



## Clinical trial results:

**The efficacy and safety of erdosteine in the long-term therapy of chronic obstructive pulmonary disease (COPD). A 12-month, randomised, double-blind, placebo-controlled, parallel group, multicenter study.**

### Summary

|                          |                         |
|--------------------------|-------------------------|
| EudraCT number           | 2008-008192-34          |
| Trial protocol           | IT GB CZ FR DK SK BE BG |
| Global end of trial date | 15 February 2013        |

### Results information

|                                   |                                       |
|-----------------------------------|---------------------------------------|
| Result version number             | v1                                    |
| This version publication date     | 13 November 2016                      |
| First version publication date    | 13 November 2016                      |
| Summary attachment (see zip file) | Study Synopsis (RESTORE SYNOPSIS.pdf) |

### Trial information

#### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | ERD-01-08/EP |
|-----------------------|--------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01032304 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Edmond Pharma Srl  |
| Sponsor organisation address | via F. Serpero 2, Masate (Mi), Italy, 20060                              |
| Public contact               | Pozzi Edoardo, Edmond Pharma, +39 029500461, edoardo.pozzi@recipharm.com |
| Scientific contact           | Pozzi Edoardo, Edmond Pharma, +39 029500461, edoardo.pozzi@recipharm.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                       | 27 July 2016     |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 15 February 2013 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The principal objective of the study is to evaluate if erdosteine is effective in reducing the risk of acute exacerbations in patients affected by moderate-to-severe COPD during a 12-month treatment period.

Protection of trial subjects:

The efficacy of erdosteine has been evaluated using the experimental drug as add-on to a regular maintenance therapy of COPD. Patients continued their standard treatment for COPD, established by the physician according to the best clinical practice and guidelines. Since patients, in any case, receive the appropriate COPD standard treatment, the administration of placebo to half of them do not posed particular ethical concerns, while being at the same time scientifically sounded in order to establish the additional benefits of adding erdosteine to regular maintenance COPD treatment.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 02 November 2009 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                     |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | Romania: 126        |
| Country: Number of subjects enrolled | Poland: 114         |
| Country: Number of subjects enrolled | Slovakia: 11        |
| Country: Number of subjects enrolled | United Kingdom: 22  |
| Country: Number of subjects enrolled | Belgium: 11         |
| Country: Number of subjects enrolled | Bulgaria: 14        |
| Country: Number of subjects enrolled | Czech Republic: 100 |
| Country: Number of subjects enrolled | Denmark: 16         |
| Country: Number of subjects enrolled | France: 5           |
| Country: Number of subjects enrolled | Italy: 109          |
| Worldwide total number of subjects   | 528                 |
| EEA total number of subjects         | 528                 |

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)                      | 254 |
| From 65 to 84 years                       | 274 |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

First patient in 02-11-2009; last patient in 15/02/2013 . Countries involved: Italy, United Kingdom, Denmark, Czech Republic, France, Poland, Romania, Moldvia, Bulgaria.

### Pre-assignment

Screening details:

Outpatients of both sexes, aged between 40 and 80 years with diagnosis of COPD (Stage II and III according to GOLD 2007); with a stable therapeutic regimen for COPD for at least 8 weeks prior to inclusion, 61 screening failure were registered due to consent withdrawn or lost to visit 1

### Pre-assignment period milestones

|                            |     |
|----------------------------|-----|
| Number of subjects started | 528 |
|----------------------------|-----|

|                              |     |
|------------------------------|-----|
| Number of subjects completed | 467 |
|------------------------------|-----|

### Pre-assignment subject non-completion reasons

|                            |                        |
|----------------------------|------------------------|
| Reason: Number of subjects | Physician decision: 61 |
|----------------------------|------------------------|

### Period 1

|                |                |
|----------------|----------------|
| Period 1 title | overall period |
|----------------|----------------|

|                              |     |
|------------------------------|-----|
| Is this the baseline period? | Yes |
|------------------------------|-----|

|                   |                         |
|-------------------|-------------------------|
| Allocation method | Randomised - controlled |
|-------------------|-------------------------|

|               |              |
|---------------|--------------|
| Blinding used | Double blind |
|---------------|--------------|

|               |                                |
|---------------|--------------------------------|
| Roles blinded | Subject, Investigator, Monitor |
|---------------|--------------------------------|

### Arms

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

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

Arm description:

blinded capsules erdosteine 300 mg

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|  |            |
|--|------------|
| Investigational medicinal product name | erdosteine |
|--|------------|

|  |  |
|--|--|
| Investigational medicinal product code |  |
|--|--|

|            |  |
|------------|--|
| Other name |  |
|------------|--|

|                      |         |
|----------------------|---------|
| Pharmaceutical forms | Capsule |
|----------------------|---------|

|                          |          |
|--------------------------|----------|
| Routes of administration | Oral use |
|--------------------------|----------|

Dosage and administration details:

300 mg BID

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

Arm description:

Placebo

|          |         |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

|  |            |
|--|------------|
| Investigational medicinal product name | erdosteine |
|--|------------|

|  |  |
|--|--|
| Investigational medicinal product code |  |
|--|--|

|            |  |
|------------|--|
| Other name |  |
|------------|--|

|                      |         |
|----------------------|---------|
| Pharmaceutical forms | Capsule |
|----------------------|---------|

|                          |          |
|--------------------------|----------|
| Routes of administration | Oral use |
|--------------------------|----------|

Dosage and administration details:

300 mg BID

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Active | Placebo |
|---|--------|---------|
| Started   | 228    | 239     |
| Completed   | 203    | 213     |
| Not completed                                       | 25     | 26      |
| Adverse event, serious fatal                        | 1      | 2       |
| Consent withdrawn by subject                        | 14     | 20      |
| Adverse event, non-fatal                            | 10     | 4       |

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Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 61 patients were considered as "screening failure" before the therapy assignment

## Baseline characteristics

### Reporting groups

|                       |                |
|-----------------------|----------------|
| Reporting group title | overall period |
|-----------------------|----------------|

Reporting group description: -

| Reporting group values               | overall period | Total |  |
|--------------------------------------|----------------|-------|--|
| Number of subjects                   | 467            | 467   |  |
| Age categorical                      |                |       |  |
| patient aged between 40 and 80 years |                |       |  |
| Units: Subjects                      |                |       |  |
| 40-80 yrs                            | 467            | 467   |  |
| Age continuous                       |                |       |  |
| Units: years                         |                |       |  |
| median                               | 64.769         |       |  |
| standard deviation                   | ± 8.34         | -     |  |
| Gender categorical                   |                |       |  |
| Units: Subjects                      |                |       |  |
| Female                               | 122            | 122   |  |
| Male                                 | 345            | 345   |  |
| Population characteristic            |                |       |  |
| Units: Subjects                      |                |       |  |
| COPD                                 | 467            | 467   |  |

## End points

### End points reporting groups

|  |         |
|--|---------|
| Reporting group title  | Active  |
| Reporting group description:<br>blinded capsules erdosteine 300 mg |         |
| Reporting group title  | Placebo |
| Reporting group description:<br>Placebo                            |         |

### Primary: overall number of exacerbations

|  |                                 |
|--|---------------------------------|
| End point title                          | overall number of exacerbations |
| End point description:                   |                                 |
| End point type                           | Primary                         |
| End point timeframe:<br>treatment period |                                 |

| End point values            | Active          | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 228             | 239             |  |  |
| Units: exact number         |                 |                 |  |  |
| exacerbations               | 196             | 261             |  |  |

### Statistical analyses

|  |                             |
|--|-----------------------------|
| Statistical analysis title   | overall exacerbations rate  |
| Statistical analysis description:<br>A predefined analysis of exacerbation frequency was performed using a Poisson regression model, with the covariates of treatment, age, sex, Body Mass Index, and FEV1 at the baseline to estimate the rate ratio. The natural logarithm of the duration, expressed as months in the study, was used as an offset variable to correct for differences in the time individuals spent under observation. |                             |
| Comparison groups  | Active v Placebo            |
| Number of subjects included in analysis  | 467                         |
| Analysis specification   | Pre-specified               |
| Analysis type  | superiority                 |
| P-value  | < 0.05                      |
| Method   | Wilcoxon (Mann-Whitney)     |
| Parameter estimate   | Poisson regression estimate |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

treatment duration 12 months

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | erdosteine |
|-----------------------|------------|

Reporting group description: -

|                       |         |
|-----------------------|---------|
| Reporting group title | placebo |
|-----------------------|---------|

Reporting group description: -

| Serious adverse events                            | erdosteine        | placebo           |  |
|---|-------------------|-------------------|--|
| Total subjects affected by serious adverse events |                   |                   |  |
| subjects affected / exposed                       | 41 / 228 (17.98%) | 33 / 239 (13.81%) |  |
| number of deaths (all causes)                     | 1                 | 2                 |  |
| number of deaths resulting from adverse events    |                   |                   |  |
| Investigations                                    |                   |                   |  |
| laryngoscopy                                      |                   |                   |  |
| subjects affected / exposed                       | 1 / 228 (0.44%)   | 0 / 239 (0.00%)   |  |
| occurrences causally related to treatment / all   | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all        | 0 / 0             | 0 / 0             |  |
| Injury, poisoning and procedural complications    |                   |                   |  |
| carbon monoxide poisoning                         |                   |                   |  |
| alternative dictionary used: MedDRA 17.1          |                   |                   |  |
| alternative assessment type: Non-systematic       |                   |                   |  |
| subjects affected / exposed                       | 1 / 228 (0.44%)   | 0 / 239 (0.00%)   |  |
| occurrences causally related to treatment / all   | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all        | 0 / 0             | 0 / 0             |  |
| Vascular disorders                                |                   |                   |  |
| transient cerebrovascular insufficiency           |                   |                   |  |
| subjects affected / exposed                       | 0 / 228 (0.00%)   | 1 / 239 (0.42%)   |  |
| occurrences causally related to treatment / all   | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all        | 0 / 0             | 0 / 0             |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Transient ischaemic attack                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 228 (0.44%) | 0 / 239 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Aneurysm  |                 |                 |  |
| subjects affected / exposed                     | 1 / 228 (0.44%) | 0 / 239 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| atrial fibrillation                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 228 (0.44%) | 0 / 239 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Coronary artery disease                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 228 (0.44%) | 0 / 239 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| heart failure                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 228 (0.44%) | 0 / 239 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Angina pectoris                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 228 (0.00%) | 1 / 239 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders            |                 |                 |  |
| Thrombocytopenia                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 228 (0.44%) | 0 / 239 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |
| chest/epigastric pain                           |                 |                 |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 3 / 228 (1.32%)  | 1 / 239 (0.42%)  |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatobiliary disorders                         |                  |                  |  |
| Cholecystectomy                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 228 (0.44%)  | 0 / 239 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Respiratory, thoracic and mediastinal disorders |                  |                  |  |
| COPD exacerbation                               |                  |                  |  |
| subjects affected / exposed                     | 20 / 228 (8.77%) | 16 / 239 (6.69%) |  |
| occurrences causally related to treatment / all | 0 / 20           | 0 / 16           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pneumonia                                       |                  |                  |  |
| subjects affected / exposed                     | 4 / 228 (1.75%)  | 3 / 239 (1.26%)  |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Acute respiratory failure                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 228 (0.00%)  | 1 / 239 (0.42%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Renal and urinary disorders                     |                  |                  |  |
| cancer  |                  |                  |  |
| subjects affected / exposed                     | 1 / 228 (0.44%)  | 0 / 239 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urinary tract infection                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 228 (0.44%)  | 0 / 239 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Musculoskeletal and connective tissue disorders |                  |                  |  |
| vertebral pain                                  |                  |                  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 228 (0.44%) | 0 / 239 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

Frequency threshold for reporting non-serious adverse events: 1 %

| <b>Non-serious adverse events</b>                     | erdosteine          | placebo            |  |
|---|---------------------|--------------------|--|
| Total subjects affected by non-serious adverse events |                     |                    |  |
| subjects affected / exposed                           | 228 / 228 (100.00%) | 206 / 239 (86.19%) |  |
| Surgical and medical procedures                       |                     |                    |  |
| Infiltration anaesthesia                              |                     |                    |  |
| subjects affected / exposed                           | 1 / 228 (0.44%)     | 0 / 239 (0.00%)    |  |
| occurrences (all)                                     | 1                   | 0                  |  |
| General disorders and administration site conditions  |                     |                    |  |
| Liver function test abnormal                          |                     |                    |  |
| subjects affected / exposed                           | 1 / 228 (0.44%)     | 2 / 239 (0.84%)    |  |
| occurrences (all)                                     | 1                   | 2                  |  |
| Chills  |                     |                    |  |
| subjects affected / exposed                           | 1 / 228 (0.44%)     | 0 / 239 (0.00%)    |  |
| occurrences (all)                                     | 1                   | 0                  |  |
| Fatigue   |                     |                    |  |
| subjects affected / exposed                           | 2 / 228 (0.88%)     | 0 / 239 (0.00%)    |  |
| occurrences (all)                                     | 2                   | 0                  |  |
| Asthenia  |                     |                    |  |
| subjects affected / exposed                           | 0 / 228 (0.00%)     | 1 / 239 (0.42%)    |  |
| occurrences (all)                                     | 0                   | 1                  |  |
| Haemoptysis   |                     |                    |  |
| subjects affected / exposed                           | 1 / 228 (0.44%)     | 0 / 239 (0.00%)    |  |
| occurrences (all)                                     | 1                   | 0                  |  |
| Headache  |                     |                    |  |
| subjects affected / exposed                           | 0 / 228 (0.00%)     | 5 / 239 (2.09%)    |  |
| occurrences (all)                                     | 0                   | 5                  |  |
| Insomnia  |                     |                    |  |
| subjects affected / exposed                           | 0 / 228 (0.00%)     | 2 / 239 (0.84%)    |  |
| occurrences (all)                                     | 0                   | 3                  |  |

|  |                      |                        |  |
|--|----------------------|------------------------|--|
| Tooth abscess<br>subjects affected / exposed<br>occurrences (all)      | 1 / 228 (0.44%)<br>2 | 1 / 239 (0.42%)<br>1   |  |
| Toothache<br>subjects affected / exposed<br>occurrences (all)          | 0 / 228 (0.00%)<br>0 | 1 / 239 (0.42%)<br>2   |  |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)   | 1 / 228 (0.44%)<br>1 | 0 / 239 (0.00%)<br>0   |  |
| Respiratory, thoracic and mediastinal disorders                        |                      |                        |  |
| Viral infection<br>subjects affected / exposed<br>occurrences (all)    | 1 / 228 (0.44%)<br>1 | 0 / 239 (0.00%)<br>0   |  |
| Bronchopneumopathy<br>subjects affected / exposed<br>occurrences (all) | 1 / 228 (0.44%)<br>1 | 0 / 239 (0.00%)<br>0   |  |
| Rhinitis<br>subjects affected / exposed<br>occurrences (all)           | 5 / 228 (2.19%)<br>5 | 3 / 239 (1.26%)<br>5   |  |
| Chest pain<br>subjects affected / exposed<br>occurrences (all)         | 2 / 228 (0.88%)<br>2 | 0 / 239 (0.00%)<br>0   |  |
| Cough<br>subjects affected / exposed<br>occurrences (all)              | 2 / 228 (0.88%)<br>2 | 3 / 239 (1.26%)<br>3   |  |
| Throat irritation<br>subjects affected / exposed<br>occurrences (all)  | 1 / 228 (0.44%)<br>1 | 4 / 239 (1.67%)<br>4   |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)           | 3 / 228 (1.32%)<br>3 | 10 / 239 (4.18%)<br>11 |  |
| Sputum discoloured<br>subjects affected / exposed<br>occurrences (all) | 1 / 228 (0.44%)<br>1 | 0 / 239 (0.00%)<br>0   |  |
| Ear infection  |                      |                        |  |

|  |                          |                           |  |
|--|--------------------------|---------------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 0 / 228 (0.00%)<br>0     | 1 / 239 (0.42%)<br>1      |  |
| Painful respiration<br>subjects affected / exposed<br>occurrences (all)  | 1 / 228 (0.44%)<br>1     | 0 / 239 (0.00%)<br>0      |  |
| Sinusitis<br>subjects affected / exposed<br>occurrences (all)  | 1 / 228 (0.44%)<br>1     | 1 / 239 (0.42%)<br>1      |  |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 228 (0.00%)<br>0     | 1 / 239 (0.42%)<br>1      |  |
| COPD exacerbations<br>subjects affected / exposed<br>occurrences (all)   | 99 / 228 (43.42%)<br>185 | 136 / 239 (56.90%)<br>258 |  |
| Investigations<br>Mitral valve replacement<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 228 (0.00%)<br>0     | 1 / 239 (0.42%)<br>1      |  |
| Injury, poisoning and procedural complications<br>Chest injury<br>subjects affected / exposed<br>occurrences (all) | 0 / 228 (0.00%)<br>0     | 1 / 239 (0.42%)<br>1      |  |
| Cardiac disorders<br>Atrial fibrillation<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 228 (0.44%)<br>1     | 1 / 239 (0.42%)<br>1      |  |
| Cardiac disorder<br>subjects affected / exposed<br>occurrences (all)   | 1 / 228 (0.44%)<br>1     | 0 / 239 (0.00%)<br>0      |  |
| Palpitations<br>subjects affected / exposed<br>occurrences (all)   | 0 / 228 (0.00%)<br>0     | 2 / 239 (0.84%)<br>2      |  |
| Arrhythmia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 228 (0.00%)<br>0     | 1 / 239 (0.42%)<br>1      |  |
| Coronary artery disease  |                          |                           |  |

|   |                      |                      |  |
|---|----------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)  | 0 / 228 (0.00%)<br>0 | 1 / 239 (0.42%)<br>1 |  |
| Hypertension<br>subjects affected / exposed<br>occurrences (all)                                    | 8 / 228 (3.51%)<br>9 | 1 / 239 (0.42%)<br>1 |  |
| Hypocalcaemia<br>subjects affected / exposed<br>occurrences (all)                                   | 1 / 228 (0.44%)<br>1 | 1 / 239 (0.42%)<br>1 |  |
| Tachycardia paroxysmal<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 228 (0.00%)<br>0 | 1 / 239 (0.42%)<br>1 |  |
| Nervous system disorders<br>Anxiety<br>subjects affected / exposed<br>occurrences (all)             | 1 / 228 (0.44%)<br>1 | 0 / 239 (0.00%)<br>0 |  |
| Depression<br>subjects affected / exposed<br>occurrences (all)                                      | 2 / 228 (0.88%)<br>3 | 0 / 239 (0.00%)<br>0 |  |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                                       | 0 / 228 (0.00%)<br>0 | 1 / 239 (0.42%)<br>1 |  |
| Tremor<br>subjects affected / exposed<br>occurrences (all)  | 0 / 228 (0.00%)<br>0 | 1 / 239 (0.42%)<br>1 |  |
| Sleep disorder<br>subjects affected / exposed<br>occurrences (all)                                  | 0 / 228 (0.00%)<br>0 | 1 / 239 (0.42%)<br>1 |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all) | 1 / 228 (0.44%)<br>1 | 0 / 239 (0.00%)<br>0 |  |
| Anaemia folate deficiency<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 228 (0.44%)<br>1 | 0 / 239 (0.00%)<br>0 |  |
| Hypoxia   |                      |                      |  |

|   |                      |                      |  |
|---|----------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)                      | 1 / 228 (0.44%)<br>0 | 1 / 239 (0.42%)<br>1 |  |
| Arterial disorder<br>subjects affected / exposed<br>occurrences (all) | 1 / 228 (0.44%)<br>2 | 0 / 239 (0.00%)<br>0 |  |
| Eye disorders   |                      |                      |  |
| Cataract<br>subjects affected / exposed<br>occurrences (all)          | 1 / 228 (0.44%)<br>2 | 0 / 239 (0.00%)<br>0 |  |
| Corneal abrasion<br>subjects affected / exposed<br>occurrences (all)  | 1 / 228 (0.44%)<br>1 | 0 / 239 (0.00%)<br>0 |  |
| Pain<br>subjects affected / exposed<br>occurrences (all)              | 1 / 228 (0.44%)<br>3 | 0 / 239 (0.00%)<br>0 |  |
| Gastrointestinal disorders  |                      |                      |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)    | 4 / 228 (1.75%)<br>4 | 3 / 239 (1.26%)<br>3 |  |
| Reflux gastritis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 228 (0.00%)<br>0 | 1 / 239 (0.42%)<br>1 |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)         | 2 / 228 (0.88%)<br>3 | 1 / 239 (0.42%)<br>1 |  |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)         | 1 / 228 (0.44%)<br>1 | 6 / 239 (2.51%)<br>6 |  |
| Gastric ulcer<br>subjects affected / exposed<br>occurrences (all)     | 2 / 228 (0.88%)<br>2 | 0 / 239 (0.00%)<br>0 |  |
| Acidosis<br>subjects affected / exposed<br>occurrences (all)          | 0 / 228 (0.00%)<br>0 | 1 / 239 (0.42%)<br>2 |  |
| Nausea  |                      |                      |  |



|  |                      |                      |  |
|--|----------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 0 / 228 (0.00%)<br>0 | 1 / 239 (0.42%)<br>1 |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)   | 1 / 228 (0.44%)<br>1 | 0 / 239 (0.00%)<br>0 |  |
| Hepatobiliary disorders<br>Bladder spasm<br>subjects affected / exposed<br>occurrences (all)           | 1 / 228 (0.44%)<br>1 | 0 / 239 (0.00%)<br>0 |  |
| Cholecystitis<br>subjects affected / exposed<br>occurrences (all)                                      | 0 / 228 (0.00%)<br>0 | 1 / 239 (0.42%)<br>1 |  |
| Salivary hypersecretion<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 228 (0.00%)<br>0 | 1 / 239 (0.42%)<br>1 |  |
| Skin and subcutaneous tissue disorders<br>Pruritus<br>subjects affected / exposed<br>occurrences (all) | 1 / 228 (0.44%)<br>1 | 1 / 239 (0.42%)<br>1 |  |
| Rash<br>subjects affected / exposed<br>occurrences (all)   | 0 / 228 (0.00%)<br>0 | 1 / 239 (0.42%)<br>1 |  |
| Infection<br>subjects affected / exposed<br>occurrences (all)  | 1 / 228 (0.44%)<br>1 | 0 / 239 (0.00%)<br>0 |  |
| Renal and urinary disorders<br>Urinary retention<br>subjects affected / exposed<br>occurrences (all)   | 1 / 228 (0.44%)<br>1 | 0 / 239 (0.00%)<br>0 |  |
| Cystitis<br>subjects affected / exposed<br>occurrences (all)   | 1 / 228 (0.44%)<br>1 | 1 / 239 (0.42%)<br>1 |  |
| Urinary tract inflammation<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 228 (0.00%)<br>0 | 1 / 239 (0.42%)<br>1 |  |
| Proteinuria  |                      |                      |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 228 (0.00%) | 1 / 239 (0.42%) |  |
| occurrences (all)                               | 0               | 1               |  |
| Urinary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 4 / 228 (1.75%) | 1 / 239 (0.42%) |  |
| occurrences (all)                               | 4               | 0               |  |
| Incontinence                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 228 (0.44%) | 0 / 239 (0.00%) |  |
| occurrences (all)                               | 1               | 0               |  |
| Endocrine disorders                             |                 |                 |  |
| Diabetes mellitus                               |                 |                 |  |
| subjects affected / exposed                     | 2 / 228 (0.88%) | 1 / 239 (0.42%) |  |
| occurrences (all)                               | 2               | 1               |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Back pain                                       |                 |                 |  |
| subjects affected / exposed                     | 3 / 228 (1.32%) | 3 / 239 (1.26%) |  |
| occurrences (all)                               | 3               | 3               |  |
| Contusion                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 228 (0.00%) | 1 / 239 (0.42%) |  |
| occurrences (all)                               | 0               | 1               |  |
| Bite  |                 |                 |  |
| subjects affected / exposed                     | 0 / 228 (0.00%) | 1 / 239 (0.42%) |  |
| occurrences (all)                               | 0               | 1               |  |
| Fibromyalgia                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 228 (0.44%) | 2 / 239 (0.84%) |  |
| occurrences (all)                               | 1               | 2               |  |
| Joint abscess                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 228 (0.00%) | 1 / 239 (0.42%) |  |
| occurrences (all)                               | 0               | 1               |  |
| Bone pain                                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 228 (0.88%) | 1 / 239 (0.42%) |  |
| occurrences (all)                               | 2               | 1               |  |
| Oedema  |                 |                 |  |
| subjects affected / exposed                     | 2 / 228 (0.88%) | 1 / 239 (0.42%) |  |
| occurrences (all)                               | 0               | 0               |  |
| Infections and infestations                     |                 |                 |  |

|                                    |                 |                 |  |
|------------------------------------|-----------------|-----------------|--|
| Influenza                          |                 |                 |  |
| subjects affected / exposed        | 3 / 228 (1.32%) | 3 / 239 (1.26%) |  |
| occurrences (all)                  | 3               | 3               |  |
| Pyrexia                            |                 |                 |  |
| subjects affected / exposed        | 1 / 228 (0.44%) | 0 / 239 (0.00%) |  |
| occurrences (all)                  | 1               | 0               |  |
| Mycobacterial infection            |                 |                 |  |
| subjects affected / exposed        | 1 / 228 (0.44%) | 0 / 239 (0.00%) |  |
| occurrences (all)                  | 1               | 0               |  |
| Fungal infection                   |                 |                 |  |
| subjects affected / exposed        | 0 / 228 (0.00%) | 2 / 239 (0.84%) |  |
| occurrences (all)                  | 0               | 2               |  |
| Pneumonia                          |                 |                 |  |
| subjects affected / exposed        | 1 / 228 (0.44%) | 1 / 239 (0.42%) |  |
| occurrences (all)                  | 2               | 1               |  |
| Viraemia                           |                 |                 |  |
| subjects affected / exposed        | 1 / 228 (0.44%) | 2 / 239 (0.84%) |  |
| occurrences (all)                  | 1               | 2               |  |
| Metabolism and nutrition disorders |                 |                 |  |
| Hyper HDL cholesterolaemia         |                 |                 |  |
| subjects affected / exposed        | 1 / 228 (0.44%) | 0 / 239 (0.00%) |  |
| occurrences (all)                  | 1               | 0               |  |
| Cachexia                           |                 |                 |  |
| subjects affected / exposed        | 0 / 228 (0.00%) | 1 / 239 (0.42%) |  |
| occurrences (all)                  | 0               | 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