0 / 192 (0.00%) | 1 / 187 (0.53%) |
| occurrences (all) | 2 | 0 | 1 |
| Anorexia | | | |
| subjects affected / exposed | 1 / 186 (0.54%) | 5 / 192 (2.60%) | 1 / 187 (0.53%) |
| occurrences (all) | 3 | 6 | 1 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 02 February 2007 | Amendment INT-1 included the following changes - Updated information on cases of elevated liver enzymes, reduction of the lower limit for body weight from 40 kg to 35 kg, extension of baseline platelet count and haemoglobin test value ranges, and requirement of the dosage of concomitant anti-epileptic drugs (AEDs) to be stable for at least 1 month (changed from 2 months) with no new AEDs to be added for the previous 2 months before screening. In addition, subjects with congenital short QT syndrome were now excluded and periodic use of acetaminophen up to 2,500 mg/d was now allowed throughout the study. For the efficacy analyses, the statistical method for the step-down procedure performed as the primary analysis for the United States was revised to exclude the responder rate as an end point to be analysed sequentially. Clarification to the analysis of EuroQol 5D scores was also made. For the safety analyses, the categories for analysis of subjects with elevated liver enzyme tests were changed from 5 to 8 times the upper limit of normal (ULN) to 5 to 10 x ULN, and from >8 x ULN to >10 x ULN. |
| 04 September 2007 | The study objectives, hypotheses, statistical methods, and efficacy analyses were revised to present the primary and secondary efficacy end points by group for registration in the United States and the ROW and in the countries of Europe, Australia, New Zealand, and South Africa, to meet United States and Committee for Human Medicinal Products (CHMP) guideline requirements. Additional cardiovascular assessment procedures were added to further establish cardiac risk factors, including the collection of smoking history and family history of coronary artery disease and sudden death at the screening visit and evaluation and measurement of the QTc interval using Fridericia's correction (QTcF). Analysis of additional SSQ domains, vital signs, physical and neurologic examinations, and Physician Withdrawal Check-list scores were also made. |
| 02 November 2007 | Changes were made to correct minor errors in Amendment INT-2; there were no changes made to study conduct or statistical analyses. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported