# Clinical trial results:
# A Placebo-Controlled, Double-Blind Randomized Withdrawal Study to Evaluate the Safety and Efficacy of CNV1014802 in Patients with Trigeminal Neuragia

## Summary

| | |
|---|---|
| EudraCT number | 2010-023963-16 |
| Trial protocol | GB DE DK IT ES LV LT EE |
| Global end of trial date | 26 February 2014 |

**Results information**

| | |
|---|---|
| Result version number | v3 (current) |
| This version publication date | 08 June 2016 |
| First version publication date | 07 August 2015 |
| Version creation reason | • Correction of full data set<br>"Other name" correction required. |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 1014802/202 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01540630 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Convergence Pharmaceuticals Ltd |
| Sponsor organisation address | Maia Building, Babraham Research Campus, Cambridge, United Kingdom, CB22 3AT |
| Public contact | Clinical Trials Information, Convergence Pharmaceuticals Ltd, clinicaltrials@biogen.com |
| Scientific contact | Clinical Trials Information, Convergence Pharmaceuticals Ltd, clinicaltrials@biogen.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 | 26 February 2014 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 26 February 2014 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To investigate the effect of repeat oral dosing of CNV1014802 on the pain experienced in trigeminal neuralgia (TG).

Protection of trial subjects:

Written informed consent was obtained from each subject prior to evaluations being performed for eligibility. Subjects were given adequate time to review the information in the informed consent and were allowed to ask, and have answered, questions concerning all portions of the conduct of the study. Through the informed consent process each subject was made aware of the purpose of the study, the procedures, the benefits and risks of the study, the discomforts and the precautions taken. Any side effects or other health issues occurring during the study were followed up by the study doctor. Subjects were able to stop taking part in the study at any time without giving any reason. Subjects could discontinue the study at any time due to an adverse event.

Because of the severe nature of the pain associated with TN, subjects are unlikely to accept extended periods of placebo treatment. Therefore, a two-stage enriched randomized withdrawal design was selected for the study, whereby responders to CNV1014802 are identified in an initial open-label phase, and eligible responders are randomised to a second, placebo-controlled, double blind, withdrawal phase. Any subjects who were not responders in the initial open-label period were discontinued from the study and did not enter the randomized withdrawal period. Placebo was incorporated into the study as a control. However, as treatment failure was the primary outcome, subjects who received placebo and did not achieve pain relief (despite availability of rescue medication) were rapidly discontinued from the study and standard therapy re-introduced.

| | |
|---|---|
| Background therapy: - | |
| Evidence for comparator: - | |
| Actual start date of recruitment | 23 April 2012 |
| 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 | South Africa: 8 |
| Country: Number of subjects enrolled | Spain: 2 |
| Country: Number of subjects enrolled | Switzerland: 3 |
| Country: Number of subjects enrolled | United Kingdom: 1 |
| Country: Number of subjects enrolled | Denmark: 6 |
| Country: Number of subjects enrolled | Estonia: 9 |
| Country: Number of subjects enrolled | France: 5 |
| Country: Number of subjects enrolled | Germany: 4 |
| Country: Number of subjects enrolled | Italy: 16 |

| | |
|---|---|
| Country: Number of subjects enrolled | Latvia: 5 |
| Country: Number of subjects enrolled | Lithuania: 5 |
| Country: Number of subjects enrolled | Romania: 3 |
| Worldwide total number of subjects | 67 |
| EEA total number of subjects | 56 |

Notes:

**Subjects enrolled per age group**

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 43 |
| From 65 to 84 years | 24 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

125 subjects were screened, of which 67 were eligible for participation in the study.

### Period 1

| | |
|---|---|
| Period 1 title | Open-label Phase |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| **Arm title** | Open-label CNV1014802 |

Arm description:

Subjects received CNV1014802 150 mg three times daily (tid) for 21 days.

(Any subjects who were not responders in this phase were discontinued from the study and did not enter the randomised, double-blind, placebo-controlled phase.)

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | CNV1014802 |
| Investigational medicinal product code | |
| Other name | BIIB074 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects were advised to take medication in the morning, midday and in the evening approximately 8 hours apart, plus or minus 1 hour. Medication was to be taken at least 1 hour before or after food.

| **Number of subjects in period 1** | Open-label CNV1014802 |
|---|---|
| Started | 67 |
| Completed | 44 |
| Not completed | 23 |
| Consent withdrawn by subject | 2 |
| Adverse event, non-fatal | 3 |
| Lack of efficacy | 18 |

## Period 2

| | |
|---|---|
| Period 2 title | Double-blind Phase |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

## Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Double-blind CNV1014802 |

Arm description:

Subjects received CNV1014802 150 mg tid for up to 28 days.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | CNV1014802 |
| Investigational medicinal product code | |
| Other name | BIIB074 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects were advised to take medication in the morning, midday and in the evening approximately eight hours apart, plus or minus 1 hour. Medication was to be taken at least 1 hour before or after food.

| | |
|---|---|
| **Arm title** | Double-blind Placebo |

Arm description:

Subjects received placebo tid for up to 28 days.

| | |
|---|---|
| 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:

Subjects were advised to take medication in the morning, midday and in the evening approximately eight hours apart, plus or minus 1 hour. Medication was to be taken at least 1 hour before or after food.

| **Number of subjects in period 2[1]** | Double-blind CNV1014802 | Double-blind Placebo |
|---|---|---|
| Started | 15 | 14 |
| Completed | 10 | 7 |
| Not completed | 5 | 7 |
| Consent withdrawn by subject | 1 | - |
| Lack of efficacy | 4 | 7 |

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Of the 44 patients who completed the open-label phase, 30 were eligible for randomisation to the double-blind phase. One subject was randomised but did not receive a dose of double-blind medication, therefore, the number of subjects in the double-blind phase that received at least 1 dose of

study medication was 29 (the Intent-to-treat [ITT] population).

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Open-label Phase |

Reporting group description: -

| Reporting group values | Open-label Phase | Total | |
|---|---|---|---|
| Number of subjects | 67 | 67 | |
| Age categorical | | | |
| Age | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 44 | 44 | |
| From 65-84 years | 23 | 23 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 58.7 | | |
| standard deviation | ± 12.43 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 44 | 44 | |
| Male | 23 | 23 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Open-label CNV1014802 |

Reporting group description:

Subjects received CNV1014802 150 mg three times daily (tid) for 21 days.

(Any subjects who were not responders in this phase were discontinued from the study and did not enter the randomised, double-blind, placebo-controlled phase.)

| | |
|---|---|
| Reporting group title | Double-blind CNV1014802 |

Reporting group description:

Subjects received CNV1014802 150 mg tid for up to 28 days.

| | |
|---|---|
| Reporting group title | Double-blind Placebo |

Reporting group description:

Subjects received placebo tid for up to 28 days.

| | |
|---|---|
| Subject analysis set title | Randomized Subjects ITT Population Only |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The ITT analysis set included all subjects who were randomized into the double-blind period of the study and received at least one dose of double-blind medication.

| | |
|---|---|
| Subject analysis set title | Open-label Period: Non-randomized Subjects |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Subjects with PK assessment data in the open-label period who were not randomized in the double-blind period.

| | |
|---|---|
| Subject analysis set title | Open-label Period: Placebo Randomized Subjects |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Subjects with PK assessment data in the open-label period who were randomized to placebo in the double-blind period.

| | |
|---|---|
| Subject analysis set title | Open-label Period: CNV Randomized Subjects |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Subjects with PK assessment data in the open-label period who were randomized to CNV in the double-blind period.

| | |
|---|---|
| Subject analysis set title | Double-blind Period: CNV Randomized Subjects |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Subjects with PK assessment data in the double-blind period who were randomized to CNV in the double-blind period.

| | |
|---|---|
| Subject analysis set title | CNV1014802 Overall |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

All subjects who received at least 1 dose of CNV1014802 at any time during the study.

### Primary: Number of Subjects Reaching Treatment Failure in the Double-blind Period

| | |
|---|---|
| End point title | Number of Subjects Reaching Treatment Failure in the Double-blind Period |

End point description:

Subjects were classified as a treatment failure if they met one of the following criteria:
- 50% increase in the frequency of paroxysms compared to the final 7 days of the open-label period, to more than 3 paroxysms
- When more than 3 paroxysms were reported in a 7-day period, a 50% increase in the severity of pain experienced in the paroxysms compared with the final 7 days of the open-label period

- A Patient Global Improvement of Change rating of much worse/very much worse
- The subject discontinued the study due to 'lack of efficacy' in the double-blind phase. (Any subject who took more than 1 dose of a prohibited oral sodium channel blocker to treat their TN was considered to be a treatment failure and was withdrawn from the study due to lack of efficacy.)
- The subject discontinued due to an adverse reaction or poor tolerability.
ITT population: subjects who were randomized and received a dose of double blind medication.

| End point type | Primary |
|---|---|

End point timeframe:

Double-blind period: Week 4 (Day 22) through Week 7 (Day 49)

| **End point values** | Double-blind CNV1014802 | Double-blind Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 15 | 14 | | |
| Units: subjects | 5 | 9 | | |

### Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

Treatment failure rates were compared between CNV1014802 and placebo during the double-blind treatment period.

| Comparison groups | Double-blind Placebo v Double-blind CNV1014802 |
|---|---|
| Number of subjects included in analysis | 29 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0974 [1] |
| Method | Fisher exact |

Notes:

[1] - one-sided Fisher's exact test

## Secondary: Number of Subjects Reaching Treatment Failure, by Week

| End point title | Number of Subjects Reaching Treatment Failure, by Week |
|---|---|

End point description:

Subjects were classified as a treatment failure if they met one of the following criteria outlined in the primary endpoint (see previous endpoint). ITT population: subjects who were randomized and received a dose of double blind medication. Note: Subjects may show up in more than one category and a subject may meet different categories on different weeks if they met treatment failure criteria but were not withdrawn from the study in error.

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

End point timeframe:

Weeks 4, 5, 6, and 7

| End point values | Double-blind CNV1014802 | Double-blind Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 5[2] | 9[3] | | |
| Units: subjects | | | | |
| Treatment failure (all categories) - Week 4 | 1 | 6 | | |
| Treatment failure (all categories) - Week 5 | 4 | 4 | | |
| Treatment failure (all categories) - Week 6 | 0 | 3 | | |
| Treatment failure (all categories) - Week 7 | 1 | 1 | | |

Notes:

[2] - subjects in the ITT population experiencing treatment failure

[3] - subjects in the ITT population experiencing treatment failure

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Mean Number of Paroxysms per Day During the Open-label Phase

| End point title | Change From Baseline in Mean Number of Paroxysms per Day During the Open-label Phase |
|---|---|

End point description:

Safety population for the open-label phase: subjects who received at least one dose of open-label study medication. Observed cases; n=number of subjects with available data at given time point.

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

End point timeframe:

Baseline (Run-in [Days -7 to -1]), Weeks 1, 2, and 3 of the open-label phase

| End point values | Open-label CNV1014802 | Randomized Subjects ITT Population Only | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 67 | 29 | | |
| Units: paroxysms per day | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (Run-in [Days -1 to -7]); n=67, 29 | 8.7 (± 8.08) | 9.4 (± 8.96) | | |
| Change from Baseline at Week 1; n=66, 29 | -0.9 (± 10.1) | -4.1 (± 9.03) | | |
| Change from Baseline at Week 2; n=53, 29 | -2.7 (± 5.7) | -4.7 (± 6.42) | | |
| Change from Baseline at Week 3; n=45, 29 | -2.7 (± 4.83) | -5 (± 3.79) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Mean Number of Paroxysms per Day During the Double-blind Phase

| End point title | Change From Baseline in Mean Number of Paroxysms per Day During the Double-blind Phase |
|---|---|

End point description:

ITT population: subjects who were randomized and received a dose of double blind medication. Observed cases; n=number of subjects with available data at given time point.

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

End point timeframe:

Baseline (Week 3), Weeks 4, 5, 6, and 7 of the double-blind phase

| End point values | Double-blind CNV1014802 | Double-blind Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 15 | 14 | | |
| Units: paroxysms per day | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (Mean of Week 3); n=15, 14 | 5 (± 9.82) | 3.8 (± 2.57) | | |
| Change from Baseline at Week 4; n=15, 14 | 0.3 (± 5.8) | 3.1 (± 4.86) | | |
| Change from Baseline at Week 5; n=11, 9 | 0 (± 0.59) | -0.2 (± 1.83) | | |
| Change from Baseline at Week 6; n=11, 7 | -0.8 (± 1.56) | -0.8 (± 2.16) | | |
| Change from Baseline at Week 7; n=10, 5 | -1.1 (± 1.65) | -0.6 (± 3.22) | | |

### Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

The ratio comparing the changes from baseline in the number of paroxysms for the two groups (i.e. ΔCNV/Δplacebo)

| Comparison groups | Double-blind Placebo v Double-blind CNV1014802 |
|---|---|
| Number of subjects included in analysis | 29 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.028 [4] |
| Method | Generalized Estimating Equations |
| Parameter estimate | ratio of ΔCNV/Δplacebo |
| Point estimate | 0.55 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.3 |
| upper limit | 1.02 |

Notes:

[4] - one-sided test

## Secondary: Clinician Global Impression of Change (CGIC)

| End point title | Clinician Global Impression of Change (CGIC) |
|---|---|

End point description:

Changes on the CGIC were relative to Day 21 at Day 49/Premature Discontinuation. For the summary data, "Improvement" includes the following categories: much improved, very much improved, minimally improved. "No improvement" includes the following categories: no change, minimally worse, much worse, very much worse. ITT population: subjects who were randomized and received a dose of double blind medication who had available data.

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

End point timeframe:

Day 21, Day 49/premature discontinuation (end of double-blind period)

| End point values | Double-blind CNV1014802 | Double-blind Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 14 | 13 | | |
| Units: subjects | | | | |
| Day 49: Very much improved | 5 | 1 | | |
| Day 49: Much improved | 4 | 2 | | |
| Day 49: Minimally improved | 3 | 2 | | |
| Day 49: No change | 1 | 4 | | |
| Day 49: Minimally worse | 0 | 1 | | |
| Day 49: Much worse | 1 | 1 | | |
| Day 49: Very much worse | 0 | 2 | | |
| Day 49: Improvement | 12 | 5 | | |
| Day 49: No improvement | 2 | 8 | | |

### Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

CNV versus placebo: Day 21

| Comparison groups | Double-blind CNV1014802 v Double-blind Placebo |
|---|---|
| Number of subjects included in analysis | 27 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3674 |
| Method | Wilcoxon rank sum test |

| Statistical analysis title | Statistical Analysis 2 |
|---|---|

Statistical analysis description:

CNV versus placebo: Day 49 (1 subject's data was missing from each arm for this time point; 27 of the

29 subjects were included in this analysis)

| | |
|---|---|
| Comparison groups | Double-blind CNV1014802 v Double-blind Placebo |
| Number of subjects included in analysis | 27 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0051 |
| Method | Wilcoxon rank sum test |

## Secondary: Patient Global Impression of Change (PGIC)

| | |
|---|---|
| End point title | Patient Global Impression of Change (PGIC) |

End point description:

Changes on the PGIC were relative to Day 21 at Day 49/Premature Discontinuation. For the summary data, "Improvement" includes the following categories: much improved, very much improved, minimally improved. "No improvement" includes the following categories: no change, minimally worse, much worse, very much worse. ITT population: subjects who were randomized and received a dose of double blind medication who had available data.

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

End point timeframe:

Day 21, Day 49/premature discontinuation (end of double-blind period)

| End point values | Double-blind CNV1014802 | Double-blind Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 14 | 13 | | |
| Units: subjects | | | | |
| Day 49: Very much improved | 4 | 1 | | |
| Day 49: Much improved | 5 | 3 | | |
| Day 49: Minimally improved | 2 | 3 | | |
| Day 49: No change | 1 | 1 | | |
| Day 49: Minimally worse | 2 | 2 | | |
| Day 49: Much worse | 0 | 2 | | |
| Day 49: Very much worse | 0 | 1 | | |
| Day 49: Improvement | 11 | 7 | | |
| Day 49: No improvement | 3 | 6 | | |

### Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

CNV versus placebo: Day 21

| | |
|---|---|
| Comparison groups | Double-blind Placebo v Double-blind CNV1014802 |

| | |
|---|---|
| Number of subjects included in analysis | 27 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1402 |
| Method | Wilcoxon rank sum test |

| **Statistical analysis title** | Statistical Analysis 2 |
|---|---|

Statistical analysis description:

CNV versus placebo: Day 49 (1 subject's data was missing from each arm for this time point; 27 of the 29 subjects were included in this analysis)

| | |
|---|---|
| Comparison groups | Double-blind Placebo v Double-blind CNV1014802 |
| Number of subjects included in analysis | 27 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0265 |
| Method | Wilcoxon rank sum test |

## Secondary: Change From Baseline Brief Pain Inventory - Facial (BPI-F)

| End point title | Change From Baseline Brief Pain Inventory - Facial (BPI-F) |
|---|---|

End point description:

The BPI-F is a reliable and validated multidimensional tool that consists of 18 questions. It measures 3 domains of pain: 1) pain intensity (worst and average pain intensity), 2) interference with general activities of daily living (ADL), and 3) face-specific pain interference. The BPI-F was used as an assessment measure for quality of life in TG subjects. The BPI-F uses an 11-point Likert scale, ranging from 0 (no pain/interference) to 10 (worst pain /interference imaginable). ITT population: subjects who were randomized and received a dose of double blind medication. n=number of subjects with available data at given time point.

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

End point timeframe:

Baseline (pre-dose assessment on Day 0), Day 21 (end of open-label period), Day 49 (end of double-blind period), Follow-up (Day 56)

| **End point values** | Double-blind CNV1014802 | Double-blind Placebo | Randomized Subjects ITT Population Only | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 15 | 14 | 29 | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (Day 0); n=15, 14, 29 | 84.7 (± 36.09) | 90.8 (± 36.9) | 87.7 (± 35.96) | |
| Change from Baseline at Day 21; n=15, 14, 29 | -49.53 (± 29.051) | -45.29 (± 31.089) | -47.48 (± 29.587) | |
| Change from Baseline at Day 49; n=10, 7, 17 | -71.8 (± 33.041) | -32 (± 37.251) | -55.41 (± 39.27) | |
| Change from Baseline at Follow-up; n=14, 13, 27 | -63.36 (± 35.783) | -55.08 (± 39.267) | -59.37 (± 37.008) | |

## Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|
| Comparison groups | Double-blind Placebo v Double-blind CNV1014802 |
| Number of subjects included in analysis | 29 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1278 [5] |
| Method | Generalized Estimating Equations |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -14.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -39.5 |
| upper limit | 10.5 |

Notes:

[5] - one-sided test

## Secondary: Median Time to Failure

| End point title | Median Time to Failure |
|---|---|

End point description:

Kaplan-Meier analysis of time to failure during the randomized double-blind phase. ITT population: subjects who were randomized and received a dose of double-blind medication.

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

End point timeframe:

Double-blind period (Day 22 to Day 49)

| End point values | Double-blind CNV1014802 | Double-blind Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 15[6] | 14[7] | | |
| Units: days | | | | |
| median (confidence interval 95%) | 9999 (7 to 99999) | 14 (1 to 99999) | | |

Notes:

[6] - 9999="Not Reached," as the 50% quartile was not reached. 99999=blank (1-sided confidence interval).

[7] - 9999=blank (1-sided confidence interval).

## Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|
| Comparison groups | Double-blind Placebo v Double-blind CNV1014802 |
| Number of subjects included in analysis | 29 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0306 [8] |
| Method | Logrank |

Notes:

[8] - *The p-value from the log-rank test was 0.0611, but as the CNV group showed improvement over placebo during the double-blind phase, it was appropriate to derive the one-sided p-value of 0.0306.

## Secondary: Change From Baseline in Mean Severity of Paroxysms per Day During the Open-label Phase

| End point title | Change From Baseline in Mean Severity of Paroxysms per Day During the Open-label Phase |
|---|---|

End point description:

Subjects rated the severity of the pain during each paroxysm on an 11-point pain intensity numerical rating scale (PI-NRS) from 0 to 10, where 0 represents "no pain" and 10 represents "maximum pain imaginable." Safety population for the open-label phase: subjects who received at least one dose of open-label study medication. Observed cases; n=number of subjects with available data at given time point.

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

End point timeframe:

Baseline (Run-in [Days -7 to -1]), Weeks 1, 2, and 3 of the open-label phase

| End point values | Open-label CNV1014802 | Randomized Subjects ITT Population Only | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 67 | 29 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (Run-in [Days -1 to -7]); n=67, 29 | 6 (± 1.52) | 5.7 (± 1.47) | | |
| Change from Baseline at Week 1; n=66, 29 | -0.4 (± 1.61) | -1 (± 1.58) | | |
| Change from Baseline at Week 2; n=53, 29 | -1.4 (± 2.02) | -2.1 (± 1.87) | | |
| Change from Baseline at Week 3; n=45, 29 | -2 (± 2.04) | -2.9 (± 1.8) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Mean Severity of Paroxysms per Day During the Double-blind Phase

| End point title | Change From Baseline in Mean Severity of Paroxysms per Day During the Double-blind Phase |
|---|---|

End point description:

Subjects rated the severity of the pain during each paroxysm on an 11-point pain intensity numerical rating scale (PI-NRS) from 0 to 10, where 0 represents "no pain" and 10 represents "maximum pain imaginable." Observed cases; n=number of subjects with available data at given time point.

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

End point timeframe:

Baseline (Week 3), Weeks 4, 5, 6, and 7 of the double-blind phase

| **End point values** | Double-blind CNV1014802 | Double-blind Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 15 | 14 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (Mean of Week 3); n=15, 14 | 2.4 (± 2.27) | 3.2 (± 2.08) | | |
| Change from Baseline at Week 4; n=15, 14 | 0.5 (± 1.19) | 1.3 (± 2.61) | | |
| Change from Baseline at Week 5; n=11, 9 | 0.1 (± 1.65) | 0 (± 1.16) | | |
| Change from Baseline at Week 6; n=11, 7 | -0.3 (± 0.45) | -0.5 (± 1.88) | | |
| Change from Baseline at Week 7; n=10, 5 | -0.3 (± 1.62) | -0.7 (± 1.71) | | |

## Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

The ratio comparing the changes from baseline in the severity of paroxysms for the two groups (i.e. ΔCNV/Δplacebo)

| Comparison groups | Double-blind CNV1014802 v Double-blind Placebo |
|---|---|
| Number of subjects included in analysis | 29 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.0846 [9] |
| Method | Generalized Estimating Equations |
| Parameter estimate | ratio of ΔCNV/Δplacebo |
| Point estimate | 0.74 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.49 |
| upper limit | 1.13 |

Notes:

[9] - one-sided test

## Secondary: Change From Baseline in Average 24-hour Pain Intensity Numerical Rating Scale (PI-NRS) During the Open-label Phase

| End point title | Change From Baseline in Average 24-hour Pain Intensity Numerical Rating Scale (PI-NRS) During the Open-label Phase |
|---|---|

End point description:

Subjects were asked to rate their pain intensity averaged over the last 24 hours on each day, before retiring to bed. This constituted the Daily Pain Score. The 11-point PI-NRS scores ranged from 0 to 10, where 0 represents "no pain" and 10 represents "maximum pain imaginable" was used for the subject assessment of the pain. The subject's average pain was calculated for each week. Safety population for the open-label phase: subjects who received at least one dose of open-label study medication. n=number of subjects with available data at given time point.

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

End point timeframe:

Baseline (Run-in [Days -7 to -1]), Weeks 1, 2, and 3 of the open-label phase

| **End point values** | Open-label CNV1014802 | Randomized Subjects ITT Population Only | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 67 | 29 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (Run-in [Days -1 to -7]); n=67, 29 | 5.9 (± 1.64) | 5.7 (± 1.61) | | |
| Change from Baseline at Week 1; n=65, 29 | -0.7 (± 1.87) | -1.5 (± 1.58) | | |
| Change from Baseline at Week 2; n=52, 29 | -1.7 (± 2.03) | -2.5 (± 1.83) | | |
| Change from Baseline at Week 3; n=45, 29 | -1.9 (± 2.14) | -3.1 (± 1.67) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Mean Average 24-hour PI-NRS During the Double-blind Phase

| End point title | Change From Baseline in Mean Average 24-hour PI-NRS During the Double-blind Phase |
|---|---|

End point description:

Subjects were asked to rate their pain intensity averaged over the last 24 hours on each day, before retiring to bed. This constituted the Daily Pain Score. The 11-point PI-NRS scores ranged from 0 to 10, where 0 represents "no pain" and 10 represents "maximum pain imaginable" was used for the subject assessment of the pain. The subject's average pain was calculated for each week. ITT population: subjects who were randomized and received a dose of double-blind medication. n=number of subjects with available data at given time point.

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

End point timeframe:

Baseline (Week 3), Weeks 4, 5, 6, and 7 of the double-blind phase

| End point values | Double-blind CNV1014802 | Double-blind Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 15 | 14 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (Week 3); n=15, 14 | 2.3 (± 2.18) | 3 (± 2.19) | | |
| Change from Baseline at Week 4; n=15, 13 | 0.2 (± 0.67) | 2.1 (± 2.95) | | |
| Change from Baseline at Week 5; n=11, 8 | -0.1 (± 0.64) | 0.3 (± 0.92) | | |
| Change from Baseline at Week 6; n=10, 6 | -0.5 (± 0.72) | 0.9 (± 1.59) | | |
| Change from Baseline at Week 7; n=10, 4 | -0.9 (± 0.95) | 0.2 (± 1.64) | | |

### Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|

Statistical analysis description:

The ratio comparing the changes from baseline in PI-NRS for the two groups (i.e. ΔCNV/Δplacebo)

| | |
|---|---|
| Comparison groups | Double-blind CNV1014802 v Double-blind Placebo |
| Number of subjects included in analysis | 29 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0009 [10] |
| Method | Generalized Estimating Equations |
| Parameter estimate | ratio of ΔCNV/Δplacebo |
| Point estimate | 0.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.33 |
| upper limit | 0.77 |

Notes:

[10] - one-sided test

### Secondary: Maximal Plasma Concentration at Steady State (Cmax-ss) and Minimal Plasma Concentration at Steady State (Cmin-ss)

| End point title | Maximal Plasma Concentration at Steady State (Cmax-ss) and Minimal Plasma Concentration at Steady State (Cmin-ss) |
|---|---|

End point description:

PK population: all enrolled subjects who received at least one dose of investigational medicinal product with at least one quantifiable plasma concentration after dosing and available data.

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

End point timeframe:

Day 0: pre-dose; Day 7: pre-dose, 2 hours post-dose; Day 21 pre-dose, 2 hours post-dose; Day 35 pre-dose, 2 hours post-dose; Day 49 pre-dose, 2 hours post-dose.

| End point values | Open-label Period: Non-randomized Subjects | Open-label Period: Placebo Randomized Subjects | Open-label Period: CNV Randomized Subjects | Double-blind Period: CNV Randomized Subjects |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 24 | 13 | 15 | 15 |
| Units: µg/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Cmax-ss | 1.96 (± 19) | 1.98 (± 15) | 2.02 (± 17) | 2.01 (± 17) |
| Cmin-ss | 0.87 (± 36) | 0.87 (± 32) | 0.99 (± 31) | 0.94 (± 34) |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects Experiencing Treatment-emergent Adverse Events (TEAEs)

| End point title | Number of Subjects Experiencing Treatment-emergent Adverse Events (TEAEs) |
|---|---|

End point description:

Adverse event (AE): Any untoward medical occurrence in a subject, which does not necessarily have to have a causal relationship with this treatment. Serious AE: An adverse event that at any dose: results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; is considered to be an important medical event. TEAE: an AE occurring any time after the first administration of study treatment. Safety population: subjects who received at least one dose of CNV1014802. Subjects were analysed according to the actual treatment and dose they received. Safety population for the open-label phase: subjects who received at least one dose of open-label study medication. Safety population for the double-blind phase: subjects who received at least one dose of study medication after randomization.
least one dose of study medication

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

End point timeframe:

AEs were collected from start of Run-in (Day -7) through follow up (Day 56)

| End point values | Open-label CNV1014802 | Double-blind CNV1014802 | Double-blind Placebo | CNV1014802 Overall |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Subject analysis set |
| Number of subjects analysed | 67 | 15 | 14 | 67 |
| Units: subjects | | | | |
| TEAEs | 37 | 4 | 5 | 38 |
| Serious TEAEs | 2 | 0 | 1 | 2 |
| TEAEs leading to discontinuation | 5 | 0 | 0 | 5 |
| Severe TEAEs | 6 | 0 | 1 | 6 |
| Related TEAEs | 23 | 2 | 2 | 24 |
| TEAEs resulting in death | 0 | 0 | 0 | 0 |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects With Potentially Clinically Significant (PCS) Vital Sign and Electrocardiogram (ECG) Abnormalities

| End point title | Number of Subjects With Potentially Clinically Significant (PCS) Vital Sign and Electrocardiogram (ECG) Abnormalities |
|---|---|

End point description:

Systolic and diastolic BP and heart rate were assessed using a digital BP monitor while sitting. Standard ten second 12-lead ECGs were obtained using ECG machines provided by an ECG core lab. Safety population: subjects who received at least one dose of CNV1014802. Subjects were analysed according to the actual treatment and dose they received. Safety population for the open-label phase: subjects who received at least one dose of open-label study medication. Safety population for the double-blind phase: subjects who received at least one dose of study medication after randomization.

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

End point timeframe:

Screening through Day 56

| End point values | Open-label CNV1014802 | Double-blind CNV1014802 | Double-blind Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 67 | 15 | 14 | |
| Units: subjects | | | | |
| Vital signs | 0 | 0 | 0 | |
| ECGs | 0 | 0 | 0 | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects With Changes in Laboratory Values Reported as AEs

| End point title | Number of Subjects With Changes in Laboratory Values Reported as AEs |
|---|---|

End point description:

Hematology, clinical chemistry, urinalysis and additional parameters were tested at visits throughout the study. Safety population: subjects who received at least one dose of CNV1014802. Subjects were analysed according to the actual treatment and dose they received. Safety population for the open-label phase: subjects who received at least one dose of open-label study medication. Safety population for the double-blind phase: subjects who received at least one dose of study medication after randomization.

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

End point timeframe:

Screening through Day 56

| End point values | Open-label CNV1014802 | Double-blind CNV1014802 | Double-blind Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 67 | 15 | 14 | |
| Units: subjects | 0 | 1 | 1 | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| AEs were collected from start of Run-in (Day -7) through follow up (Day 56) | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 14.1 |

| Reporting groups | |
|---|---|
| Reporting group title | Open-label CNV1014802 |
| Reporting group description: | |
| Subjects received CNV1014802 150 mg tid for 21 days.<br><br>(Any subjects who were not responders in this phase were discontinued from the study and did not enter the randomised, double-blind, placebo-controlled phase.) | |
| Reporting group title | Double-blind CNV1014802 |
| Reporting group description: | |
| Subjects received CNV1014802 150 mg tid for up to 28 days. | |
| Reporting group title | Double-blind placebo |
| Reporting group description: | |
| Subjects received placebo tid for up to 28 days. | |

| Serious adverse events | Open-label CNV1014802 | Double-blind CNV1014802 | Double-blind placebo |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 67 (2.99%) | 0 / 15 (0.00%) | 1 / 14 (7.14%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Nervous system disorders | | | |
| Trigeminal neuralgia | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 15 (0.00%) | 0 / 14 (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 |
| Gastrointestinal disorders | | | |
| Abdominal adhesions | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 0 / 15 (0.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Bacterial food poisoning | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 15 (0.00%) | 0 / 14 (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 |

Frequency threshold for reporting non-serious adverse events: 0 %

| **Non-serious adverse events** | Open-label CNV1014802 | Double-blind CNV1014802 | Double-blind placebo |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 35 / 67 (52.24%) | 4 / 15 (26.67%) | 5 / 14 (35.71%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 4 / 67 (5.97%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 67 (4.48%) | 1 / 15 (6.67%) | 0 / 14 (0.00%) |
| occurrences (all) | 5 | 1 | 0 |
| Chills | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Asthenia | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Thirst | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 0 / 15 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 2 |
| Dyspnoea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nasal mucosal disorder | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 0 / 15 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Psychiatric disorders | | | |
| Sleep disorder | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 1 / 15 (6.67%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Restlessness | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Abnormal dreams | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Depression | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Insomnia | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 15 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 0 | 1 |
| Investigations | | | |
| Blood sodium decreased | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 0 / 15 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin turgor decreased | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Heat exhaustion | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 0 / 15 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Procedural pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 67 (0.00%) | 0 / 15 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Cardiac disorders | | | |
| Palpitations | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 13 / 67 (19.40%) | 1 / 15 (6.67%) | 1 / 14 (7.14%) |
| occurrences (all) | 26 | 5 | 3 |
| Dizziness | | | |
| subjects affected / exposed | 6 / 67 (8.96%) | 0 / 15 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 8 | 0 | 2 |
| Memory impairment | | | |
| subjects affected / exposed | 2 / 67 (2.99%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Somnolence | | | |
| subjects affected / exposed | 2 / 67 (2.99%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Trigeminal neuralgia | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Balance disorder | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dysgeusia | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 10 | 0 | 0 |
| Disturbance in attention | | | |
| subjects affected / exposed | 3 / 67 (4.48%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Tremor | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 67 (1.49%) | 1 / 15 (6.67%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Blood and lymphatic system disorders | | | |
| Leukocytosis | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 15 (6.67%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Eye disorders | | | |
| Vision blurred | | | |
| subjects affected / exposed | 2 / 67 (2.99%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Diplopia | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Visual impairment | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Dyspepsia | | | |
| subjects affected / exposed | 4 / 67 (5.97%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 20 | 0 | 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 4 / 67 (5.97%) | 0 / 15 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 6 | 0 | 1 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 4 / 67 (5.97%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| Constipation | | | |
| subjects affected / exposed | 3 / 67 (4.48%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 3 / 67 (4.48%) | 0 / 15 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 3 | 0 | 1 |
| Enterocele | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 0 / 15 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 0 | 0 | 1 |
| Gingival disorder | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Melaena | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Toothache | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 15 (6.67%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Abdominal discomfort | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 15 (0.00%) | 1 / 14 (7.14%) |
| occurrences (all) | 1 | 0 | 1 |
| Dry mouth | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Gastrointestinal sounds abnormal | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nausea | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Oral pruritus | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Photosensitivity reaction | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rash | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 15 (6.67%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|---|---|---|---|
| Renal and urinary disorders | | | |
| Micturition urgency | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Musculoskeletal stiffness | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Neck pain | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Infections and infestations | | | |
| Influenza | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 1 / 15 (6.67%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 67 (0.00%) | 1 / 15 (6.67%) | 0 / 14 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 67 (1.49%) | 0 / 15 (0.00%) | 0 / 14 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 07 May 2012 | The protocol was amended to increase the age limit of subjects to 80 years of age. The rationale for this amendment was that TN is a condition that is associated with increasing age. Many subjects are diagnosed in the 60-70 year age range and consequently the population of subjects requiring treatment extends into subjects aged 80 and older. Following review of the demographic data for TN subjects the sponsor changed the maximum age for inclusion in this study to 80 years. The population within the study would therefore more closely reflect the final intended target population. |
| 27 March 2013 | 1) Addition of a genotyping sample. The rationale was that a genetic substrate for neuropathic pain is an accepted hypothesis in the scientific community. Recently, sodium channel gene mutations causing cell hyperexcitability have been identified in groups of subjects with painful neuropathy. Calcium channelopathies have also been linked to migraine and epilepsy. Given the importance of sodium and calcium channels in the generation, propagation and plasticity of pain signals, it was decided to genotype five sodium channel (Nav1.1, Nav1.2, Nav1.3, Nav1.6 and Nav1.7) and two calcium channel (Cav2.2 and Cav2.1) genes in all subjects entering the study to explore whether mutations in these genes are present in TN and whether these are related to response to treatment with CNV1014802. Genotyping was not mandatory for subjects participating in the study and was carried out for research purposes only.<br>2) Clarification of Withdrawal criteria for Primary Endpoint. This amendment updated the primary endpoint withdrawal criteria to require at least three paroxysms within a 7 day period to be experienced and that thereafter a 50% increase in either the number of paroxysms or in severity of pain would result in the need to withdraw subjects.<br>Data from the planned interim analysis on the first 10 subjects treated in the open label indicated that some subjects had a very marked response to CNV1014802, such that they had no paroxysms in the final week of open label treatment. To avoid withdrawing subjects who only had one paroxysm in a 7 day period, the withdrawal criterion concerning number of paroxysms was changed to require at least three paroxysms/7 day period and thereafter a 50% increase in number or severity of paroxysms. The other withdrawal criteria remained unchanged. |
| 15 August 2013 | Increase Subject numbers. The number of subjects recruited to the open-label period of the study was increased from up to 40 subjects to up to 70 subjects. The target recruitment for the trial was to randomize 30 subjects with TN. At the outset of the trial, Convergence estimated that 'Approximately 40 subjects will be recruited into the open-label period to aim to randomize 30 subjects into the double-blind phase'. At the time of the amendment, 37 subjects had been enrolled into the open-label treatment period of study and only 14 had been eligible for randomisation to the double-blind period. It was apparent from the enrolment at this time point that a greater number of subjects would be required to enter the open-label treatment period than was stated in the protocol. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported