



## Clinical trial results:

### A Double-Blind, Randomised, Exploratory Study to Investigate the Safety, Efficacy and Pharmacokinetics of PRX167700 in Subjects with Knee Osteoarthritis.

These results have been removed from public view whilst they are reviewed and may need to be corrected before being returned to public view

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2013-001970-33 |
| Trial protocol           | GB             |
| Global end of trial date | 28 August 2014 |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 24 July 2016 |
| First version publication date | 24 July 2016 |

#### Trial information

##### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | 167700-002CL |
|-----------------------|--------------|

##### Additional study identifiers

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

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Proximagen Limited   |
| Sponsor organisation address | Minerva Building 250, Babraham Research Campus, Cambridge, United Kingdom, CB22 3AT    |
| Public contact               | Clinical Trial Information, Proximagen Limited, 0044 1223 497 300, info@proximagen.com |
| Scientific contact           | Clinical Trial Information, Proximagen Limited, 0044 1223 497 300, info@proximagen.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:

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## Results analysis stage

|  |                 |
|--|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 16 October 2014 |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 28 August 2014  |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 28 August 2014  |
| Was the trial ended prematurely?                     | No              |

Notes:

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## General information about the trial

Main objective of the trial:

To assess the effect of PRX167700 treatment on Pain Intensity after walking and at rest in subjects with moderate to severe pain caused by osteoarthritis (OA) of the knee.

Protection of trial subjects:

This study was conducted in accordance with Good Clinical Practice as required by the International Conference on Harmonisation E6 Guideline. Compliance with these requirements also constitutes conformity with the ethical principles of the Declaration of Helsinki and any local regulations and applicable laws were followed appropriately.

Prior to the conduct of any study-related procedures, informed consent was obtained from all subjects. Before obtaining informed consent, information was given in a language and at a level of complexity understandable to the subject in both oral and written form by the Investigator. Each subject had the opportunity to discuss the study and its alternatives with the Investigator. Subjects were also informed of their right to withdraw from the study at any time.

Background therapy:

Prohibited concomitant therapy:

All analgesic therapy, including over-the-counter pain medications and topical analgesics for OA pain. Medications considered to be analgesics for the treatment of OA pain included non-selective NSAIDs, COX-2 selective NSAIDs, paracetamol, tramadol, and opioid-containing preparations  
Oral corticosteroids.

Therapeutic injections into the target knee joint (e. g., corticosteroid and hyaluronic acid).

Other therapies such as methotrexate, gold salts, penicillamine, antimalarials, sulfasalazine, azathioprine, cyclosporine and any anti-inflammatory biological therapy which could be used off-label for the treatment of OA were not permitted. Strong inhibitors of CYP3A4 and CYP2D6 and strong inducers of CYP3A4 were also not permitted.

Permitted concomitant therapy:

Medications, other than the prohibited medications listed above, for the treatment of other underlying diseases or conditions were permitted and were to be maintained at a stable dose during the treatment period, unless a change was medically indicated. All concomitant medications used by the subject at screening (Visit 1), changes to those medications, or introduction of new medications after screening were to be recorded in the electronic consent record form.

Subjects who were taking a stable dose of chondroitin or keratin sulphate, glucosamine, non-specific rubefacients, and nutraceutical products were permitted to continue treatment at the same dose. An established physiotherapy programme could be continued provided it had commenced at least 2 weeks before screening and the session duration or frequency was continued during the study. Low dose aspirin ( $\leq 75$  mg/day) as prophylactic cardioprotective therapy was also permitted if continued at the same dose.

Rescue medication: Paracetamol (1000 mg) was permitted on an as-needed basis as rescue analgesia during the study, up to a total dose of 4 g per day.

Evidence for comparator:

Not applicable; no comparators were used.

|   |                   |
|---|-------------------|
| Actual start date of recruitment                          | 09 September 2013 |
| Long term follow-up planned                               | No                |
| Independent data monitoring committee (IDMC) involvement? | No                |

Notes:

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### Population of trial subjects

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#### Subjects enrolled per country

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|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 74 |
| Worldwide total number of subjects   | 74                 |
| EEA total number of subjects         | 74                 |

Notes:

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#### Subjects enrolled per age group

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|   |    |
|---|----|
| 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)                      | 24 |
| From 65 to 84 years                       | 50 |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

The first subject first visit was on 09 September 2013 and the last subject last visit was on 28 August 2014.

### Pre-assignment

Screening details:

Screening was performed 7-10 days before start of the treatment period. After screening, eligible subjects were enrolled in a washout period (placebo therapy), and subjects still eligible at the end of this period (7-10 days) were randomised to treatment groups.

### Pre-assignment period milestones

|                              |                    |
|------------------------------|--------------------|
| Number of subjects started   | 176 <sup>[1]</sup> |
| Number of subjects completed | 74                 |

### Pre-assignment subject non-completion reasons

|                            |  |
|----------------------------|--|
| Reason: Number of subjects | Not deemed eligible for randomisation: 102 |
|----------------------------|--|

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: A total of 176 subjects entered the washout period, of which 74 eligible subjects were randomised and treated in the treatment period, as planned in the study protocol.

### Period 1

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

Blinding implementation details:

The Sponsor and personnel at the study site were blinded to the treatment allocated to individual subjects, except when a medical emergency required knowledge of the treatment randomisation. If the randomisation code for a subject was broken by the study site, the subject was withdrawn from the study and a final assessment completed.

### Arms

|                              |           |
|------------------------------|-----------|
| Are arms mutually exclusive? | Yes       |
| Arm title                    | PRX167700 |

Arm description:

Subjects who received PRX167700 400mg 3 times per day.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | PRX167700    |
| Investigational medicinal product code | PRX167700    |
| Other name                             |              |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

PRX167700 400 mg 3 times per day (separated by 6 to 8 hours)

|           |         |
|-----------|---------|
| Arm title | Placebo |
|-----------|---------|

Arm description:

Subjects who received Placebo taken 3 times per day.

|  |          |
|--|----------|
| Arm type                               | Placebo  |
| Investigational medicinal product name | Placebo  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Capsule  |
| Routes of administration               | Oral use |

Dosage and administration details:

Placebo (lactose capsules) was taken 3 times per day (separated by 6 to 8 hours).

| <b>Number of subjects in period 1</b> | PRX167700 | Placebo |
|---------------------------------------|-----------|---------|
| Started                               | 36        | 38      |
| Completed                             | 35        | 35      |
| Not completed                         | 1         | 3       |
| Adverse event, non-fatal              | 1         | 2       |
| Protocol deviation                    | -         | 1       |

## Baseline characteristics

### Reporting groups

|  |           |
|--|-----------|
| Reporting group title                                  | PRX167700 |
| Reporting group description:                           |           |
| Subjects who received PRX167700 400mg 3 times per day. |           |
| Reporting group title                                  | Placebo   |
| Reporting group description:                           |           |
| Subjects who received Placebo taken 3 times per day.   |           |

| Reporting group values | PRX167700 | Placebo | Total |
|------------------------|-----------|---------|-------|
| Number of subjects     | 36        | 38      | 74    |
| Age categorical        |           |         |       |
| Units: Subjects        |           |         |       |

|  |         |         |    |
|--|---------|---------|----|
| Age continuous   |         |         |    |
| Subject age  |         |         |    |
| Units: years   |         |         |    |
| arithmetic mean  | 65.3    | 66.1    |    |
| standard deviation   | ± 7.24  | ± 6.33  | -  |
| Gender categorical   |         |         |    |
| Units: Subjects  |         |         |    |
| Female   | 14      | 18      | 32 |
| Male   | 22      | 20      | 42 |
| Race   |         |         |    |
| Units: Subjects  |         |         |    |
| White  | 35      | 36      | 71 |
| Asian  | 1       | 0       | 1  |
| Afro-Caribbean   | 0       | 1       | 1  |
| Other  | 0       | 1       | 1  |
| Body mass index  |         |         |    |
| Units: kg/square metre   |         |         |    |
| arithmetic mean  | 29.14   | 29.74   |    |
| standard deviation   | ± 3.842 | ± 3.713 | -  |
| Pain Intensity Assessment Score - Rest   |         |         |    |
| Pain Intensity at rest at Visit 2 measured using the 11-point numerical rating scale.  |         |         |    |
| Units: Assessment scale (1-11)   |         |         |    |
| arithmetic mean  | 4.72    | 4.89    |    |
| standard deviation   | ± 1.892 | ± 1.984 | -  |
| Pain Intensity Assessment Score - Post-walk  |         |         |    |
| Pain Intensity after walking 100m on a flat course at Visit 2 measured using the 11-point numerical rating scale.  |         |         |    |
| Units: Assessment scale (1-11)   |         |         |    |
| arithmetic mean  | 6.67    | 7.03    |    |
| standard deviation   | ± 1.549 | ± 1.619 | -  |
| WOMAC Index (total score)  |         |         |    |
| Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index completed at Visit 2. The paper questionnaire (5-point Likert scale version) consisted of 3 sections (subscales) assessing pain, stiffness, and difficulty performing daily activities. |         |         |    |

|                     |          |          |   |
|---------------------|----------|----------|---|
| Units: Rating scale |          |          |   |
| arithmetic mean     | 57.91    | 57.37    |   |
| standard deviation  | ± 11.126 | ± 11.748 | - |

## End points

### End points reporting groups

|  |           |
|--|-----------|
| Reporting group title  | PRX167700 |
| Reporting group description:<br>Subjects who received PRX167700 400mg 3 times per day. |           |
| Reporting group title  | Placebo   |
| Reporting group description:<br>Subjects who received Placebo taken 3 times per day.   |           |

### Primary: Pain Intensity Assessment Score - Visit 6

|  |   |
|--|---|
| End point title  | Pain Intensity Assessment Score - Visit 6 |
| End point description:<br>The average of the 3 assessments in the target knee joint performed at 1, 2, and 3 hours post-dose. Baseline was the pre-walk (rest) or post-walk value recorded at Visit 2. Change from baseline values are reported. |   |
| End point type   | Primary                                   |
| End point timeframe:<br>At specified study visit.  |   |

| End point values                     | PRX167700       | Placebo         |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 35              | 34              |  |  |
| Units: Assessment scale (1-11)       |                 |                 |  |  |
| arithmetic mean (standard deviation) |                 |                 |  |  |
| Rest                                 | -1.67 (± 2.031) | -0.93 (± 2.135) |  |  |
| Post-walk                            | -3.21 (± 2.013) | -2.43 (± 2.188) |  |  |

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Pain intensity at rest - 3 hours post-dose |
| Comparison groups                       | PRX167700 v Placebo                        |
| Number of subjects included in analysis | 69   |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | superiority <sup>[1]</sup>                 |
| P-value                                 | = 0.1242                                   |
| Method                                  | Mixed models analysis                      |
| Parameter estimate                      | Treatment effect                           |
| Point estimate                          | -0.76                                      |



|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -1.73                      |
| upper limit          | 0.21                       |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 0.49                       |

Notes:

[1] - Mixed effect model with repeated measurement to determine the treatment effect over time.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Pain intensity post-walk - 3 hours post-dose |
| Comparison groups                       | PRX167700 v Placebo                          |
| Number of subjects included in analysis | 69   |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           | superiority <sup>[2]</sup>                   |
| P-value                                 | = 0.153                                      |
| Method                                  | Mixed models analysis                        |
| Parameter estimate                      | Treatment effect                             |
| Point estimate                          | -0.75  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided                                      |
| lower limit                             | -1.79  |
| upper limit                             | 0.29   |
| Variability estimate                    | Standard error of the mean                   |
| Dispersion value                        | 0.52   |

Notes:

[2] - Mixed effect model with repeated measurement to determine the treatment effect over time.

### Primary: Pain Intensity Responder Analysis - Visit 6

|  |  |
|--|--|
| End point title  | Pain Intensity Responder Analysis - Visit 6 <sup>[3]</sup> |
| End point description:   |  |
| Subjects with pain intensity response (percentage decrease from baseline). |  |
| End point type   | Primary  |
| End point timeframe:   |  |
| At specified study visit.  |  |

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Pain intensity response (percentage change from baseline) is displayed showing number of subjects in each category of response. Statistical analysis was performed on pain intensity assessment scores, and is reported under these endpoints.

|                             |                 |                 |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>     | PRX167700       | Placebo         |  |  |
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 36              | 38              |  |  |
| Units: Number of subjects   |                 |                 |  |  |
| Pre-walk ≥ 30%              | 20              | 14              |  |  |
| Pre-walk ≥ 50%              | 13              | 11              |  |  |
| Pre-walk ≥ 70%              | 6               | 6               |  |  |
| Post-walk ≥ 30%             | 26              | 16              |  |  |

|                      |    |    |  |  |
|----------------------|----|----|--|--|
| Post-walk $\geq$ 50% | 17 | 11 |  |  |
| Post-walk $\geq$ 70% | 8  | 9  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Total WOMAC Index score

|                 |                         |
|-----------------|-------------------------|
| End point title | Total WOMAC Index score |
|-----------------|-------------------------|

End point description:

Total Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index score.

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

End point timeframe:

At specified study visit.

|                                      |                         |                          |  |  |
|--------------------------------------|-------------------------|--------------------------|--|--|
| <b>End point values</b>              | PRX167700               | Placebo                  |  |  |
| Subject group type                   | Reporting group         | Reporting group          |  |  |
| Number of subjects analysed          | 36                      | 38                       |  |  |
| Units: Rating scale                  |                         |                          |  |  |
| arithmetic mean (standard deviation) |                         |                          |  |  |
| Visit 6                              | 37.27 ( $\pm$<br>18.71) | 49.56 ( $\pm$<br>16.022) |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All adverse events were collected from the time of signature of informed consent throughout the washout, treatment, and follow-up periods.

Adverse event reporting additional description:

If a subject experienced more than one AE, they were counted once for each system organ class and preferred term.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 15.1 |
|--------------------|------|

### Reporting groups

|                       |           |
|-----------------------|-----------|
| Reporting group title | PRX167700 |
|-----------------------|-----------|

Reporting group description:

Subjects treated with PRX167700

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subjects receiving placebo

| Serious adverse events                            | PRX167700      | Placebo        |  |
|---|----------------|----------------|--|
| Total subjects affected by serious adverse events |                |                |  |
| subjects affected / exposed                       | 0 / 36 (0.00%) | 1 / 38 (2.63%) |  |
| number of deaths (all causes)                     | 0              | 0              |  |
| number of deaths resulting from adverse events    | 0              | 0              |  |
| Musculoskeletal and connective tissue disorders   |                |                |  |
| Lower limb fracture                               |                |                |  |
| subjects affected / exposed                       | 0 / 36 (0.00%) | 1 / 38 (2.63%) |  |
| occurrences causally related to treatment / all   | 0 / 0          | 0 / 1          |  |
| deaths causally related to treatment / all        | 0 / 0          | 0 / 0          |  |

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

| Non-serious adverse events                            | PRX167700        | Placebo          |  |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events |                  |                  |  |
| subjects affected / exposed                           | 14 / 36 (38.89%) | 21 / 38 (55.26%) |  |
| General disorders and administration site conditions  |                  |                  |  |

|   |                     |                     |  |
|---|---------------------|---------------------|--|
| Chest pain<br>subjects affected / exposed<br>occurrences (all)  | 0 / 36 (0.00%)<br>0 | 1 / 38 (2.63%)<br>1 |  |
| Chills<br>subjects affected / exposed<br>occurrences (all)  | 1 / 36 (2.78%)<br>2 | 0 / 38 (0.00%)<br>0 |  |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)   | 1 / 36 (2.78%)<br>1 | 0 / 38 (0.00%)<br>0 |  |
| Thirst<br>subjects affected / exposed<br>occurrences (all)  | 1 / 36 (2.78%)<br>1 | 0 / 38 (0.00%)<br>0 |  |
| Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)   | 0 / 36 (0.00%)<br>0 | 1 / 38 (2.63%)<br>1 |  |
| Reproductive system and breast disorders<br>Penile pain<br>subjects affected / exposed<br>occurrences (all)               | 1 / 36 (2.78%)<br>1 | 0 / 38 (0.00%)<br>0 |  |
| Respiratory, thoracic and mediastinal disorders<br>Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all) | 1 / 36 (2.78%)<br>1 | 1 / 38 (2.63%)<br>1 |  |
| Cough<br>subjects affected / exposed<br>occurrences (all)   | 0 / 36 (0.00%)<br>0 | 1 / 38 (2.63%)<br>1 |  |
| Sinus congestion<br>subjects affected / exposed<br>occurrences (all)  | 0 / 36 (0.00%)<br>0 | 1 / 38 (2.63%)<br>1 |  |
| Psychiatric disorders<br>Initial insomnia<br>subjects affected / exposed<br>occurrences (all)                             | 1 / 36 (2.78%)<br>1 | 0 / 38 (0.00%)<br>0 |  |
| Nightmare<br>subjects affected / exposed<br>occurrences (all)   | 1 / 36 (2.78%)<br>1 | 0 / 38 (0.00%)<br>0 |  |

|  |                |                |  |
|--|----------------|----------------|--|
| Investigations                                 |                |                |  |
| Blood glucose increased                        |                |                |  |
| subjects affected / exposed                    | 0 / 36 (0.00%) | 1 / 38 (2.63%) |  |
| occurrences (all)                              | 0              | 1              |  |
| Platelet count increased                       |                |                |  |
| subjects affected / exposed                    | 0 / 36 (0.00%) | 1 / 38 (2.63%) |  |
| occurrences (all)                              | 0              | 1              |  |
| Injury, poisoning and procedural complications |                |                |  |
| Contusion                                      |                |                |  |
| subjects affected / exposed                    | 0 / 36 (0.00%) | 1 / 38 (2.63%) |  |
| occurrences (all)                              | 0              | 1              |  |
| Excoriation                                    |                |                |  |
| subjects affected / exposed                    | 0 / 36 (0.00%) | 1 / 38 (2.63%) |  |
| occurrences (all)                              | 0              | 1              |  |
| Laceration                                     |                |                |  |
| subjects affected / exposed                    | 0 / 36 (0.00%) | 1 / 38 (2.63%) |  |
| occurrences (all)                              | 0              | 1              |  |
| Nervous system disorders                       |                |                |  |
| Headache                                       |                |                |  |
| subjects affected / exposed                    | 2 / 36 (5.56%) | 2 / 38 (5.26%) |  |
| occurrences (all)                              | 2              | 2              |  |
| Dizziness                                      |                |                |  |
| subjects affected / exposed                    | 1 / 36 (2.78%) | 2 / 38 (5.26%) |  |
| occurrences (all)                              | 1              | 2              |  |
| Somnolence                                     |                |                |  |
| subjects affected / exposed                    | 0 / 36 (0.00%) | 1 / 38 (2.63%) |  |
| occurrences (all)                              | 0              | 1              |  |
| Ear and labyrinth disorders                    |                |                |  |
| Tinnitus                                       |                |                |  |
| subjects affected / exposed                    | 0 / 36 (0.00%) | 1 / 38 (2.63%) |  |
| occurrences (all)                              | 0              | 1              |  |
| Eye disorders                                  |                |                |  |
| Diplopia                                       |                |                |  |
| subjects affected / exposed                    | 0 / 36 (0.00%) | 1 / 38 (2.63%) |  |
| occurrences (all)                              | 0              | 1              |  |
| Gastrointestinal disorders                     |                |                |  |

|  |                 |                |  |
|--|-----------------|----------------|--|
| Diarrhoea                              |                 |                |  |
| subjects affected / exposed            | 4 / 36 (11.11%) | 1 / 38 (2.63%) |  |
| occurrences (all)                      | 4               | 1              |  |
| Abdominal pain                         |                 |                |  |
| subjects affected / exposed            | 3 / 36 (8.33%)  | 1 / 38 (2.63%) |  |
| occurrences (all)                      | 3               | 1              |  |
| Dyspepsia                              |                 |                |  |
| subjects affected / exposed            | 2 / 36 (5.56%)  | 2 / 38 (5.26%) |  |
| occurrences (all)                      | 2               | 2              |  |
| Abdominal pain upper                   |                 |                |  |
| subjects affected / exposed            | 1 / 36 (2.78%)  | 1 / 38 (2.63%) |  |
| occurrences (all)                      | 1               | 1              |  |
| Constipation                           |                 |                |  |
| subjects affected / exposed            | 0 / 36 (0.00%)  | 1 / 38 (2.63%) |  |
| occurrences (all)                      | 0               | 1              |  |
| Flatulence                             |                 |                |  |
| subjects affected / exposed            | 1 / 36 (2.78%)  | 0 / 38 (0.00%) |  |
| occurrences (all)                      | 1               | 0              |  |
| Gingival pain                          |                 |                |  |
| subjects affected / exposed            | 0 / 36 (0.00%)  | 1 / 38 (2.63%) |  |
| occurrences (all)                      | 0               | 1              |  |
| Mouth ulceration                       |                 |                |  |
| subjects affected / exposed            | 0 / 36 (0.00%)  | 1 / 38 (2.63%) |  |
| occurrences (all)                      | 0               | 1              |  |
| Nausea                                 |                 |                |  |
| subjects affected / exposed            | 0 / 36 (0.00%)  | 1 / 38 (2.63%) |  |
| occurrences (all)                      | 0               | 1              |  |
| Toothache                              |                 |                |  |
| subjects affected / exposed            | 1 / 36 (2.78%)  | 0 / 38 (0.00%) |  |
| occurrences (all)                      | 1               | 0              |  |
| Abdominal distension                   |                 |                |  |
| subjects affected / exposed            | 1 / 36 (2.78%)  | 0 / 38 (0.00%) |  |
| occurrences (all)                      | 1               | 0              |  |
| Skin and subcutaneous tissue disorders |                 |                |  |
| Onychoclasia                           |                 |                |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 0 / 36 (0.00%) | 1 / 38 (2.63%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Pruritus  |                |                |  |
| subjects affected / exposed                     | 1 / 36 (2.78%) | 0 / 38 (0.00%) |  |
| occurrences (all)                               | 1              | 0              |  |
| Musculoskeletal and connective tissue disorders |                |                |  |
| Arthralgia                                      |                |                |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) | 1 / 38 (2.63%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Back pain                                       |                |                |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) | 1 / 38 (2.63%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Joint swelling                                  |                |                |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) | 1 / 38 (2.63%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Muscle spasms                                   |                |                |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) | 1 / 38 (2.63%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Pain in extremity                               |                |                |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) | 1 / 38 (2.63%) |  |
| occurrences (all)                               | 0              | 1              |  |
| Osteoarthritis                                  |                |                |  |
| subjects affected / exposed                     | 1 / 36 (2.78%) | 1 / 38 (2.63%) |  |
| occurrences (all)                               | 1              | 1              |  |
| Infections and infestations                     |                |                |  |
| Nasopharyngitis                                 |                |                |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) | 2 / 38 (5.26%) |  |
| occurrences (all)                               | 0              | 2              |  |
| Upper respiratory tract infection               |                |                |  |
| subjects affected / exposed                     | 2 / 36 (5.56%) | 0 / 38 (0.00%) |  |
| occurrences (all)                               | 2              | 0              |  |
| Urinary tract infection                         |                |                |  |
| subjects affected / exposed                     | 1 / 36 (2.78%) | 0 / 38 (0.00%) |  |
| occurrences (all)                               | 1              | 0              |  |
| Viral infection                                 |                |                |  |

|  |                     |                     |  |
|--|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all) | 1 / 36 (2.78%)<br>1 | 0 / 38 (0.00%)<br>0 |  |
| Metabolism and nutrition disorders               |                     |                     |  |
| Decreased appetite                               |                     |                     |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 36 (2.78%)<br>1 | 0 / 38 (0.00%)<br>0 |  |
| Hypoglycaemia                                    |                     |                     |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 36 (0.00%)<br>0 | 1 / 38 (2.63%)<br>1 |  |



## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported