Clinical trial results:
A randomized, double-blind, placebo controlled study to assess the safety and the efficacy of Neridronate ampoules 25 mg, after repeated intramuscular administrations, in patients with Complex Regional Pain Syndrome type I (CRPS-I)

Summary

EudraCT number	2014-001156-28
Trial protocol	IT
Global end of trial date	18 March 2020

Results information

Result version number	v1 (current)
This version publication date	13 December 2021
First version publication date	13 December 2021

Trial information

Trial identification

Sponsor protocol code	NAIMES/32

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Abiogen Pharma S.p.A.
Sponsor organisation address	Via Meucci, 36, Pisa, Italy,
Public contact	Fabrizio Nannipieri, Abiogen Pharma S.p.A., fabrizio.nannipieri@abiogen.it
Scientific contact	Fabrizio Nannipieri, Abiogen Pharma S.p.A., fabrizio.nannipieri@abiogen.it

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	19 May 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to assess the efficacy of the investigational medicinal product (IMP) as a proportion of patients showing a 50% or more reduction of pain intensity, as measured using a 100 mm visual analogue scale (VAS), from the baseline visit to the last visit of the double-blind phase.

Protection of trial subjects:

In case of insufficient pain relief during the double-blind phase, patients are allowed to take Paracetamol 500 mg oral tablet as rescue medication, up to a maximum daily dose of 2 g.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 April 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	10 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 78
Worldwide total number of subjects	78
EEA total number of subjects	78

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)	52
From 65 to 84 years	26

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

M, F. Age ≥ 18 years
Confirmed diagnosis of CRPS-I
Disease duration ≤ 4 months
Spontaneous pain (100 mm VAS scale) > 50 mm in the selected extremity
Opioid and non-opioid analgesics, NSAIDs, anticonvulsants, antidepressant drugs and other non-drug therapies may be continued provided the dose is stable for at least 4 weeks before treatment start

Period 1

Period 1 title	Double blind phase
Is this the baseline period?	Yes
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	Neridronate 25 mg i.m.

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Neridronate 25 mg i.m.
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One i.m. injection for 16 consecutive days.

Arm title	Placebo i.m.

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo i.m.
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

One i.m. injection for 16 consecutive days.

Number of subjects in period 1	Neridronate 25 mg i.m.	Placebo i.m.
Started	41	37
Completed	40	34
Not completed	1	3
Consent withdrawn by subject	1	1
Lost during double-blind	-	1
Failure to comply with protocol	-	1

Period 2	
Period 2 title	Open label phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	Neridronate 100 mg i.v.

Arm description: -

Arm type	Approved therapy
Investigational medicinal product name	Neridronate 100 mg i.v.
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

A dose of four 100 mg i.v. infusions (one every third day) in a 10-day treatment cycle (i.e. on Days 1, 4, 7 and 10 of the cycle).

Arm title	No treatment

Arm description: -

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Neridronate 100 mg i.v.	No treatment
Started	32	42
Completed	31	42
Not completed	1	0
Consent withdrawn by subject	1	-

Period 3	
Period 3 title	Follow-up phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded
Arms	
Are arms mutually exclusive?	Yes
Arm title	Neridronate 25 mg i.m.
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Neridronate 100 mg i.v.
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Placebo i.m.
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 3	Neridronate 25 mg i.m.	Neridronate 100 mg i.v.	Placebo i.m.
Started	40	31	2
Completed	35	23	2
Not completed	5	8	0
Consent withdrawn by subject	2	5	-
Lost to follow-up	3	3	-

Baseline characteristics

Reporting groups	
Reporting group title	Neridronate 25 mg i.m.
Reporting group description: -	
Reporting group title	Placebo i.m.
Reporting group description: -	

Reporting group values	Neridronate 25 mg i.m.	Placebo i.m.	Total
Number of subjects	41	37	78
Age categorical Units: Subjects			
Adults (18-64 years)	30	22	52
From 65-84 years	11	15	26
Age continuous Units: years			
arithmetic mean	59.3	59.7	
standard deviation	± 10.23	± 10.53	-
Gender categorical Units: Subjects			
Female	25	27	52
Male	16	10	26

End points

End points reporting groups	
Reporting group title	Neridronate 25 mg i.m.
Reporting group description: -	
Reporting group title	Placebo i.m.
Reporting group description: -	
Reporting group title	Neridronate 100 mg i.v.
Reporting group description: -	
Reporting group title	No treatment
Reporting group description: -	
Reporting group title	Neridronate 25 mg i.m.
Reporting group description: -	
Reporting group title	Neridronate 100 mg i.v.
Reporting group description: -	
Reporting group title	Placebo i.m.
Reporting group description: -	

Primary: Proportion of Patients Showing a Reduction >= 50% in VAS for Pain at Day 30	
End point title	Proportion of Patients Showing a Reduction >= 50% in VAS for Pain at Day 30
End point description:	
End point type	Primary
End point timeframe: Day 30	

End point values	Neridronate 25 mg i.m.	Placebo i.m.		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	37		
Units: percent				
number (confidence interval 95%)	65.9 (49.4 to 79.9)	29.7 (15.9 to 47.0)		

Statistical analyses	
Statistical analysis title	Comparison between Neridronate and Placebo
Comparison groups	Placebo i.m. v Neridronate 25 mg i.m.

Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0017
Method	Fisher exact

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From the time of subject signing the ICF to the end of the study	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0
Reporting groups	
Reporting group title	Neridronate 25 mg i.m. - double blind phase
Reporting group description: -	
Reporting group title	Placebo i.m. - double blind phase
Reporting group description: -	
Reporting group title	Neridronate 100 mg i.v. - open label phase
Reporting group description: -	
Reporting group title	Neridronate 25 mg i.m. - follow-up phase
Reporting group description: -	
Reporting group title	Placebo i.m. - follow-up phase
Reporting group description: -	

Serious adverse events	Neridronate 25 mg i.m. - double blind phase	Placebo i.m. - double blind phase	Neridronate 100 mg i.v. - open label phase
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 41 (0.00%)	0 / 37 (0.00%)	0 / 32 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Forearm fracture			
subjects affected / exposed	0 / 41 (0.00%)	0 / 37 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 41 (0.00%)	0 / 37 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skull fracture			

subjects affected / exposed	0 / 41 (0.00%)	0 / 37 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 41 (0.00%)	0 / 37 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 41 (0.00%)	0 / 37 (0.00%)	0 / 32 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Neridronate 25 mg i.m. - follow-up	Placebo i.m. - follow-up phase	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 41 (7.32%)	0 / 35 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Forearm fracture			
subjects affected / exposed	1 / 41 (2.44%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 41 (2.44%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fracture			
subjects affected / exposed	1 / 41 (2.44%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			

subjects affected / exposed	1 / 41 (2.44%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Neridronate 25 mg i.m. - double blind phase	Placebo i.m. - double blind phase	Neridronate 100 mg i.v. - open label phase
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 41 (65.85%)	14 / 37 (37.84%)	12 / 32 (37.50%)
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 41 (17.07%)	3 / 37 (8.11%)	1 / 32 (3.13%)
occurrences (all)	8	3	2
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	10 / 41 (24.39%)	1 / 37 (2.70%)	3 / 32 (9.38%)
occurrences (all)	18	1	3
Injection site pain			
subjects affected / exposed	7 / 41 (17.07%)	4 / 37 (10.81%)	0 / 32 (0.00%)
occurrences (all)	8	7	0
Malaise			
subjects affected / exposed	4 / 41 (9.76%)	0 / 37 (0.00%)	1 / 32 (3.13%)
occurrences (all)	6	0	1
Pain			
subjects affected / exposed	4 / 41 (9.76%)	3 / 37 (8.11%)	1 / 32 (3.13%)
occurrences (all)	9	5	1
Asthenia			
subjects affected / exposed	3 / 41 (7.32%)	2 / 37 (5.41%)	3 / 32 (9.38%)
occurrences (all)	3	4	3
Acute phase reaction			

subjects affected / exposed	1 / 41 (2.44%)	1 / 37 (2.70%)	2 / 32 (6.25%)
occurrences (all)	1	1	3
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 41 (17.07%)	4 / 37 (10.81%)	2 / 32 (6.25%)
occurrences (all)	10	5	2
Myalgia			
subjects affected / exposed	7 / 41 (17.07%)	1 / 37 (2.70%)	2 / 32 (6.25%)
occurrences (all)	14	1	2
Pain in extremity			
subjects affected / exposed	6 / 41 (14.63%)	1 / 37 (2.70%)	2 / 32 (6.25%)
occurrences (all)	9	1	2
Back pain			
subjects affected / exposed	5 / 41 (12.20%)	2 / 37 (5.41%)	1 / 32 (3.13%)
occurrences (all)	10	2	1
Musculoskeletal pain			
subjects affected / exposed	3 / 41 (7.32%)	1 / 37 (2.70%)	1 / 32 (3.13%)
occurrences (all)	3	2	1

Non-serious adverse events	Neridronate 25 mg i.m. - follow-up	Placebo i.m. - follow-up phase	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 41 (2.44%)	1 / 35 (2.86%)	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 41 (0.00%)	0 / 35 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Injection site pain			
subjects affected / exposed	0 / 41 (0.00%)	0 / 35 (0.00%)	
occurrences (all)	0	0	
Malaise			
subjects affected / exposed	0 / 41 (0.00%)	0 / 35 (0.00%)	
occurrences (all)	0	0	

Pain			
subjects affected / exposed	0 / 41 (0.00%)	0 / 35 (0.00%)	
occurrences (all)	0	0	
Asthenia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 35 (0.00%)	
occurrences (all)	0	0	
Acute phase reaction			
subjects affected / exposed	0 / 41 (0.00%)	0 / 35 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 35 (0.00%)	
occurrences (all)	0	0	
Myalgia			
subjects affected / exposed	0 / 41 (0.00%)	0 / 35 (0.00%)	
occurrences (all)	0	0	
Pain in extremity			
subjects affected / exposed	0 / 41 (0.00%)	0 / 35 (0.00%)	
occurrences (all)	0	0	
Back pain			
subjects affected / exposed	1 / 41 (2.44%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal pain			
subjects affected / exposed	0 / 41 (0.00%)	0 / 35 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 June 2018	One substantial protocol amendment was submitted for notification, to change the type of CRFs from electronic CRF to paper CRF.
10 January 2020	Amendment done to change the name of the study coordinator.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported