



## Clinical trial results:

**A randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy, safety and tolerability of RWJ333369 as adjunctive therapy in subjects with partial onset seizure**

### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2006-003941-17  |
| Trial protocol           | HU DK           |
| Global end of trial date | 12 October 2007 |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1           |
| This version publication date  | 06 July 2016 |
| First version publication date | 31 July 2015 |

### Trial information

#### Trial identification

|                       |               |
|-----------------------|---------------|
| Sponsor protocol code | 333369EPY3002 |
|-----------------------|---------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00433667 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |                                                                                                        |
|------------------------------|--------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Janssen-Cilag International N.V.                                                                       |
| Sponsor organisation address | Antwerpseweg 15-17, B-2340 Beerse, Belgium,                                                            |
| Public contact               | Clinical Registry Group, Janssen Research & Development, +353 21 4673500, ClinicalTrialsEU@its.jnj.com |
| Scientific contact           | Clinical Registry Group, Janssen Research & Development, +353 21 4673500, ClinicalTrialsEU@its.jnj.com |

Notes:

### Paediatric regulatory details

|                                                                      |                     |
|----------------------------------------------------------------------|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP)       | Yes                 |
| EMA paediatric investigation plan number(s)                          | EMA-000360-PIP01-08 |
| 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? | Yes                 |

Notes:

## Results analysis stage

|                                                      |                 |
|------------------------------------------------------|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 12 October 2007 |
| Is this the analysis of the primary completion data? | No              |

|                                  |                 |
|----------------------------------|-----------------|
| Global end of trial reached?     | Yes             |
| Global end of trial date         | 12 October 2007 |
| Was the trial ended prematurely? | No              |

Notes:

## General information about the trial

Main objective of the trial:

Percent reduction in seizure frequency (average monthly seizure rate per 28 days) of all simple partial motor and/or complex partial, and/or secondarily generalized seizures during the double-blind treatment phase, relative to the pretreatment phase

Protection of trial subjects:

Safety was evaluated by monitoring of the frequency, severity, and timing of AEs, and by clinical laboratory test results, 12-lead electrocardiogram (ECG) recordings, vital signs measurements, physical and neurologic examinations, and pregnancy tests for females of child-bearing potential. In addition to safety monitoring by the Sponsor, a Data Safety Monitoring Board (DSMB) consisting of independent experts in the fields of epilepsy and biostatistics met to evaluate unblinded safety data from the study at pre-specified intervals in accordance with the DSMB charter.

Background therapy:

All subjects were receiving from 1-3 other antiepileptic drugs

Evidence for comparator:

Not a comparator study

|                                                           |                   |
|-----------------------------------------------------------|-------------------|
| Actual start date of recruitment                          | 25 September 2006 |
| 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 | Bulgaria: 35      |
| Country: Number of subjects enrolled | Canada: 21        |
| Country: Number of subjects enrolled | China: 74         |
| Country: Number of subjects enrolled | Hong Kong: 15     |
| Country: Number of subjects enrolled | Hungary: 28       |
| Country: Number of subjects enrolled | India: 78         |
| Country: Number of subjects enrolled | Norway: 13        |
| Country: Number of subjects enrolled | Poland: 67        |
| Country: Number of subjects enrolled | Taiwan: 51        |
| Country: Number of subjects enrolled | Thailand: 40      |
| Country: Number of subjects enrolled | Ukraine: 95       |
| Country: Number of subjects enrolled | United States: 45 |
| Worldwide total number of subjects   | 562               |
| EEA total number of subjects         | 143               |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|-------------------------------------------|-----|
| 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)                 | 21  |
| Adults (18-64 years)                      | 531 |
| From 65 to 84 years                       | 10  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

A total of 721 subjects met the study entry criteria and were enrolled in the 8 week prospective baseline period from 12 countries.

### Pre-assignment

Screening details:

In pre-treatment phase (Day -56 to -1) subjects continued with their Antiepileptic Drug (AED). Subject who met the following criteria: 1) at least 6 simple partial motor, complex partial, or secondarily generalized seizures per 56 days and no seizure-free interval for more than 3 weeks randomly assigned to double-blind treatment.

### 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                | Investigator, Carer, Subject        |

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | Placebo |

Arm description:

Subject received placebo matching with carisbamate orally twice daily from Day 1 up to Week 12.

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

Dosage and administration details:

Placebo matching with Carisbamate orally twice daily from Day 1 up to Week 12

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | Carisbamate 200 mg |
|------------------|--------------------|

Arm description:

The dosages of carisbamate were 200 milligram/day (mg/day), administered in 2 equally divided doses.

|                                        |                                |
|----------------------------------------|--------------------------------|
| Arm type                               | Experimental                   |
| Investigational medicinal product name | Carisbamate 200 milligram (mg) |
| Investigational medicinal product code |                                |
| Other name                             |                                |
| Pharmaceutical forms                   | Tablet                         |
| Routes of administration               | Oral use                       |

Dosage and administration details:

Subject received Carisbamate 200 mg orally in 2 equally divided doses twice daily from Day 1 up to Week 12.

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | Carisbamate 400 mg |
|------------------|--------------------|

Arm description:

Subject received Carisbamate 200 mg orally in 2 equally divided doses twice daily from Day 1 up to Week 12.

|          |                   |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

|                                        |                    |
|----------------------------------------|--------------------|
| Investigational medicinal product name | Carisbamate 400 mg |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Tablet             |
| Routes of administration               | Oral use           |

Dosage and administration details:

Subject received Carisbamate 400 mg orally in 2 equally divided doses twice daily from Day 1 up to Week 12.

| <b>Number of subjects in period 1</b> | Placebo | Carisbamate 200 mg | Carisbamate 400 mg |
|---------------------------------------|---------|--------------------|--------------------|
| Started                               | 189     | 188                | 185                |
| Completed                             | 178     | 176                | 174                |
| Not completed                         | 11      | 12                 | 11                 |
| Consent withdrawn by subject          | 5       | 5                  | 4                  |
| Adverse event, non-fatal              | 1       | 4                  | 6                  |
| Other                                 | -       | 2                  | -                  |
| Lost to follow-up                     | 4       | -                  | -                  |
| Protocol deviation                    | 1       | 1                  | 1                  |

## Baseline characteristics

### Reporting groups

|                                                                                                             |                    |
|-------------------------------------------------------------------------------------------------------------|--------------------|
| Reporting group title                                                                                       | Placebo            |
| Reporting group description:                                                                                |                    |
| Subject received placebo matching with carisbamate orally twice daily from Day 1 up to Week 12.             |                    |
| Reporting group title                                                                                       | Carisbamate 200 mg |
| Reporting group description:                                                                                |                    |
| The dosages of carisbamate were 200 milligram/day (mg/day), administered in 2 equally divided doses.        |                    |
| Reporting group title                                                                                       | Carisbamate 400 mg |
| Reporting group description:                                                                                |                    |
| Subject received Carisbamate 200 mg orally in 2 equally divided doses twice daily from Day 1 up to Week 12. |                    |

| Reporting group values                      | Placebo | Carisbamate 200 mg | Carisbamate 400 mg |
|---------------------------------------------|---------|--------------------|--------------------|
| Number of subjects                          | 189     | 188                | 185                |
| Title for AgeCategorical<br>Units: subjects |         |                    |                    |
| Children (2-11 years)                       | 0       | 0                  | 0                  |
| Adolescents (12-17 years)                   | 5       | 3                  | 13                 |
| Adults (18-64 years)                        | 181     | 183                | 167                |
| From 65 to 84 years                         | 3       | 2                  | 5                  |
| 85 years and over                           | 0       | 0                  | 0                  |
| Title for AgeContinuous<br>Units: Years     |         |                    |                    |
| arithmetic mean                             | 36      | 36.3               | 35.3               |
| standard deviation                          | ± 12.25 | ± 11.69            | ± 13.82            |
| Title for Gender<br>Units: subjects         |         |                    |                    |
| Female                                      | 110     | 92                 | 88                 |
| Male                                        | 79      | 96                 | 97                 |

| Reporting group values                      | Total |  |  |
|---------------------------------------------|-------|--|--|
| Number of subjects                          | 562   |  |  |
| Title for AgeCategorical<br>Units: subjects |       |  |  |
| Children (2-11 years)                       | 0     |  |  |
| Adolescents (12-17 years)                   | 21    |  |  |
| Adults (18-64 years)                        | 531   |  |  |
| From 65 to 84 years                         | 10    |  |  |
| 85 years and over                           | 0     |  |  |
| Title for AgeContinuous<br>Units: Years     |       |  |  |
| arithmetic mean                             |       |  |  |
| standard deviation                          | -     |  |  |
| Title for Gender<br>Units: subjects         |       |  |  |
| Female                                      | 290   |  |  |
| Male                                        | 272   |  |  |



## End points

### End points reporting groups

|                                                                                                                                                                                                            |                                  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|
| Reporting group title                                                                                                                                                                                      | Placebo                          |
| Reporting group description:<br>Subject received placebo matching with carisbamate orally twice daily from Day 1 up to Week 12.                                                                            |                                  |
| Reporting group title                                                                                                                                                                                      | Carisbamate 200 mg               |
| Reporting group description:<br>The dosages of carisbamate were 200 milligram/day (mg/day), administered in 2 equally divided doses.                                                                       |                                  |
| Reporting group title                                                                                                                                                                                      | Carisbamate 400 mg               |
| Reporting group description:<br>Subject received Carisbamate 200 mg orally in 2 equally divided doses twice daily from Day 1 up to Week 12.                                                                |                                  |
| Subject analysis set title                                                                                                                                                                                 | Intent-to-treat (ITT) population |
| Subject analysis set type                                                                                                                                                                                  | Intention-to-treat               |
| Subject analysis set description:<br>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. |                                  |

### Primary: Percentage of Subjects who were Responders

|                                                                                                                                                                                                                         |                                            |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
| End point title                                                                                                                                                                                                         | Percentage of Subjects who were Responders |
| End point description:<br>Responders are defined as subjects with $\geq 50\%$ reduction in partial onset seizures (POS) frequency during the double-blind treatment phase, relative to the pretreatment baseline phase. |                                            |
| End point type                                                                                                                                                                                                          | Primary                                    |
| End point timeframe:<br>Day 85                                                                                                                                                                                          |                                            |

| End point values              | Placebo            | Carisbamate 200 mg | Carisbamate 400 mg |  |
|-------------------------------|--------------------|--------------------|--------------------|--|
| Subject group type            | Reporting group    | Reporting group    | Reporting group    |  |
| Number of subjects analysed   | 188 <sup>[1]</sup> | 186 <sup>[2]</sup> | 181 <sup>[3]</sup> |  |
| Units: Percentage of Subjects |                    |                    |                    |  |
| number (not applicable)       | 21.3               | 23.1               | 23.8               |  |

Notes:

[1] - ITT Population

[2] - ITT Population

[3] - ITT Population

### Statistical analyses

|                            |                              |
|----------------------------|------------------------------|
| Statistical analysis title | Statistical analysis         |
| Comparison groups          | Placebo v Carisbamate 200 mg |

|                                         |                                          |
|-----------------------------------------|------------------------------------------|
| Number of subjects included in analysis | 374                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.637 <sup>[4]</sup>                   |
| Method                                  | Generalized Cochran-Mantel-Haenszel test |
| Parameter estimate                      | Difference between treatment groups      |
| Point estimate                          | 1.84                                     |
| Confidence interval                     |                                          |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -6.58                                    |
| upper limit                             | 10.26                                    |

Notes:

[4] - Pairwise comparison: p-values from Generalized Cochran-Mantel-Haenszel test for nonzero correlation controlling for pooled country.

|                                         |                                         |
|-----------------------------------------|-----------------------------------------|
| <b>Statistical analysis title</b>       | Statistical analysis                    |
| Comparison groups                       | Carisbamate 400 mg v Placebo            |
| Number of subjects included in analysis | 369                                     |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority                             |
| P-value                                 | = 0.553 <sup>[5]</sup>                  |
| Method                                  | Generalized Cochran-Mantel-Haenszel tes |
| Parameter estimate                      | Difference between treatment groups     |
| Point estimate                          | 2.48                                    |
| Confidence interval                     |                                         |
| level                                   | 95 %                                    |
| sides                                   | 2-sided                                 |
| lower limit                             | -6.04                                   |
| upper limit                             | 11                                      |

Notes:

[5] - p-values from Generalized Cochran-Mantel-Haenszel test for nonzero correlation controlling for pooled country.

### **Secondary: Change From Baseline to the end of the Double-Blind Treatment Phase in the Recovery (After Seizures) Composite Score of the Seizure Severity Questionnaire (SSQ) Score**

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

End point description:

The SSQ is a 10-item questionnaire designed to track seizure severity. It is organized into 3 components: the Warning, Activity-movement, and Recovery aspects of seizures. The score of SSQ ranges on a 7-point Likert scale (ranging from very mild/helpful/no bother at all [1] to very severe/no help/bothersome [7]) and lower scores represent better function. Recovery Phase Composite Score were reported.

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

End point timeframe:

Baseline up to Day 85

| End point values                     | Placebo            | Carisbamate 200 mg | Carisbamate 400 mg |  |
|--------------------------------------|--------------------|--------------------|--------------------|--|
| Subject group type                   | Reporting group    | Reporting group    | Reporting group    |  |
| Number of subjects analysed          | 188 <sup>[6]</sup> | 185 <sup>[7]</sup> | 180 <sup>[8]</sup> |  |
| Units: Unit on a Scale               |                    |                    |                    |  |
| arithmetic mean (standard deviation) | -0.6 (± 1.91)      | -0.8 (± 2.02)      | -1 (± 2.01)        |  |

Notes:

[6] - ITT Population

[7] - ITT Population

[8] - ITT Population

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline to the end of the Double-Blind Treatment Phase in Overall and Subscale Scores of Seizure Severity Questionnaire (SSQ) Score

|                 |                                                                                                                                                  |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Change From Baseline to the end of the Double-Blind Treatment Phase in Overall and Subscale Scores of Seizure Severity Questionnaire (SSQ) Score |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The SSQ is a 10-item questionnaire designed to track seizure severity. It is organized into 3 components: the Warning, Activity-movement, and Recovery aspects of seizures. The score of SSQ ranges on a 7-point Likert scale (ranging from very mild/helpful/no bother at all [1] to very severe/no help/bothersome [7]) and lower scores represent better function.

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

End point timeframe:

Baseline up to Day 85 (Endpoint)

| End point values                                  | Placebo            | Carisbamate 200 mg  | Carisbamate 400 mg  |  |
|---------------------------------------------------|--------------------|---------------------|---------------------|--|
| Subject group type                                | Reporting group    | Reporting group     | Reporting group     |  |
| Number of subjects analysed                       | 173 <sup>[9]</sup> | 171 <sup>[10]</sup> | 168 <sup>[11]</sup> |  |
| Units: Unit on a scale                            |                    |                     |                     |  |
| arithmetic mean (standard deviation)              |                    |                     |                     |  |
| Baseline (BL): Total SSQ score                    | 3.9 (± 1.3)        | 3.8 (± 1.22)        | 3.9 (± 1.31)        |  |
| Change at Endpoint (EP): Total SSQ score          | -0.8 (± 1.58)      | -0.9 (± 1.66)       | -0.9 (± 1.59)       |  |
| BL: Before seizures component score               | 3.6 (± 2.14)       | 3.6 (± 1.97)        | 3.8 (± 1.77)        |  |
| Change at EP: Before seizures component score     | -0.4 (± 2.36)      | -0.5 (± 2.43)       | -0.6 (± 2.01)       |  |
| BL: During seizures component score               | 4.3 (± 1.5)        | 4.3 (± 1.5)         | 4.3 (± 1.58)        |  |
| Change at EP: During seizures component score     | -0.8 (± 1.78)      | -0.9 (± 1.99)       | -0.8 (± 2.06)       |  |
| BL: Severity and bother component score           | 4.4 (± 1.48)       | 4.4 (± 1.25)        | 4.4 (± 1.37)        |  |
| Change at EP: Severity and bother component score | -0.9 (± 1.82)      | -1.1 (± 1.84)       | -0.9 (± 1.9)        |  |
| BL: cognitive subcomponent score                  | 2.8 (± 2.64)       | 2.9 (± 2.54)        | 2.8 (± 2.6)         |  |
| Change at EP: cognitive subcomponent score        | -0.6 (± 2.45)      | -0.9 (± 2.38)       | -1.1 (± 2.45)       |  |
| BL: emotional subcomponent score                  | 2.2 (± 2.52)       | 2.3 (± 2.54)        | 2.2 (± 2.53)        |  |
| Change at EP: emotional subcomponent score        | -0.5 (± 2.41)      | -0.8 (± 2.2)        | -0.8 (± 2.57)       |  |

|                                                   |               |               |               |  |
|---------------------------------------------------|---------------|---------------|---------------|--|
| BL: physical effects subcomponent score           | 3.4 (± 2.55)  | 3.1 (± 2.53)  | 3.5 (± 2.52)  |  |
| Change at EP: physical effects subcomponent score | -0.8 (± 2.34) | -0.9 (± 2.63) | -1.2 (± 2.46) |  |
| BL: frequency subcomponent score                  | 3.1 (± 2.3)   | 3 (± 2.36)    | 3.1 (± 2.33)  |  |
| Change at EP: frequency subcomponent score        | -0.7 (± 2.13) | -0.8 (± 2.2)  | -1.1 (± 2.15) |  |
| BL: severity subcomponent score                   | 2.6 (± 2.03)  | 2.6 (± 2.11)  | 2.6 (± 2.03)  |  |
| Change at EP: severity subcomponent score         | -0.6 (± 1.82) | -0.8 (± 1.96) | -1 (± 1.95)   |  |
| BL: bother subcomponent score                     | 2.7 (± 2.14)  | 2.7 (± 2.24)  | 2.7 (± 2.23)  |  |
| Change at EP: bother subcomponent score           | -0.6 (± 2)    | -0.9 (± 2.13) | -1 (± 2.17)   |  |

Notes:

[9] - ITT Population

[10] - ITT Population

[11] - ITT Population

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline to the end of the Double-Blind Treatment Phase in Overall and Subscale Scores of Quality of Life in Epilepsy-31-Problems (QOLIE-31-P) Score

|                 |                                                                                                                                                                  |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Change From Baseline to the end of the Double-Blind Treatment Phase in Overall and Subscale Scores of Quality of Life in Epilepsy-31-Problems (QOLIE-31-P) Score |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The QOLIE-31-P is an expansion of the QOLIE-31 which includes items to assess distress associated with each quality of life domain, overall change in distress, and priority of importance of each domain. It is a 39-item self-administered questionnaire designed to assess generic and epilepsy specific health-related issues. It includes 7 subscales: seizure worry, overall quality of life (QOL), emotional well-being, energy-fatigue, cognitive functioning, medication effects, social function, the health status item, and the additional items on distress and priority of importance of each of the domains. Higher scores represent better function.

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

End point timeframe:

Baseline up Day 85 (Endpoint)

| End point values                       | Placebo             | Carisbamate 200 mg  | Carisbamate 400 mg  |  |
|----------------------------------------|---------------------|---------------------|---------------------|--|
| Subject group type                     | Reporting group     | Reporting group     | Reporting group     |  |
| Number of subjects analysed            | 174 <sup>[12]</sup> | 169 <sup>[13]</sup> | 169 <sup>[14]</sup> |  |
| Units: Unit on a scale                 |                     |                     |                     |  |
| arithmetic mean (standard deviation)   |                     |                     |                     |  |
| Baseline (BL): Overall Score           | 57 (± 14.96)        | 55.7 (± 16.32)      | 55.3 (± 16.47)      |  |
| Change at Endpoint (EP): Overall Score | 4.3 (± 10.75)       | 3.6 (± 10.53)       | 4.5 (± 10.85)       |  |
| BL: Seizure worry                      | 43.6 (± 27.81)      | 43 (± 25.39)        | 43.3 (± 27.47)      |  |
| Change at EP: Seizure worry            | 7.2 (± 21.03)       | 6.4 (± 19.89)       | 6 (± 22.34)         |  |
| BL: Overall quality of life            | 58.2 (± 15.56)      | 56.8 (± 16)         | 54.8 (± 16.85)      |  |
| Change at EP: Overall quality of life  | 5.6 (± 15.63)       | 5.2 (± 15.05)       | 5.1 (± 14.36)       |  |
| BL: Emotional well-being               | 62.6 (± 18.07)      | 61.3 (± 18.29)      | 60.7 (± 19.17)      |  |
| Change at EP: Emotional well-being     | 3.6 (± 14.63)       | 2.2 (± 14.25)       | 4.1 (± 16.03)       |  |

|                                           |                |                |                |  |
|-------------------------------------------|----------------|----------------|----------------|--|
| BL: Energy-fatigue                        | 54 (± 16.07)   | 55.3 (± 18.18) | 55.6 (± 19.38) |  |
| Change at EP: Energy-fatigue              | 4.3 (± 14.96)  | 3.2 (± 16.34)  | 3.9 (± 16.66)  |  |
| BL: Cognitive function                    | 57.6 (± 23.41) | 55.7 (± 24.37) | 56.2 (± 22.34) |  |
| Change at EP: Cognitive function          | 4.1 (± 16.93)  | 2.4 (± 16.81)  | 4.2 (± 17.19)  |  |
| BL: Medication effects                    | 59.6 (± 27.11) | 56.8 (± 28.27) | 59.1 (± 25.27) |  |
| Change at EP: Medication effects          | -0.8 (± 27.32) | 5.3 (± 23.51)  | 1.6 (± 22.34)  |  |
| BL: Social function                       | 57.8 (± 22.3)  | 55.8 (± 23.45) | 54.7 (± 24.98) |  |
| Change at EP: Social function             | 4 (± 21.02)    | 4.2 (± 20.41)  | 5.1 (± 21.79)  |  |
| BL: Visual analog health status           | 60.2 (± 17.32) | 59.2 (± 18.39) | 55.3 (± 19.7)  |  |
| Change at EP: Visual analog health status | 3.7 (± 19.75)  | 5.1 (± 17.29)  | 6.1 (± 18.74)  |  |

Notes:

[12] - ITT population

[13] - ITT Population

[14] - ITT Population

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline to the end of the Double-Blind Treatment Phase in Hospital Anxiety and Depression Scale (HADS) Score

|                 |                                                                                                                           |
|-----------------|---------------------------------------------------------------------------------------------------------------------------|
| End point title | Change From Baseline to the end of the Double-Blind Treatment Phase in Hospital Anxiety and Depression Scale (HADS) Score |
|-----------------|---------------------------------------------------------------------------------------------------------------------------|

End point description:

The HADS is a brief, self-administered questionnaire designed to assess the presence of an anxiety or depressive disorder in medically ill outpatients in non-psychiatric hospital settings. The HADS consists of Anxiety and Depression subscales. Each item is rated on a 4-point scale from 0 to 3 representing frequency of symptoms. For each subscale, higher scores indicate greater dysfunction.

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

End point timeframe:

Baseline up to Day 85 (Endpoint)

| End point values                     | Placebo             | Carisbamate 200 mg  | Carisbamate 400 mg  |  |
|--------------------------------------|---------------------|---------------------|---------------------|--|
| Subject group type                   | Reporting group     | Reporting group     | Reporting group     |  |
| Number of subjects analysed          | 174 <sup>[15]</sup> | 168 <sup>[16]</sup> | 169 <sup>[17]</sup> |  |
| Units: Unit on a Scale               |                     |                     |                     |  |
| arithmetic mean (standard deviation) |                     |                     |                     |  |
| Baseline: Depression score           | 6 (± 3.97)          | 5.7 (± 3.7)         | 5.9 (± 3.88)        |  |
| Change at Endpoint: Depression score | -0.9 (± 3.74)       | -0.9 (± 3.18)       | -0.8 (± 3.09)       |  |
| Baseline: Anxiety score              | 7.4 (± 3.87)        | 7.9 (± 3.8)         | 7.5 (± 3.72)        |  |
| Change at Endpoint: Anxiety score    | -0.8 (± 3.4)        | -1 (± 2.91)         | -1.2 (± 3.18)       |  |

Notes:

[15] - ITT Population

[16] - ITT Population

[17] - ITT Population

## Statistical analyses

**Secondary: Change From Baseline to the end of the Double-Blind Treatment Phase in EuroQol-5D (EQ-5D) Score**

|                 |                                                                                                 |
|-----------------|-------------------------------------------------------------------------------------------------|
| End point title | Change From Baseline to the end of the Double-Blind Treatment Phase in EuroQol-5D (EQ-5D) Score |
|-----------------|-------------------------------------------------------------------------------------------------|

## End point description:

The EQ-5D is a 5-dimensional health state classification to assess preference-based health-related functional status. The 5 dimensions are mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated by a single question on a 3-point ordinal scale (no problems, some problems, extreme problems). Higher scores on this self-administered scale represent better health.

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

## End point timeframe:

Baseline up to Day 85 (Endpoint)

| End point values                            | Placebo             | Carisbamate 200 mg  | Carisbamate 400 mg  |  |
|---------------------------------------------|---------------------|---------------------|---------------------|--|
| Subject group type                          | Reporting group     | Reporting group     | Reporting group     |  |
| Number of subjects analysed                 | 174 <sup>[18]</sup> | 167 <sup>[19]</sup> | 169 <sup>[20]</sup> |  |
| Units: Unit on a scale                      |                     |                     |                     |  |
| arithmetic mean (standard deviation)        |                     |                     |                     |  |
| Baseline: Overall utility score             | 0.75 (± 0.232)      | 0.78 (± 0.214)      | 0.76 (± 0.224)      |  |
| Change at Endpoint: Overall utility score   | 0.04 (± 0.241)      | 0.03 (± 0.233)      | 0.08 (± 0.209)      |  |
| Baseline: Self-reported VAS score           | 65.89 (± 17.549)    | 66.07 (± 18.771)    | 63.83 (± 21.705)    |  |
| Change at Endpoint: Self-reported VAS score | 2.18 (± 18.272)     | 3.31 (± 16.013)     | 4.09 (± 18.697)     |  |

## Notes:

[18] - ITT Population

[19] - ITT Population

[20] - ITT Population

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Percent Reduction From Baseline to Double Blind Treatment in Generalized Seizures**

|                 |                                                                                   |
|-----------------|-----------------------------------------------------------------------------------|
| End point title | Percent Reduction From Baseline to Double Blind Treatment in Generalized Seizures |
|-----------------|-----------------------------------------------------------------------------------|

## End point description:

Change in generalized seizure frequency evaluated as the percent reduction from the pretreatment baseline phase in generalized seizure frequency compared with the double blind treatment phase

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

## End point timeframe:

Baseline up to Day 85 (Endpoint)

| End point values              | Placebo            | Carisbamate 200 mg | Carisbamate 400 mg |  |
|-------------------------------|--------------------|--------------------|--------------------|--|
| Subject group type            | Reporting group    | Reporting group    | Reporting group    |  |
| Number of subjects analysed   | 84 <sup>[21]</sup> | 95 <sup>[22]</sup> | 81 <sup>[23]</sup> |  |
| Units: Percent Change         |                    |                    |                    |  |
| median (full range (min-max)) |                    |                    |                    |  |
| Baseline                      | 3.1 (0 to 34)      | 2.4 (0 to 72)      | 2.5 (0 to 62)      |  |
| Percent Change at Endpoint    | 28.3 (-340 to 100) | 35.9 (-340 to 100) | 29.3 (-340 to 100) |  |

Notes:

[21] - ITT Population

[22] - ITT Population

[23] - ITT Population

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percent Reduction from Baseline to Double Blind Treatment in Average Monthly Seizure-Free Days

|                 |                                                                                                |
|-----------------|------------------------------------------------------------------------------------------------|
| End point title | Percent Reduction from Baseline to Double Blind Treatment in Average Monthly Seizure-Free Days |
|-----------------|------------------------------------------------------------------------------------------------|

End point description:

Seizure-free days evaluated as the percent change from the pretreatment baseline phase in average monthly seizure-free days per 28 days compared with the double-blind treatment phase.

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

End point timeframe:

Baseline up to Day 85 (Endpoint)

| End point values                     | Placebo             | Carisbamate 200 mg  | Carisbamate 400 mg  |  |
|--------------------------------------|---------------------|---------------------|---------------------|--|
| Subject group type                   | Reporting group     | Reporting group     | Reporting group     |  |
| Number of subjects analysed          | 188 <sup>[24]</sup> | 186 <sup>[25]</sup> | 181 <sup>[26]</sup> |  |
| Units: Percent Chanes                |                     |                     |                     |  |
| arithmetic mean (standard deviation) |                     |                     |                     |  |
| Baseline                             | 20 (± 6.18)         | 20 (± 5.81)         | 20.2 (± 5.28)       |  |
| Percent Change at Endpoint           | 15.9 (± 75.86)      | 33.6 (± 265.6)      | 17.6 (± 102.32)     |  |

Notes:

[24] - ITT Population

[25] - ITT Population

[26] - ITT Population

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percent Reduction from Baseline to Double Blind Treatment in Partial Onset Seizure Frequency

|                 |                                                                                              |
|-----------------|----------------------------------------------------------------------------------------------|
| End point title | Percent Reduction from Baseline to Double Blind Treatment in Partial Onset Seizure Frequency |
|-----------------|----------------------------------------------------------------------------------------------|

---

End point description:

Change in Partial Onset Seizure Frequency evaluated as the percent reduction from the pretreatment baseline phase in Partial Onset Seizure Frequency compared with the double blind treatment phase

---

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

---

End point timeframe:

Baseline up to Day 85 (Endpoint)

---

| End point values              | Placebo             | Carisbamate<br>200 mg | Carisbamate<br>400 mg |  |
|-------------------------------|---------------------|-----------------------|-----------------------|--|
| Subject group type            | Reporting group     | Reporting group       | Reporting group       |  |
| Number of subjects analysed   | 188 <sup>[27]</sup> | 186 <sup>[28]</sup>   | 181 <sup>[29]</sup>   |  |
| Units: Percent change         |                     |                       |                       |  |
| median (full range (min-max)) |                     |                       |                       |  |
| Baseline                      | 6.75 (2.5 to 260.4) | 7 (2 to 274.2)        | 7.5 (2 to 258.2)      |  |
| Percentage Change at Endpoint | 15.11 (-308 to 100) | 21.59 (-280 to 100)   | 21.03 (-692 to 100)   |  |

Notes:

[27] - ITT Population

[28] - ITT Population

[29] - ITT Population

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Day 1 to End of treatment

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

### Dictionary used

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

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

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subject received placebo matching with carisbamate orally twice daily from Day 1 up to Week 12.

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Carisbamate 400 mg |
|-----------------------|--------------------|

Reporting group description:

Subject received Carisbamate 200 mg orally in 2 equally divided doses twice daily from Day 1 up to Week 12.

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | Carisbamate 200 mg |
|-----------------------|--------------------|

Reporting group description:

The dosages of carisbamate were 200 milligram/day (mg/day), administered in 2 equally divided doses.

| Serious adverse events                                              | Placebo         | Carisbamate 400 mg | Carisbamate 200 mg |
|---------------------------------------------------------------------|-----------------|--------------------|--------------------|
| Total subjects affected by serious adverse events                   |                 |                    |                    |
| subjects affected / exposed                                         | 5 / 189 (2.65%) | 5 / 185 (2.70%)    | 4 / 188 (2.13%)    |
| number of deaths (all causes)                                       | 0               | 0                  | 0                  |
| number of deaths resulting from adverse events                      |                 |                    |                    |
| Investigations                                                      |                 |                    |                    |
| Electrocardiogram T Wave Inversion                                  |                 |                    |                    |
| subjects affected / exposed                                         | 0 / 189 (0.00%) | 0 / 185 (0.00%)    | 1 / 188 (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              |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                 |                    |                    |
| Neoplasm Progression                                                |                 |                    |                    |
| subjects affected / exposed                                         | 0 / 189 (0.00%) | 1 / 185 (0.54%)    | 0 / 188 (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              |
| Injury, poisoning and procedural complications                      |                 |                    |                    |
| Ankle Fracture                                                      |                 |                    |                    |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 189 (0.53%) | 0 / 185 (0.00%) | 0 / 188 (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           |
| Contusion                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 189 (0.00%) | 0 / 185 (0.00%) | 1 / 188 (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           |
| Femur Fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 189 (0.00%) | 0 / 185 (0.00%) | 1 / 188 (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           |
| Lumbar Vertebral Fracture                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 189 (0.53%) | 0 / 185 (0.00%) | 0 / 188 (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           |
| Road Traffic Accident                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 189 (0.53%) | 0 / 185 (0.00%) | 0 / 188 (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                     | 1 / 189 (0.53%) | 0 / 185 (0.00%) | 0 / 188 (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           |
| Extrapyramidal Disorder                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 189 (0.00%) | 1 / 185 (0.54%) | 0 / 188 (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           |
| Blood and lymphatic system disorders            |                 |                 |                 |
| Lymphadenitis                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 189 (0.00%) | 0 / 185 (0.00%) | 1 / 188 (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                      |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Gastritis                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 189 (0.00%) | 1 / 185 (0.54%) | 0 / 188 (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           |
| Haematochezia                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 189 (0.53%) | 0 / 185 (0.00%) | 0 / 188 (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           |
| Vomiting                                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 189 (0.00%) | 1 / 185 (0.54%) | 0 / 188 (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           |
| Renal and urinary disorders                     |                 |                 |                 |
| Nephrolithiasis                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 189 (0.53%) | 0 / 185 (0.00%) | 0 / 188 (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           |
| Infections and infestations                     |                 |                 |                 |
| Abscess                                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 189 (0.00%) | 0 / 185 (0.00%) | 1 / 188 (0.53%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Furuncle                                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 189 (0.00%) | 1 / 185 (0.54%) | 0 / 188 (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           |
| Hepatitis B                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 189 (0.00%) | 1 / 185 (0.54%) | 0 / 188 (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           |
| Viral Infection                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 189 (0.00%) | 1 / 185 (0.54%) | 0 / 188 (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           |

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

| <b>Non-serious adverse events</b>                     | Placebo           | Carisbamate 400 mg | Carisbamate 200 mg |
|-------------------------------------------------------|-------------------|--------------------|--------------------|
| Total subjects affected by non-serious adverse events |                   |                    |                    |
| subjects affected / exposed                           | 85 / 189 (44.97%) | 96 / 185 (51.89%)  | 86 / 188 (45.74%)  |
| Vascular disorders                                    |                   |                    |                    |
| Hypertension                                          |                   |                    |                    |
| subjects affected / exposed                           | 3 / 189 (1.59%)   | 1 / 185 (0.54%)    | 0 / 188 (0.00%)    |
| occurrences (all)                                     | 11                | 1                  | 0                  |
| General disorders and administration site conditions  |                   |                    |                    |
| Asthenia                                              |                   |                    |                    |
| subjects affected / exposed                           | 1 / 189 (0.53%)   | 3 / 185 (1.62%)    | 3 / 188 (1.60%)    |
| occurrences (all)                                     | 1                 | 3                  | 3                  |
| Chest Pain                                            |                   |                    |                    |
| subjects affected / exposed                           | 1 / 189 (0.53%)   | 1 / 185 (0.54%)    | 2 / 188 (1.06%)    |
| occurrences (all)                                     | 1                 | 1                  | 3                  |
| Fatigue                                               |                   |                    |                    |
| subjects affected / exposed                           | 3 / 189 (1.59%)   | 7 / 185 (3.78%)    | 4 / 188 (2.13%)    |
| occurrences (all)                                     | 4                 | 7                  | 5                  |
| Irritability                                          |                   |                    |                    |
| subjects affected / exposed                           | 1 / 189 (0.53%)   | 0 / 185 (0.00%)    | 3 / 188 (1.60%)    |
| occurrences (all)                                     | 1                 | 0                  | 3                  |
| Oedema Peripheral                                     |                   |                    |                    |
| subjects affected / exposed                           | 2 / 189 (1.06%)   | 0 / 185 (0.00%)    | 2 / 188 (1.06%)    |
| occurrences (all)                                     | 2                 | 0                  | 3                  |
| Pyrexia                                               |                   |                    |                    |
| subjects affected / exposed                           | 2 / 189 (1.06%)   | 4 / 185 (2.16%)    | 6 / 188 (3.19%)    |
| occurrences (all)                                     | 2                 | 4                  | 6                  |
| Respiratory, thoracic and mediastinal disorders       |                   |                    |                    |
| Cough                                                 |                   |                    |                    |
| subjects affected / exposed                           | 1 / 189 (0.53%)   | 0 / 185 (0.00%)    | 2 / 188 (1.06%)    |
| occurrences (all)                                     | 2                 | 0                  | 2                  |

|                                                                                              |                      |                       |                      |
|----------------------------------------------------------------------------------------------|----------------------|-----------------------|----------------------|
| Pharyngolaryngeal Pain<br>subjects affected / exposed<br>occurrences (all)                   | 3 / 189 (1.59%)<br>3 | 1 / 185 (0.54%)<br>1  | 1 / 188 (0.53%)<br>1 |
| Psychiatric disorders                                                                        |                      |                       |                      |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)                                  | 2 / 189 (1.06%)<br>2 | 1 / 185 (0.54%)<br>2  | 2 / 188 (1.06%)<br>2 |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                                 | 3 / 189 (1.59%)<br>3 | 5 / 185 (2.70%)<br>10 | 1 / 188 (0.53%)<br>1 |
| Investigations                                                                               |                      |                       |                      |
| Alanine Aminotransferase Increased<br>subjects affected / exposed<br>occurrences (all)       | 3 / 189 (1.59%)<br>3 | 3 / 185 (1.62%)<br>3  | 2 / 188 (1.06%)<br>2 |
| Aspartate Aminotransferase Increased<br>subjects affected / exposed<br>occurrences (all)     | 3 / 189 (1.59%)<br>3 | 3 / 185 (1.62%)<br>3  | 2 / 188 (1.06%)<br>2 |
| Blood Alkaline Phosphatase Increased<br>subjects affected / exposed<br>occurrences (all)     | 2 / 189 (1.06%)<br>2 | 0 / 185 (0.00%)<br>0  | 3 / 188 (1.60%)<br>3 |
| Blood Creatine Phosphokinase Increased<br>subjects affected / exposed<br>occurrences (all)   | 1 / 189 (0.53%)<br>1 | 1 / 185 (0.54%)<br>1  | 3 / 188 (1.60%)<br>4 |
| Blood Glucose Increased<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 189 (0.00%)<br>0 | 1 / 185 (0.54%)<br>1  | 2 / 188 (1.06%)<br>2 |
| International Normalised Ratio Increased<br>subjects affected / exposed<br>occurrences (all) | 1 / 189 (0.53%)<br>1 | 2 / 185 (1.08%)<br>2  | 0 / 188 (0.00%)<br>0 |
| Neutrophil Count Decreased<br>subjects affected / exposed<br>occurrences (all)               | 1 / 189 (0.53%)<br>1 | 0 / 185 (0.00%)<br>0  | 3 / 188 (1.60%)<br>4 |
| Platelet Count Decreased                                                                     |                      |                       |                      |

|                                                                                      |                      |                      |                      |
|--------------------------------------------------------------------------------------|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                                     | 2 / 189 (1.06%)<br>2 | 1 / 185 (0.54%)<br>2 | 2 / 188 (1.06%)<br>2 |
| Red Blood Cell Count Decreased<br>subjects affected / exposed<br>occurrences (all)   | 0 / 189 (0.00%)<br>0 | 0 / 185 (0.00%)<br>0 | 2 / 188 (1.06%)<br>2 |
| Weight Increased<br>subjects affected / exposed<br>occurrences (all)                 | 3 / 189 (1.59%)<br>3 | 0 / 185 (0.00%)<br>0 | 1 / 188 (0.53%)<br>1 |
| White Blood Cell Count Decreased<br>subjects affected / exposed<br>occurrences (all) | 3 / 189 (1.59%)<br>3 | 1 / 185 (0.54%)<br>1 | 2 / 188 (1.06%)<br>2 |
| Injury, poisoning and procedural complications                                       |                      |                      |                      |
| Contusion<br>subjects affected / exposed<br>occurrences (all)                        | 1 / 189 (0.53%)<br>1 | 2 / 185 (1.08%)<br>2 | 0 / 188 (0.00%)<br>0 |
| Excoriation<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 189 (0.00%)<br>0 | 0 / 185 (0.00%)<br>0 | 3 / 188 (1.60%)<br>4 |
| Skin Laceration<br>subjects affected / exposed<br>occurrences (all)                  | 2 / 189 (1.06%)<br>2 | 1 / 185 (0.54%)<br>1 | 1 / 188 (0.53%)<br>1 |
| Cardiac disorders                                                                    |                      |                      |                      |
| Palpitations<br>subjects affected / exposed<br>occurrences (all)                     | 2 / 189 (1.06%)<br>2 | 1 / 185 (0.54%)<br>1 | 0 / 188 (0.00%)<br>0 |
| Sinus Bradycardia<br>subjects affected / exposed<br>occurrences (all)                | 0 / 189 (0.00%)<br>0 | 3 / 185 (1.62%)<br>3 | 1 / 188 (0.53%)<br>1 |
| Nervous system disorders                                                             |                      |                      |                      |
| Amnesia<br>subjects affected / exposed<br>occurrences (all)                          | 1 / 189 (0.53%)<br>1 | 2 / 185 (1.08%)<br>2 | 0 / 188 (0.00%)<br>0 |
| Balance Disorder<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 189 (0.53%)<br>1 | 0 / 185 (0.00%)<br>0 | 4 / 188 (2.13%)<br>5 |
| Coordination Abnormal                                                                |                      |                      |                      |

|                                      |                   |                   |                   |
|--------------------------------------|-------------------|-------------------|-------------------|
| subjects affected / exposed          | 0 / 189 (0.00%)   | 0 / 185 (0.00%)   | 2 / 188 (1.06%)   |
| occurrences (all)                    | 0                 | 0                 | 2                 |
| Dizziness                            |                   |                   |                   |
| subjects affected / exposed          | 13 / 189 (6.88%)  | 24 / 185 (12.97%) | 16 / 188 (8.51%)  |
| occurrences (all)                    | 16                | 30                | 23                |
| Epilepsy                             |                   |                   |                   |
| subjects affected / exposed          | 1 / 189 (0.53%)   | 4 / 185 (2.16%)   | 2 / 188 (1.06%)   |
| occurrences (all)                    | 1                 | 4                 | 3                 |
| Headache                             |                   |                   |                   |
| subjects affected / exposed          | 22 / 189 (11.64%) | 22 / 185 (11.89%) | 24 / 188 (12.77%) |
| occurrences (all)                    | 80                | 51                | 82                |
| Hypokinesia                          |                   |                   |                   |
| subjects affected / exposed          | 0 / 189 (0.00%)   | 0 / 185 (0.00%)   | 2 / 188 (1.06%)   |
| occurrences (all)                    | 0                 | 0                 | 2                 |
| Memory Impairment                    |                   |                   |                   |
| subjects affected / exposed          | 2 / 189 (1.06%)   | 0 / 185 (0.00%)   | 1 / 188 (0.53%)   |
| occurrences (all)                    | 2                 | 0                 | 1                 |
| Paraesthesia                         |                   |                   |                   |
| subjects affected / exposed          | 0 / 189 (0.00%)   | 1 / 185 (0.54%)   | 2 / 188 (1.06%)   |
| occurrences (all)                    | 0                 | 1                 | 3                 |
| Somnolence                           |                   |                   |                   |
| subjects affected / exposed          | 7 / 189 (3.70%)   | 17 / 185 (9.19%)  | 17 / 188 (9.04%)  |
| occurrences (all)                    | 9                 | 17                | 26                |
| Speech Disorder                      |                   |                   |                   |
| subjects affected / exposed          | 0 / 189 (0.00%)   | 0 / 185 (0.00%)   | 2 / 188 (1.06%)   |
| occurrences (all)                    | 0                 | 0                 | 2                 |
| Tremor                               |                   |                   |                   |
| subjects affected / exposed          | 1 / 189 (0.53%)   | 1 / 185 (0.54%)   | 3 / 188 (1.60%)   |
| occurrences (all)                    | 1                 | 1                 | 5                 |
| Blood and lymphatic system disorders |                   |                   |                   |
| Anaemia                              |                   |                   |                   |
| subjects affected / exposed          | 2 / 189 (1.06%)   | 1 / 185 (0.54%)   | 0 / 188 (0.00%)   |
| occurrences (all)                    | 2                 | 1                 | 0                 |
| Ear and labyrinth disorders          |                   |                   |                   |
| Vertigo                              |                   |                   |                   |

|                                                  |                      |                      |                      |
|--------------------------------------------------|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all) | 3 / 189 (1.59%)<br>5 | 4 / 185 (2.16%)<br>4 | 4 / 188 (2.13%)<br>4 |
| Eye disorders                                    |                      |                      |                      |
| Diplopia                                         |                      |                      |                      |
| subjects affected / exposed                      | 0 / 189 (0.00%)      | 3 / 185 (1.62%)      | 1 / 188 (0.53%)      |
| occurrences (all)                                | 0                    | 6                    | 1                    |
| Lacrimation Increased                            |                      |                      |                      |
| subjects affected / exposed                      | 0 / 189 (0.00%)      | 2 / 185 (1.08%)      | 1 / 188 (0.53%)      |
| occurrences (all)                                | 0                    | 2                    | 1                    |
| Vision Blurred                                   |                      |                      |                      |
| subjects affected / exposed                      | 2 / 189 (1.06%)      | 2 / 185 (1.08%)      | 4 / 188 (2.13%)      |
| occurrences (all)                                | 2                    | 3                    | 4                    |
| Gastrointestinal disorders                       |                      |                      |                      |
| Abdominal Pain                                   |                      |                      |                      |
| subjects affected / exposed                      | 3 / 189 (1.59%)      | 1 / 185 (0.54%)      | 0 / 188 (0.00%)      |
| occurrences (all)                                | 4                    | 14                   | 0                    |
| Abdominal Pain Upper                             |                      |                      |                      |
| subjects affected / exposed                      | 7 / 189 (3.70%)      | 2 / 185 (1.08%)      | 4 / 188 (2.13%)      |
| occurrences (all)                                | 8                    | 2                    | 5                    |
| Constipation                                     |                      |                      |                      |
| subjects affected / exposed                      | 2 / 189 (1.06%)      | 3 / 185 (1.62%)      | 2 / 188 (1.06%)      |
| occurrences (all)                                | 2                    | 3                    | 3                    |
| Diarrhoea                                        |                      |                      |                      |
| subjects affected / exposed                      | 2 / 189 (1.06%)      | 6 / 185 (3.24%)      | 3 / 188 (1.60%)      |
| occurrences (all)                                | 2                    | 7                    | 3                    |
| Nausea                                           |                      |                      |                      |
| subjects affected / exposed                      | 5 / 189 (2.65%)      | 5 / 185 (2.70%)      | 5 / 188 (2.66%)      |
| occurrences (all)                                | 5                    | 5                    | 5                    |
| Toothache                                        |                      |                      |                      |
| subjects affected / exposed                      | 2 / 189 (1.06%)      | 1 / 185 (0.54%)      | 0 / 188 (0.00%)      |
| occurrences (all)                                | 2                    | 1                    | 0                    |
| Vomiting                                         |                      |                      |                      |
| subjects affected / exposed                      | 1 / 189 (0.53%)      | 3 / 185 (1.62%)      | 3 / 188 (1.60%)      |
| occurrences (all)                                | 1                    | 4                    | 6                    |
| Skin and subcutaneous tissue disorders           |                      |                      |                      |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Alopecia                                        |                 |                 |                 |
| subjects affected / exposed                     | 6 / 189 (3.17%) | 0 / 185 (0.00%) | 0 / 188 (0.00%) |
| occurrences (all)                               | 6               | 0               | 0               |
| Hyperhidrosis                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 189 (0.00%) | 2 / 185 (1.08%) | 0 / 188 (0.00%) |
| occurrences (all)                               | 0               | 2               | 0               |
| Pruritus                                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 189 (0.00%) | 2 / 185 (1.08%) | 2 / 188 (1.06%) |
| occurrences (all)                               | 0               | 2               | 2               |
| Pruritus Generalised                            |                 |                 |                 |
| subjects affected / exposed                     | 2 / 189 (1.06%) | 0 / 185 (0.00%) | 0 / 188 (0.00%) |
| occurrences (all)                               | 3               | 0               | 0               |
| Rash                                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 189 (0.00%) | 3 / 185 (1.62%) | 4 / 188 (2.13%) |
| occurrences (all)                               | 0               | 3               | 4               |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Back Pain                                       |                 |                 |                 |
| subjects affected / exposed                     | 3 / 189 (1.59%) | 3 / 185 (1.62%) | 3 / 188 (1.60%) |
| occurrences (all)                               | 3               | 3               | 3               |
| Musculoskeletal Chest Pain                      |                 |                 |                 |
| subjects affected / exposed                     | 2 / 189 (1.06%) | 0 / 185 (0.00%) | 1 / 188 (0.53%) |
| occurrences (all)                               | 2               | 0               | 1               |
| Musculoskeletal Pain                            |                 |                 |                 |
| subjects affected / exposed                     | 2 / 189 (1.06%) | 0 / 185 (0.00%) | 2 / 188 (1.06%) |
| occurrences (all)                               | 2               | 0               | 2               |
| Myalgia                                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 189 (0.53%) | 1 / 185 (0.54%) | 2 / 188 (1.06%) |
| occurrences (all)                               | 1               | 1               | 2               |
| Pain in Extremity                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 189 (0.53%) | 2 / 185 (1.08%) | 3 / 188 (1.60%) |
| occurrences (all)                               | 2               | 2               | 3               |
| Infections and infestations                     |                 |                 |                 |
| Gastroenteritis Viral                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 189 (0.00%) | 2 / 185 (1.08%) | 0 / 188 (0.00%) |
| occurrences (all)                               | 0               | 2               | 0               |
| Influenza                                       |                 |                 |                 |

|                                                                                                    |                       |                      |                        |
|----------------------------------------------------------------------------------------------------|-----------------------|----------------------|------------------------|
| subjects affected / exposed<br>occurrences (all)                                                   | 2 / 189 (1.06%)<br>2  | 1 / 185 (0.54%)<br>1 | 2 / 188 (1.06%)<br>4   |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                                | 7 / 189 (3.70%)<br>9  | 5 / 185 (2.70%)<br>6 | 7 / 188 (3.72%)<br>8   |
| Pharyngitis<br>subjects affected / exposed<br>occurrences (all)                                    | 2 / 189 (1.06%)<br>2  | 0 / 185 (0.00%)<br>0 | 0 / 188 (0.00%)<br>0   |
| Upper Respiratory Tract Infection<br>subjects affected / exposed<br>occurrences (all)              | 7 / 189 (3.70%)<br>10 | 6 / 185 (3.24%)<br>8 | 13 / 188 (6.91%)<br>16 |
| Urinary Tract Infection<br>subjects affected / exposed<br>occurrences (all)                        | 1 / 189 (0.53%)<br>1  | 3 / 185 (1.62%)<br>3 | 2 / 188 (1.06%)<br>2   |
| Metabolism and nutrition disorders<br>Anorexia<br>subjects affected / exposed<br>occurrences (all) | 0 / 189 (0.00%)<br>0  | 1 / 185 (0.54%)<br>1 | 2 / 188 (1.06%)<br>2   |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 02 February 2007  | Clarifications were made to inclusion and exclusion criteria to assist investigators with determination of subject eligibility. In addition, subjects with congenital short QT syndrome were now excluded. 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 endpoint to be analyzed sequentially. Adjustment in the total blood volume drawn as a result of the addition of coagulation tests to the final double-blind visit, deletion of a serum lipid profile at Visit 1, addition of a subject education video, instructions for the calculation of seizure frequency during the baseline period, more detailed procedures on drug accountability monitoring, a change to study drug packaging, and a change to the visit window for the final follow-up visit from 7 to 14 days after the last dose of study drug to 7 days after the last dose of study drug.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 11 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 ROW and in the countries of Europe, Australia, New Zealand, and South Africa, to meet United States and EMEA requirements. The responder rate was moved from a secondary end point in the United States and ROW to a primary end point for registration in Europe, Australia, New Zealand, and South Africa to meet 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, evaluation and measurement of the QTc interval using Fridericia's correction (QTcF), and additional cardiac-related outcomes of interest to the safety analyses. Clinically insignificant and minor variance in the hemoglobin test values at screening for menstruating women in the exclusion criterion was made acceptable, if women were asymptomatic. Analysis of additional SSQ domains was added, and clarifications were made to the statistical analyses methods for secondary efficacy end points. Clarifications to the safety analyses for vital signs, physical and neurologic examinations, and Physician Withdrawal Checklist scores were also made. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported