



## 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.,<br>fabrizio.nannipieri@abiogen.it |
| Scientific contact           | Fabrizio Nannipieri, Abiogen Pharma S.p.A.,<br>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  $\geq$  18 years

Confirmed diagnosis of CRPS-I

Disease duration  $\leq$  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 |
|------------------------------|-----|

|                  |                        |
|------------------|------------------------|
| <b>Arm title</b> | 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.

|                  |              |
|------------------|--------------|
| <b>Arm title</b> | 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.

| <b>Number of subjects in period 1</b> | 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                     |
| <b>Arm title</b>             | 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).

|   |                 |
|---|-----------------|
| <b>Arm title</b>  | No treatment    |
| Arm description: -  |                 |
| Arm type  | No intervention |
| No investigational medicinal product assigned in this arm |                 |

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| Consent withdrawn by subject          | 1                       | -            |

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

| <b>Number of subjects in period 3</b> | Neridronate 25 mg<br>i.m. | Neridronate 100 mg<br>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 $\geq 50\%$ in VAS for Pain at Day 30

|                        |  |
|------------------------|--|
| End point title        | Proportion of Patients Showing a Reduction $\geq 50\%$ 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          |

| <b>Serious adverse events</b>                     | Neridronate 25 mg<br>i.m. - follow-up | Placebo i.m. -<br>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          |  |
| <b>Vascular disorders</b>                       |                |                |  |
| 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 %

| <b>Non-serious adverse events</b>                           | Neridronate 25 mg<br>i.m. - double blind<br>phase | Placebo i.m. - double<br>blind phase | Neridronate 100 mg<br>i.v. - open label<br>phase |
|---|---|--------------------------------------|--|
| Total subjects affected by non-serious adverse events       |   |                                      |  |
| subjects affected / exposed                                 | 27 / 41 (65.85%)                                  | 14 / 37 (37.84%)                     | 12 / 32 (37.50%)                                 |
| <b>Nervous system disorders</b>                             |   |                                      |  |
| Headache  |   |                                      |  |
| subjects affected / exposed                                 | 7 / 41 (17.07%)                                   | 3 / 37 (8.11%)                       | 1 / 32 (3.13%)                                   |
| occurrences (all)   | 8   | 3                                    | 2  |
| <b>General disorders and administration site conditions</b> |   |                                      |  |
| 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<br>occurrences (all) | 1 / 41 (2.44%)<br>1 | 1 / 37 (2.70%)<br>1 | 2 / 32 (6.25%)<br>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                   |

| <b>Non-serious adverse events</b>                        | Neridronate 25 mg<br>i.m. - follow-up | Placebo i.m. -<br>follow-up phase |  |
|--|---------------------------------------|-----------------------------------|--|
| Total subjects affected by non-serious<br>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<br>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:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported