Clinical trial results:
A randomized, double-blind trial investigating the efficacy and safety of intravenous neridronic acid in subjects with complex regional pain syndrome type I (CRPS-I)

Summary

EudraCT number	2014-001915-37
Trial protocol	GB DE
Global end of trial date	02 November 2016

Results information

Result version number	v1 (current)
This version publication date	12 November 2017
First version publication date	12 November 2017

Trial information

Trial identification

Sponsor protocol code	KF7013-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02402530
WHO universal trial number (UTN)	U1111-1151-2181

Notes:

Sponsors

Sponsor organisation name	Grünenthal GmbH
Sponsor organisation address	Zieglerstr. 6, Aachen, Germany, 52099
Public contact	Grünenthal Trial Information Desk, Grünenthal GmbH, 49 2415693223, Clinical-Trials@grunenthal.com
Scientific contact	Grünenthal Trial Information Desk, Grünenthal GmbH, 49 2415693223, Clinical-Trials@grunenthal.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	23 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 November 2016
Global end of trial reached?	Yes
Global end of trial date	02 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the efficacy of neridronic acid, versus placebo, in treatment of pain associated with CRPS-I.
Cumulative doses of neridronic acid 125 mg and 250 mg were investigated in this trial to characterize a dose response and find a minimally effective dose in CRPS. Other phase 3 trials will confirm the efficacy and safety of neridronic acid 400 mg previously established.

Protection of trial subjects:

The trial was conducted according to ICH-GCP guidelines, the applicable local laws, and in accordance with the ethical principles that have their origins in the Declaration of Helsinki. Regulatory and competent authorities were notified of the trial as required by national regulations, and, where necessary, relevant authorization was obtained. The 12-week trial period was followed by an extended follow-up period with visits at Month 6, Month 9, and Month 12. The extended follow-up period was terminated for all subjects according to protocol after the last subject allocated to treatment completed their Month 6 visit.

Background therapy:

No rescue medication was planned for this trial. Subjects were to remain on stable doses of concomitant analgesic medications, including opioids, during the 12-week trial period. Other stable therapies for CRPS, including physical therapy and use of spinal cord stimulators, were permitted during the trial.
In the event of a severe pain flare, a short-acting opioid could be added to the stable analgesic regimen for up to 7 days.

Evidence for comparator:

There was no activ comparator in this trial. Use of a placebo control was considered justified as there are no established effective treatments for CRPS.

Actual start date of recruitment	01 April 2015
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	United Kingdom: 2
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	United States: 217
Worldwide total number of subjects	230
EEA total number of subjects	13

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)	221
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First subject was enrolled on the 01 Apr 2015 and the last subject completed the trial on the 02 Nov 2016.
459 Subjects signed an Informed consent form (ICF), 229 Subjects not allocated to Investigational medicinal product (IMP).

Pre-assignment

Screening details:

Subjects had to have a confirmed diagnosis of Complex regional pain syndrome type I (CRPS-I) according to the clinical diagnostic criteria recommended by the International Association for the Study of Pain and a Baseline Pain Intensity Score of at least 4 using an 11-point numerical rating scale.

Pre-assignment period milestones

Number of subjects started	459[1]
Number of subjects completed	230

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Adverse event, non-fatal: 1
Reason: Number of subjects	Consent withdrawn by subject: 18
Reason: Number of subjects	No reason given: 15
Reason: Number of subjects	Inclusion Criteria Not Met/Exclusion Criteria Met: 195

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 459 Subjects signed an Informed consent form (ICF), 229 Subjects not allocated to Investigational medicinal product (IMP). 230 Subjects allocated to IMP.

Period 1

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

Blinding implementation details:

Subjects and investigators were blinded to the subject’s treatment for the duration of the trial, including the extended follow-up period.

Arms

Are arms mutually exclusive?	Yes
Arm title	Neridronic acid 125 mg

Arm description:

Subjects received infusions of IMP during visits on Day 1, Day 4, Day 7, and Day 10 and returned for follow-up visits on Day 14 and at Week 6 and Week 12.
The 12-week trial period (milestone defined as trial completers) was followed by an extended follow-up period with visits at Month 6, Month 9, and Month 12.
The extended follow-up period was terminated for all subjects according to protocol after the last subject allocated to treatment completed their Month 6 visit.
One subject in the placebo arm received medication from a 125 mg kit and was included in the 125 mg arm.

Arm type	Experimental

Investigational medicinal product name	Sodium neridronate hemi hydrate for intravenous infusion
Investigational medicinal product code	GRT7013
Other name	Neridronic acid
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Five milliliters of IMP (equivalent to 62.5 mg neridronic acid) diluted in 500 mL normal saline and administered by intravenous infusion on Day 1 and Day 4; and 5 mL of IMP (matching placebo) diluted in 500 mL normal saline and administered by intravenous infusion on Day 7 and Day 10, resulting in a total dose of 125 mg neridronic acid.
Cumulative doses of neridronic acid 125 mg and 250 mg were investigated in this trial to characterize a dose response and find a minimally effective dose in CRPS. Other phase 3 trials will confirm the efficacy and safety of neridronic acid 400 mg previously established.

Arm title	Neridronic acid 250 mg

Arm description:

Subjects received infusions of IMP during visits on Day 1, Day 4, Day 7, and Day 10 and returned for follow-up visits on Day 14 and at Week 6 and Week 12.
The 12-week trial period (milestone defined as trial completers) was followed by an extended follow-up period with visits at Month 6, Month 9, and Month 12.
The extended follow-up period was terminated for all subjects according to protocol after the last subject allocated to treatment completed their Month 6 visit.

Arm type	Experimental
Investigational medicinal product name	Sodium neridronate hemi hydrate for intravenous infusion
Investigational medicinal product code	GRT7013
Other name	Neridronic acid
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Five milliliters of IMP (equivalent to 62.5 mg neridronic acid) diluted in 500 mL normal saline and administered by intravenous infusion on Day 1 and Day 4; and 5 mL of IMP diluted in 500 mL normal saline and administered by intravenous infusion on Day 7 and Day 10, resulting in a total dose of 250 mg neridronic acid.
Cumulative doses of neridronic acid 125 mg and 250 mg were investigated in this trial to characterize a dose response and find a minimally effective dose in CRPS. Other phase 3 trials will confirm the efficacy and safety of neridronic acid 400 mg previously established.

Arm title	Placebo

Arm description:

Subjects received infusions of IMP during visits on Day 1, Day 4, Day 7, and Day 10 and returned for follow-up visits on Day 14 and at Week 6 and Week 12.
The 12-week trial period (milestone defined as trial completers) was followed by an extended follow-up period with visits at Month 6, Month 9, and Month 12.
The extended follow-up period was terminated for all subjects according to protocol after the last subject allocated to treatment completed their Month 6 visit.
One subject in the placebo arm received medication from a 125 mg kit and was included in the 125 mg arm.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Five milliliters of IMP (matching placebo) diluted in 500 mL normal saline and administered by intravenous infusion on Day 1, Day 4, Day 7, and Day 10.

Number of subjects in period 1	Neridronic acid 125 mg	Neridronic acid 250 mg	Placebo
Started	77	77	76
12 Weeks - treatment completers	64	73	69
Completed	24	21	23
Not completed	53	56	53
Consent withdrawn by subject	7	7	8
Adverse event, non-fatal	-	-	1
Other reasons incl. planned termination after V9	38	40	35
Lost to follow-up	7	5	6
Lack of efficacy	1	4	3

Baseline characteristics

Reporting groups	
Reporting group title	Neridronic acid 125 mg
Reporting group description:	
Subjects received infusions of IMP during visits on Day 1, Day 4, Day 7, and Day 10 and returned for follow-up visits on Day 14 and at Week 6 and Week 12. The 12-week trial period (milestone defined as trial completers) was followed by an extended follow-up period with visits at Month 6, Month 9, and Month 12. The extended follow-up period was terminated for all subjects according to protocol after the last subject allocated to treatment completed their Month 6 visit. One subject in the placebo arm received medication from a 125 mg kit and was included in the 125 mg arm.	
Reporting group title	Neridronic acid 250 mg
Reporting group description:	
Subjects received infusions of IMP during visits on Day 1, Day 4, Day 7, and Day 10 and returned for follow-up visits on Day 14 and at Week 6 and Week 12. The 12-week trial period (milestone defined as trial completers) was followed by an extended follow-up period with visits at Month 6, Month 9, and Month 12. The extended follow-up period was terminated for all subjects according to protocol after the last subject allocated to treatment completed their Month 6 visit.	
Reporting group title	Placebo
Reporting group description:	
Subjects received infusions of IMP during visits on Day 1, Day 4, Day 7, and Day 10 and returned for follow-up visits on Day 14 and at Week 6 and Week 12. The 12-week trial period (milestone defined as trial completers) was followed by an extended follow-up period with visits at Month 6, Month 9, and Month 12. The extended follow-up period was terminated for all subjects according to protocol after the last subject allocated to treatment completed their Month 6 visit. One subject in the placebo arm received medication from a 125 mg kit and was included in the 125 mg arm.	

Reporting group values	Neridronic acid 125 mg	Neridronic acid 250 mg	Placebo
Number of subjects	77	77	76
Age categorical Units: Subjects			
Adults (18-64 years)	74	73	74
From 65-84 years	3	4	2
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	45.2	46.1	43.9
standard deviation	± 11.8	± 13.1	± 12.8
Gender categorical Units: Subjects			
Female	54	58	64
Male	23	19	12
Race Units: Subjects			
American Indian Or Alaska Native	1	0	1
Black Or African American	4	3	2
White	69	74	70
More than one race	0	0	2
Other	3	0	1

Ethnicity Units: Subjects			
Hispanic Or Latino	4	1	5
Not Hispanic Or Latino	73	76	71

Reporting group values	Total		
Number of subjects	230		
Age categorical Units: Subjects			
Adults (18-64 years)	221		
From 65-84 years	9		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	176		
Male	54		
Race Units: Subjects			
American Indian Or Alaska Native	2		
Black Or African American	9		
White	213		
More than one race	2		
Other	4		
Ethnicity Units: Subjects			
Hispanic Or Latino	10		
Not Hispanic Or Latino	220		

End points

End points reporting groups

Reporting group title	Neridronic acid 125 mg

Reporting group description:

Subjects received infusions of IMP during visits on Day 1, Day 4, Day 7, and Day 10 and returned for follow-up visits on Day 14 and at Week 6 and Week 12.
The 12-week trial period (milestone defined as trial completers) was followed by an extended follow-up period with visits at Month 6, Month 9, and Month 12.
The extended follow-up period was terminated for all subjects according to protocol after the last subject allocated to treatment completed their Month 6 visit.
One subject in the placebo arm received medication from a 125 mg kit and was included in the 125 mg arm.

Reporting group title	Neridronic acid 250 mg

Reporting group description:

Subjects received infusions of IMP during visits on Day 1, Day 4, Day 7, and Day 10 and returned for follow-up visits on Day 14 and at Week 6 and Week 12.
The 12-week trial period (milestone defined as trial completers) was followed by an extended follow-up period with visits at Month 6, Month 9, and Month 12.
The extended follow-up period was terminated for all subjects according to protocol after the last subject allocated to treatment completed their Month 6 visit.

Reporting group title	Placebo

Reporting group description:

Subjects received infusions of IMP during visits on Day 1, Day 4, Day 7, and Day 10 and returned for follow-up visits on Day 14 and at Week 6 and Week 12.
The 12-week trial period (milestone defined as trial completers) was followed by an extended follow-up period with visits at Month 6, Month 9, and Month 12.
The extended follow-up period was terminated for all subjects according to protocol after the last subject allocated to treatment completed their Month 6 visit.
One subject in the placebo arm received medication from a 125 mg kit and was included in the 125 mg arm.

Primary: Change in the Pain Intensity Score from baseline to Week 12

End point title	Change in the Pain Intensity Score from baseline to Week 12

End point description:

The Pain Intensity Score, related to the CRPS-affected limb, was determined from current pain intensity ratings, captured in an electronic diary, using an 11-point numerical rating scale (NRS). Subjects were asked to rate their current CRPS-related pain intensity twice daily, once in the morning and once in the evening. Subjects rated their pain on this scale from 0 = "no pain" to 10 = "pain as bad as you can imagine".
Pain Intensity Scores are weekly averages calculated as the average of 14 current pain intensity ratings obtained over the 7 days of each week. A reduction in pain intensity results in negative values.

End point type	Primary

End point timeframe:

Baseline to Week 12.

End point values	Neridronic acid 125 mg	Neridronic acid 250 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	77[1]	77[2]	76[3]	
Units: units on a scale				
least squares mean (confidence interval 95%)	-1.38 (-1.83 to -0.94)	-1.07 (-1.51 to -0.63)	-1.01 (-1.46 to -0.55)	

Notes:

[1] - Full Analysis Set

[2] - Full Analysis Set

[3] - Full Analysis Set

Statistical analyses

Statistical analysis title	Primary efficacy analysis

Statistical analysis description:

A mixed effects model for repeated measures (MMRM) was used, including pooled site, disease duration, baseline pain intensity, week, treatment, and treatment-by-week interaction as fixed effects and subject as random effect covariates.
LSmeans, standard errors, and 95% CIs for the interaction term treatment-by-week of the MMRM model representing the weekly averages of change from baseline in each week for each treatment arm were calculated.

Comparison groups	Neridronic acid 125 mg v Placebo v Neridronic acid 250 mg
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1812 [4]
Method	Mixed models analysis

Notes:

[4] - Dunnett test for comparison of two active arms to placebo at Week 12.

Secondary: Response to treatment, defined as 30 percent reduction

End point title	Response to treatment, defined as 30 percent reduction

End point description:

The response to treatment based on a reduction of 30% in the current pain intensity score from baseline to Week 12 was evaluated.

End point type	Secondary

End point timeframe:

Baseline to Week 12.

End point values	Neridronic acid 125 mg	Neridronic acid 250 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	77[5]	77[6]	76[7]	
Units: Subjects	20	16	16	

Notes:

[5] - Full Analysis Set

[6] - Full Analysis Set

[7] - Full Analysis Set

Statistical analyses

Statistical analysis title	Response to treatment

Statistical analysis description:

A logistic regression model with covariates baseline and CRPS-I duration (time in years), and factors pooled site and treatment was fitted using the responder status as response variable.

Comparison groups	Neridronic acid 125 mg v Placebo

Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.4025
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	3.13

Notes:

[8] - The statistical tests is not part of the overarching global null hypothesis and was not adjusted for multiplicity and is exploratory in nature.

Statistical analysis title	Response to treatment

Statistical analysis description:

A logistic regression model with covariates baseline and CRPS-I duration (time in years), and factors pooled site and treatment was fitted using the responder status as response variable.

Comparison groups	Neridronic acid 250 mg v Placebo
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9201
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	2.18

Secondary: Response to treatment, defined as 50 percent reduction

End point title	Response to treatment, defined as 50 percent reduction

End point description:

The response to treatment based on a reduction of 50% in the current pain intensity score from baseline to Week 12 was evaluated.

End point type	Secondary

End point timeframe:

Baseline to Week 12.

End point values	Neridronic acid 125 mg	Neridronic acid 250 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	77[9]	77[10]	76[11]	
Units: Subjects	8	10	9	

Notes:

[9] - Full Analysis Set

[10] - Full Analysis Set

[11] - Full Analysis Set

Statistical analyses

Statistical analysis title	Response to treatment

Statistical analysis description:

A logistic regression model with covariates baseline and CRPS-I duration (time in years), and factors pooled site and treatment was fitted using the responder status as response variable.

Comparison groups	Placebo v Neridronic acid 250 mg
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8125
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	3.08

Statistical analysis title	Response to treatment

Statistical analysis description:

A logistic regression model with covariates baseline and CRPS-I duration (time in years), and factors pooled site and treatment was fitted using the responder status as response variable.

Comparison groups	Neridronic acid 125 mg v Placebo
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9612
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	2.97

Secondary: Change in the Brief Pain Inventory (BPI) interference scale

End point title	Change in the Brief Pain Inventory (BPI) interference scale

End point description:

The BPI interference scale is a multi-item scale measuring the impact of pain on functioning and well-being. The 7 pain interference items: general activity, walking, work, mood, enjoyment of life, relations with others, and sleep, are each rated on a 0 to 10 scale using a 24-hour recall period, with 0 indicating "does not interfere" and 10 indicating "completely interferes". The total Pain Interference Score is calculated by adding the scores for the 7 questions and dividing by 7. This gives an interference score with a range from 0 to 10.

End point type	Secondary

End point timeframe:

Change from baseline to Week 12.

End point values	Neridronic acid 125 mg	Neridronic acid 250 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	77[12]	77[13]	76[14]	
Units: units on a scale				
least squares mean (standard error)	-1.55 (± 0.31)	-1.08 (± 0.3)	-1.22 (± 0.32)	

Notes:

[12] - Full Analysis Set

[13] - Full Analysis Set

[14] - Full Analysis Set

Statistical analyses

Statistical analysis title	Comparison Neridronic acid 125 mg to placebo

Statistical analysis description:

An ANCOVA of the change from baseline to Week 12 with covariates baseline and CRPS-I duration (time in years), and factors pooled site and treatment was performed.

Comparison groups	Neridronic acid 125 mg v Placebo
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4329
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.16
upper limit	0.5
Variability estimate	Standard error of the mean
Dispersion value	0.42

Statistical analysis title	Comparison Neridronic acid 250 mg to placebo

Statistical analysis description:

An ANCOVA of the change from baseline to Week 12 with covariates baseline and CRPS-I duration (time in years), and factors pooled site and treatment was performed.

Comparison groups	Neridronic acid 250 mg v Placebo
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7202
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.65
upper limit	0.94
Variability estimate	Standard error of the mean
Dispersion value	0.4

Secondary: Responder status based on PGIC questionnaire score

End point title	Responder status based on PGIC questionnaire score

End point description:

The Patient Global Impression of Change (PGIC) is a self-reported measure of perceived change in overall condition since the start of the study. The 7-point PGIC is a complementary assessment of analgesic efficacy. Subjects respond to the question "Since the start of the trial, my overall status is:" with 1 of 7 possible responses (very much improved, much improved, minimally improved, no change, minimally worse, much worse, very much worse. The response to treatment based on the PGIC was derived by classifying subjects with outcome "very much improved" or "much improved" as responders.

End point type	Secondary

End point timeframe:

Baseline to Week 12.

End point values	Neridronic acid 125 mg	Neridronic acid 250 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	77[15]	77[16]	76[17]	
Units: Subjects	19	18	17	

Notes:

[15] - Full Analysis Set

[16] - Full Analysis Set

[17] - Full Analysis Set

Statistical analyses

Statistical analysis title	Comparison Neridronic acid 125 mg to placebo

Statistical analysis description:

A logistic regression model with covariates current baseline pain intensity score and CRPS-I duration (time in years), and factors pooled site and treatment was fitted using the responder status as response variable.

Comparison groups	Neridronic acid 125 mg v Placebo
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5203
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	2.81

Statistical analysis title	Comparison Neridronic acid 250 mg to placebo

Statistical analysis description:

A logistic regression model with covariates current baseline pain intensity score and CRPS-I duration (time in years), and factors pooled site and treatment was fitted using the responder status as response variable.

Comparison groups	Neridronic acid 250 mg v Placebo
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9406
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	2.25

Secondary: Change in the EuroQol 5-dimension 5-level index score

End point title	Change in the EuroQol 5-dimension 5-level index score

End point description:

The EuroQol 5-dimension 5-level (EQ-5D-5L) questionnaire assesses the level of current health for 5 dimensions: mobility, selfcare, usual activities, pain and discomfort, and anxiety and depression. For each dimension, subjects selected a statement at one of 5 levels, with level 1 indicating better health state (no problems) and level 5 indicating worst health state (e.g., unable to walk about). The scoring formula developed by EuroQol Group assigns an index score for each domain in the profile.

End point type	Secondary

End point timeframe:

Change from baseline at week 12.

End point values	Neridronic acid 125 mg	Neridronic acid 250 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	77[18]	77[19]	76[20]	
Units: units on a scale				
least squares mean (confidence interval 95%)	0.06 (0.02 to 0.1)	0.02 (-0.02 to 0.06)	0.03 (-0.01 to 0.07)	

Notes:

[18] - Full Analysis Set

[19] - Full Analysis Set

[20] - Full Analysis Set

Statistical analyses

Statistical analysis title	Comparison Neridronic acid 125 mg to placebo

Statistical analysis description:

An ANCOVA of the change from baseline to Week 12 with covariates baseline and CRPS-I duration (time in years), and factors pooled site and treatment was performed.

Comparison groups	Neridronic acid 125 mg v Placebo
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2149
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.09
Variability estimate	Standard error of the mean
Dispersion value	0.03

Statistical analysis title	Comparison Neridronic acid 250 mg to placebo

Statistical analysis description:

An ANCOVA of the change from baseline to Week 12 with covariates baseline and CRPS-I duration (time in years), and factors pooled site and treatment was performed.

Comparison groups	Neridronic acid 250 mg v Placebo
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6386
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.04

Variability estimate	Standard error of the mean
Dispersion value	0.03

Secondary: Change in the EuroQol health-related visual analogue scale

End point title	Change in the EuroQol health-related visual analogue scale

End point description:

EuroQol health-related visual analogue scale (EQ-5D-5L-VAS). The EQ VAS is a self-reported measure of the subjects overall health "today". Subjects placed a mark on a 20 cm vertical scale numbered from 0 to 100, with 0 labeled as "the worst health you can imagine" and 100 labeled as "the best health you can imagine". The EQ VAS ranges from 0 to 100, with higher scores representing better overall health.

End point type	Secondary

End point timeframe:

Change from baseline at week 12.

End point values	Neridronic acid 125 mg	Neridronic acid 250 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	77[21]	77[22]	76[23]	
Units: units on a scale				
least squares mean (confidence interval 95%)	2.15 (-3.23 to 7.52)	-2.12 (-7.32 to 3.09)	4.16 (-1.27 to 9.59)	

Notes:

[21] - Full Analysis Set

[22] - Full Analysis Set

[23] - Full Analysis Set

Statistical analyses

Statistical analysis title	Comparison Neridronic acid 125 mg to placebo

Statistical analysis description:

An ANCOVA of the change from baseline to Week 12 with covariates baseline and CRPS-I duration (time in years), and factors pooled site and treatment was performed.

Comparison groups	Neridronic acid 125 mg v Placebo
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.586
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.3
upper limit	5.27
Variability estimate	Standard error of the mean
Dispersion value	3.69

Statistical analysis title	Comparison Neridronic acid 250 mg to placebo

Statistical analysis description:

An ANCOVA of the change from baseline to Week 12 with covariates baseline and CRPS-I duration (time in years), and factors pooled site and treatment was performed.

Comparison groups	Neridronic acid 250 mg v Placebo
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0784
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-6.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.28
upper limit	0.72
Variability estimate	Standard error of the mean
Dispersion value	3.55

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to end of trial. Up to 12 month.

Adverse event reporting additional description:

Adverse events are reported for the Safety Set, this included all subjects with at least 1 IMP administration (i.e. all subjects who were administered at least 1 infusion of Investigational medicinal product (full or partial dose) of Neridronic acid and matching placebo) as per randomization schedule.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	Neridronic acid 125 mg
Reporting group description: -	
Reporting group title	Neridronic acid 250 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Neridronic acid 125 mg	Neridronic acid 250 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 78 (6.41%)	2 / 77 (2.60%)	5 / 75 (6.67%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 78 (0.00%)	1 / 77 (1.30%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Complex regional pain syndrome			

subjects affected / exposed	2 / 78 (2.56%)	0 / 77 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			
subjects affected / exposed	0 / 78 (0.00%)	1 / 77 (1.30%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	0 / 75 (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
Non-cardiac chest pain			
subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	0 / 75 (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 pain			
subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	0 / 75 (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
Abdominal pain upper			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	0 / 75 (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

Impaired gastric emptying			
subjects affected / exposed	1 / 78 (1.28%)	0 / 77 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 78 (0.00%)	1 / 77 (1.30%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Staphylococcal infection			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Neridronic acid 125 mg	Neridronic acid 250 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 78 (71.79%)	61 / 77 (79.22%)	56 / 75 (74.67%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 78 (3.85%)	4 / 77 (5.19%)	7 / 75 (9.33%)
occurrences (all)	4	7	8
Headache			

subjects affected / exposed	19 / 78 (24.36%)	15 / 77 (19.48%)	18 / 75 (24.00%)
occurrences (all)	23	24	21
Paraesthesia			
subjects affected / exposed	0 / 78 (0.00%)	0 / 77 (0.00%)	4 / 75 (5.33%)
occurrences (all)	0	0	4
General disorders and administration site conditions			
Condition aggravated			
subjects affected / exposed	1 / 78 (1.28%)	3 / 77 (3.90%)	4 / 75 (5.33%)
occurrences (all)	1	4	5
Fatigue			
subjects affected / exposed	11 / 78 (14.10%)	8 / 77 (10.39%)	5 / 75 (6.67%)
occurrences (all)	12	14	7
Influenza like illness			
subjects affected / exposed	3 / 78 (3.85%)	5 / 77 (6.49%)	3 / 75 (4.00%)
occurrences (all)	5	5	5
Pain			
subjects affected / exposed	9 / 78 (11.54%)	13 / 77 (16.88%)	13 / 75 (17.33%)
occurrences (all)	11	14	15
Pyrexia			
subjects affected / exposed	6 / 78 (7.69%)	4 / 77 (5.19%)	6 / 75 (8.00%)
occurrences (all)	6	5	8
Eye disorders			
Vision blurred			
subjects affected / exposed	4 / 78 (5.13%)	1 / 77 (1.30%)	1 / 75 (1.33%)
occurrences (all)	4	1	1
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	3 / 78 (3.85%)	4 / 77 (5.19%)	2 / 75 (2.67%)
occurrences (all)	3	4	2
Diarrhoea			
subjects affected / exposed	5 / 78 (6.41%)	9 / 77 (11.69%)	6 / 75 (8.00%)
occurrences (all)	5	10	7
Nausea			
subjects affected / exposed	7 / 78 (8.97%)	10 / 77 (12.99%)	21 / 75 (28.00%)
occurrences (all)	9	16	29
Vomiting			

subjects affected / exposed	2 / 78 (2.56%)	4 / 77 (5.19%)	4 / 75 (5.33%)
occurrences (all)	2	5	5
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 78 (0.00%)	4 / 77 (5.19%)	0 / 75 (0.00%)
occurrences (all)	0	4	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 78 (6.41%)	9 / 77 (11.69%)	4 / 75 (5.33%)
occurrences (all)	6	12	4
Back pain			
subjects affected / exposed	5 / 78 (6.41%)	2 / 77 (2.60%)	4 / 75 (5.33%)
occurrences (all)	6	2	6
Muscle spasms			
subjects affected / exposed	2 / 78 (2.56%)	4 / 77 (5.19%)	3 / 75 (4.00%)
occurrences (all)	2	4	4
Musculoskeletal chest pain			
subjects affected / exposed	4 / 78 (5.13%)	2 / 77 (2.60%)	1 / 75 (1.33%)
occurrences (all)	4	2	1
Myalgia			
subjects affected / exposed	10 / 78 (12.82%)	9 / 77 (11.69%)	3 / 75 (4.00%)
occurrences (all)	11	13	5
Pain in extremity			
subjects affected / exposed	7 / 78 (8.97%)	7 / 77 (9.09%)	5 / 75 (6.67%)
occurrences (all)	12	8	6
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	0 / 78 (0.00%)	4 / 77 (5.19%)	5 / 75 (6.67%)
occurrences (all)	0	4	7
Urinary tract infection			
subjects affected / exposed	5 / 78 (6.41%)	4 / 77 (5.19%)	6 / 75 (8.00%)
occurrences (all)	5	4	7
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	2 / 78 (2.56%)	6 / 77 (7.79%)	1 / 75 (1.33%)
occurrences (all)	2	6	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 June 2015	Amendment 01: The principal change in this protocol amendment was a reduction in cumulative dose levels from neridronic acid 400 mg and 200 mg to neridronic acid 250 mg and 125 mg, respectively. Due to the reduction in cumulative dose levels, the amount of drug infused during each infusion (of active study medication) was reduced from 100 mg to 62.5 mg. To preserve the use of the packaged clinical trial supplies consisting of ampules containing neridronic acid 100 mg in 8 mL volume, the volume transferred from the ampule to the infusion bag containing normal saline was reduced to 5 mL. A witness was required for the transfer procedure to ensure the correct dose was given. Consistent with the lower dose per infusion, the infusion time was reduced from 3 hours to 2 hours.
25 August 2015	Amendment 02: • The requirements for discontinuation of IMP were modified to allow for resumption of treatment upon further assessment of laboratory changes or other findings within 7 days, if changes were transient and/or considered to be not clinically significant. This included modification of the procedure to prevent discontinuation of treatment due to spurious changes in eGFR determined from the local laboratory creatinine values or due to clinically insignificant variations in serum calcium values. The changes were implemented to improve the benefit/risk for subjects who would otherwise be discontinued due to transient, variable, or arbitrary findings. In situations where treatment was temporarily discontinued, the final IMP infusion had to be completed by 21 days after the first infusion. • Trial termination following last subject allocated was changed from 3 months to 6 months to provide a minimum of 6 months follow-up for all subjects. This provided additional long-term follow-up data to support evaluation of safety and the duration of effect of neridronic acid. • The enrollment period was extended from 28 days to 60 days (up to 90 days with approval of the sponsor) to provide sufficient time to meet requirements for repletion of vitamin D levels and to add flexibility due to issues in visit scheduling. • In consideration of the fact that CRPS is a rare disease, re-enrollment was permitted for subjects who previously failed enrollment due to reasons that were no longer included under protocol amendment 02, provided the subject met all current inclusion/exclusion criteria. Other re-enrollment was permitted (e.g., due to an erroneous enrollment failure), upon sponsor approval, provided the subject met all inclusion/exclusion criteria. • The enrollment cap for the subgroup of patients with CRPS duration ≥1 year was changed to 85% due to difficulty in enrolling subjects with duration of disease <1 year.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

For dose finding purposes, cumulative doses (125 and 250 mg) used in this trial were lower than that (400 mg) previously shown to be clearly effective (Varenna et al. 2013).

Notes: