



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	v2
This version publication date	19 February 2016
First version publication date	07 August 2015
Version creation reason	<ul style="list-style-type: none">• Correction of full data set Correction needed for an "occurrences causally related to treatment/all" value.

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	Romania: 3
Country: Number of subjects enrolled	Spain: 2
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	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	Switzerland: 3
Country: Number of subjects enrolled	South Africa: 8
Country: Number of subjects enrolled	France: 5
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	raxatrigine
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	raxatrigine
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 subjects who completed the open-label phase, 30 were eligible for randomization to the double-blind phase. One subject was randomized 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: <ul style="list-style-type: none">- 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

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. $\Delta\text{CNV}/\Delta\text{placebo}$)

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 $\Delta\text{CNV}/\Delta\text{placebo}$
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. $\Delta\text{CNV}/\Delta\text{placebo}$)

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 $\Delta\text{CNV}/\Delta\text{placebo}$
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. $\Delta\text{CNV}/\Delta\text{placebo}$)	
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 $\Delta\text{CNV}/\Delta\text{placebo}$
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 (C_{max-ss}) and Minimal Plasma Concentration at Steady State (C_{min-ss})

End point title	Maximal Plasma Concentration at Steady State (C _{max-ss}) and Minimal Plasma Concentration at Steady State (C _{min-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.

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

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

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	<p>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.</p> <p>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.</p> <p>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.</p>
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