



## Clinical trial results:

### A Phase 2, Randomized, Double-Blind, MultipleDose, FivePeriod, Incomplete-Block, Crossover Study to Examine the Pharmacodynamics, Safety and Tolerability, and Pharmacokinetics of Multiple Doses of TD4208 for 7 Days in Subjects Diagnosed With Chronic Obstructive Pulmonary Disease

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2012-004949-32 |
| Trial protocol           | GB DE          |
| Global end of trial date | 23 August 2014 |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 22 March 2020 |
| First version publication date | 22 March 2020 |

#### Trial information

##### Trial identification

|                       |      |
|-----------------------|------|
| Sponsor protocol code | 0091 |
|-----------------------|------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01704404 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Theravance Biopharma R&D, Inc.  |
| Sponsor organisation address | 901 Gateway Boulevard, South San Francisco, United States, 94080        |
| Public contact               | Theravance Biopharma R&D, Theravance Biopharma R&D, Inc., 650 808-6000, |
| Scientific contact           | Theravance Biopharma R&D, Theravance Biopharma R&D, Inc., 650 808-6000, |

Notes:

#### Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|  |                |
|--|----------------|
| Analysis stage                                       | Final          |
| Date of interim/final analysis                       | 23 August 2014 |
| Is this the analysis of the primary completion data? | Yes            |
| Primary completion date                              | 23 August 2014 |
| Global end of trial reached?                         | Yes            |
| Global end of trial date                             | 23 August 2014 |
| Was the trial ended prematurely?                     | No             |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to characterize the dose-response curve of TD-4208 after 7 days of dosing in subjects with chronic obstructive pulmonary disease (COPD). The endpoint for this evaluation of TD-4208 was forced expiratory volume in 1 second (FEV1).

Protection of trial subjects:

The study was conducted in accordance with the principles of the Declaration of Helsinki in place at the time of study conduct. The study was conducted in compliance with the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP) (Committee for Proprietary Medicinal Products [CPMP] guideline CPMP/ICH/135/95), and compliant with the European Union Clinical Trial Directive (EU CTD): Directive 2001/20/EC.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 12 December 2012 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | New Zealand: 18    |
| Country: Number of subjects enrolled | United Kingdom: 44 |
| Worldwide total number of subjects   | 62                 |
| EEA total number of subjects         | 44                 |

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)                      | 31 |
| From 65 to 84 years                       | 31 |

|                   |   |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

## Subject disposition

### Recruitment

Recruitment details:

Participants were recruited at 3 sites in the UK and New Zealand.

### Pre-assignment

Screening details:

Participants were screened over a 21-day period.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Study (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? | No      |
| <b>Arm title</b>             | Placebo |

Arm description:

Participants received placebo once daily for 7 days.

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

Dosage and administration details:

The placebo will be administered using a nebulizer as an inhaled solution.

|                  |               |
|------------------|---------------|
| <b>Arm title</b> | TD-4208 22 µg |
|------------------|---------------|

Arm description:

Participants received TD-4208 22 µg once daily for 7 days.

|  |                     |
|--|---------------------|
| Arm type                               | Experimental        |
| Investigational medicinal product name | TD-4208             |
| Investigational medicinal product code |                     |
| Other name                             |                     |
| Pharmaceutical forms                   | Inhalation solution |
| Routes of administration               | Inhalation use      |

Dosage and administration details:

TD-4208 will be administered using a nebulizer as an inhaled solution.

|                  |               |
|------------------|---------------|
| <b>Arm title</b> | TD-4208 44 µg |
|------------------|---------------|

Arm description:

Participants received TD-4208 44 µg once daily for 7 days.

|  |                     |
|--|---------------------|
| Arm type                               | Experimental        |
| Investigational medicinal product name | TD-4208             |
| Investigational medicinal product code |                     |
| Other name                             |                     |
| Pharmaceutical forms                   | Inhalation solution |
| Routes of administration               | Inhalation use      |

Dosage and administration details:

TD-4208 will be administered using a nebulizer as an inhaled solution.

|                  |               |
|------------------|---------------|
| <b>Arm title</b> | TD-4208 88 µg |
|------------------|---------------|

Arm description:

Participants received TD-4208 88 µg once daily for 7 days.

|  |                     |
|--|---------------------|
| Arm type                               | Experimental        |
| Investigational medicinal product name | TD-4208             |
| Investigational medicinal product code |                     |
| Other name                             |                     |
| Pharmaceutical forms                   | Inhalation solution |
| Routes of administration               | Inhalation use      |

Dosage and administration details:

TD-4208 will be administered using a nebulizer as an inhaled solution.

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | TD-4208 175 µg |
|------------------|----------------|

Arm description:

Participants received TD-4208 175 µg once daily for 7 days.

|  |                     |
|--|---------------------|
| Arm type                               | Experimental        |
| Investigational medicinal product name | TD-4208             |
| Investigational medicinal product code |                     |
| Other name                             |                     |
| Pharmaceutical forms                   | Inhalation solution |
| Routes of administration               | Inhalation use      |

Dosage and administration details:

TD-4208 will be administered using a nebulizer as an inhaled solution.

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | TD-4208 350 µg |
|------------------|----------------|

Arm description:

Participants received TD-4208 350 µg once daily for 7 days.

|  |                     |
|--|---------------------|
| Arm type                               | Experimental        |
| Investigational medicinal product name | TD-4208             |
| Investigational medicinal product code |                     |
| Other name                             |                     |
| Pharmaceutical forms                   | Inhalation solution |
| Routes of administration               | Inhalation use      |

Dosage and administration details:

TD-4208 will be administered using a nebulizer as an inhaled solution.

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | TD-4208 700 µg |
|------------------|----------------|

Arm description:

Participants received TD-4208 700 µg once daily for 7 days.

|  |                     |
|--|---------------------|
| Arm type                               | Experimental        |
| Investigational medicinal product name | TD-4208             |
| Investigational medicinal product code |                     |
| Other name                             |                     |
| Pharmaceutical forms                   | Inhalation solution |
| Routes of administration               | Inhalation use      |

Dosage and administration details:

TD-4208 will be administered using a nebulizer as an inhaled solution.

| <b>Number of subjects in period 1</b> | Placebo | TD-4208 22 µg | TD-4208 44 µg |
|---------------------------------------|---------|---------------|---------------|
| Started                               | 62      | 42            | 42            |
| Completed                             | 55      | 36            | 37            |
| Not completed                         | 7       | 6             | 5             |
| Consent withdrawn by subject          | 2       | 2             | 1             |
| Adverse event, non-fatal              | 5       | 4             | 4             |

| <b>Number of subjects in period 1</b> | TD-4208 88 µg | TD-4208 175 µg | TD-4208 350 µg |
|---------------------------------------|---------------|----------------|----------------|
| Started                               | 40            | 41             | 41             |
| Completed                             | 37            | 35             | 38             |
| Not completed                         | 3             | 6              | 3              |
| Consent withdrawn by subject          | 1             | 2              | -              |
| Adverse event, non-fatal              | 2             | 4              | 3              |

| <b>Number of subjects in period 1</b> | TD-4208 700 µg |
|---------------------------------------|----------------|
| Started                               | 42             |
| Completed                             | 37             |
| Not completed                         | 5              |
| Consent withdrawn by subject          | 2              |
| Adverse event, non-fatal              | 3              |

## Baseline characteristics

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | Overall Study |
|-----------------------|---------------|

Reporting group description: -

| Reporting group values                             | Overall Study | Total |  |
|--|---------------|-------|--|
| Number of subjects                                 | 62            | 62    |  |
| Age categorical                                    |               |       |  |
| Units: Subjects                                    |               |       |  |
| In utero   | 0             | 0     |  |
| Preterm newborn infants (gestational age < 37 wks) | 0             | 0     |  |
| Newborns (0-27 days)                               | 0             | 0     |  |
| Infants and toddlers (28 days-23 months)           | 0             | 0     |  |
| Children (2-11 years)                              | 0             | 0     |  |
| Adolescents (12-17 years)                          | 0             | 0     |  |
| Adults (18-64 years)                               | 31            | 31    |  |
| From 65-84 years                                   | 31            | 31    |  |
| 85 years and over                                  | 0             | 0     |  |
| Gender categorical                                 |               |       |  |
| Units: Subjects                                    |               |       |  |
| Female   | 27            | 27    |  |
| Male   | 35            | 35    |  |
| Ethnicity  |               |       |  |
| Units: Subjects                                    |               |       |  |
| Hispanic or Latino                                 | 2             | 2     |  |
| Not Hispanic or Latino                             | 60            | 60    |  |
| Race   |               |       |  |
| Units: Subjects                                    |               |       |  |
| White  | 62            | 62    |  |

## End points

### End points reporting groups

|   |                |
|---|----------------|
| Reporting group title   | Placebo        |
| Reporting group description:<br>Participants received placebo once daily for 7 days.        |                |
| Reporting group title   | TD-4208 22 µg  |
| Reporting group description:<br>Participants received TD-4208 22 µg once daily for 7 days.  |                |
| Reporting group title   | TD-4208 44 µg  |
| Reporting group description:<br>Participants received TD-4208 44 µg once daily for 7 days.  |                |
| Reporting group title   | TD-4208 88 µg  |
| Reporting group description:<br>Participants received TD-4208 88 µg once daily for 7 days.  |                |
| Reporting group title   | TD-4208 175 µg |
| Reporting group description:<br>Participants received TD-4208 175 µg once daily for 7 days. |                |
| Reporting group title   | TD-4208 350 µg |
| Reporting group description:<br>Participants received TD-4208 350 µg once daily for 7 days. |                |
| Reporting group title   | TD-4208 700 µg |
| Reporting group description:<br>Participants received TD-4208 700 µg once daily for 7 days. |                |

### Primary: Change from Baseline to Day 7 in Trough Forced Expiratory Volume in 1 Second (FEV1)

|   |   |
|---|---|
| End point title                           | Change from Baseline to Day 7 in Trough Forced Expiratory Volume in 1 Second (FEV1) |
| End point description:                    |   |
| End point type                            | Primary   |
| End point timeframe:<br>Baseline to Day 7 |   |

| End point values                    | Placebo         | TD-4208 22 µg   | TD-4208 44 µg   | TD-4208 88 µg   |
|-------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type                  | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed         | 59              | 40              | 39              | 39              |
| Units: mL                           |                 |                 |                 |                 |
| least squares mean (standard error) | 37.8 (± 16.93)  | 91.2 (± 19.21)  | 92.8 (± 20.25)  | 113.1 (± 19.55) |

| End point values | TD-4208 175 µg | TD-4208 350 µg | TD-4208 700 µg |  |
|------------------|----------------|----------------|----------------|--|
|------------------|----------------|----------------|----------------|--|



|                                     |                      |                      |                      |  |
|-------------------------------------|----------------------|----------------------|----------------------|--|
| Subject group type                  | Reporting group      | Reporting group      | Reporting group      |  |
| Number of subjects analysed         | 39                   | 39                   | 40                   |  |
| Units: mL                           |                      |                      |                      |  |
| least squares mean (standard error) | 151.9 ( $\pm$ 19.99) | 132.2 ( $\pm$ 19.02) | 119.4 ( $\pm$ 19.54) |  |

## Statistical analyses

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | Placebo vs. TD-4208 22 µg             |
| Comparison groups                       | Placebo v TD-4208 22 µg               |
| Number of subjects included in analysis | 99                                    |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.006 <sup>[1]</sup>                |
| Method                                  | Mixed-effects repeated measures model |
| Parameter estimate                      | LS Mean Difference                    |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | 16.5                                  |
| upper limit                             | 90.5                                  |

Notes:

[1] - Adjusted P-value

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | Placebo v.s TD-4208 44 µg             |
| Comparison groups                       | TD-4208 44 µg v Placebo               |
| Number of subjects included in analysis | 98                                    |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | = 0.006 <sup>[2]</sup>                |
| Method                                  | Mixed-effects repeated measures model |
| Parameter estimate                      | LS Mean Difference                    |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | 15.9                                  |
| upper limit                             | 94.1                                  |

Notes:

[2] - Adjusted P-value

|                                   |                           |
|-----------------------------------|---------------------------|
| <b>Statistical analysis title</b> | Placebo v.s TD-4208 88 µg |
| Comparison groups                 | TD-4208 88 µg v Placebo   |

|   |                                       |
|---|---------------------------------------|
| Number of subjects included in analysis | 98                                    |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | > 0.001 <sup>[3]</sup>                |
| Method                                  | Mixed-effects repeated measures model |
| Parameter estimate                      | LS Mean Difference                    |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | 37.7                                  |
| upper limit                             | 113                                   |

Notes:

[3] - Adjusted P-value

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | Placebo v.s TD-4208 175 µg            |
| Comparison groups                       | Placebo v TD-4208 175 µg              |
| Number of subjects included in analysis | 98                                    |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | < 0.001 <sup>[4]</sup>                |
| Method                                  | Mixed-effects repeated measures model |
| Parameter estimate                      | LS Mean Difference                    |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | 75.7                                  |
| upper limit                             | 152.6                                 |

Notes:

[4] - Adjusted P-value

|   |                                       |
|---|---------------------------------------|
| <b>Statistical analysis title</b>       | Placebo v.s TD-4208 350 µg            |
| Comparison groups                       | Placebo v TD-4208 350 µg              |
| Number of subjects included in analysis | 98                                    |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | < 0.001 <sup>[5]</sup>                |
| Method                                  | Mixed-effects repeated measures model |
| Parameter estimate                      | LS Mean Difference                    |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | 57.7                                  |
| upper limit                             | 131.1                                 |

Notes:

[5] - Adjusted P-value

|                                   |                            |
|-----------------------------------|----------------------------|
| <b>Statistical analysis title</b> | Placebo v.s TD-4208 700 µg |
| Comparison groups                 | TD-4208 700 µg v Placebo   |

|   |                                       |
|---|---------------------------------------|
| Number of subjects included in analysis | 99                                    |
| Analysis specification                  | Pre-specified                         |
| Analysis type                           | superiority                           |
| P-value                                 | < 0.001 <sup>[6]</sup>                |
| Method                                  | Mixed-effects repeated measures model |
| Parameter estimate                      | LS Mean Difference                    |
| Confidence interval                     |                                       |
| level                                   | 95 %                                  |
| sides                                   | 2-sided                               |
| lower limit                             | 43.8                                  |
| upper limit                             | 119.5                                 |

Notes:

[6] - Adjusted P-value

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Day 1 to End of Follow-up (Up to 14 days after Period 5)

Adverse event reporting additional description:

Adverse events are reported for the Safety Analysis Set. The Safety analysis set comprised subjects who received at least 1 dose of study treatment (TD-4208 or placebo).

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

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

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

### Reporting groups

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

Reporting group description:

Participants received placebo once daily for 7 days.

|                       |               |
|-----------------------|---------------|
| Reporting group title | TD-4208 22 µg |
|-----------------------|---------------|

Reporting group description:

Participants received TD-4208 22 µg once daily for 7 days.

|                       |               |
|-----------------------|---------------|
| Reporting group title | TD-4208 44 µg |
|-----------------------|---------------|

Reporting group description:

Participants received TD-4208 44 µg once daily for 7 days.

|                       |               |
|-----------------------|---------------|
| Reporting group title | TD-4208 88 µg |
|-----------------------|---------------|

Reporting group description:

Participants received TD-4208 88 µg once daily for 7 days.

|                       |                |
|-----------------------|----------------|
| Reporting group title | TD-4208 175 µg |
|-----------------------|----------------|

Reporting group description:

Participants received TD-4208 175 µg once daily for 7 days.

|                       |                |
|-----------------------|----------------|
| Reporting group title | TD-4208 350 µg |
|-----------------------|----------------|

Reporting group description:

Participants received TD-4208 350 µg once daily for 7 days.

|                       |                |
|-----------------------|----------------|
| Reporting group title | TD-4208 700 µg |
|-----------------------|----------------|

Reporting group description:

Participants received TD-4208 700 µg once daily for 7 days.

| Serious adverse events                            | Placebo        | TD-4208 22 µg  | TD-4208 44 µg  |
|---|----------------|----------------|----------------|
| Total subjects affected by serious adverse events |                |                |                |
| subjects affected / exposed                       | 1 / 61 (1.64%) | 2 / 41 (4.88%) | 0 / 39 (0.00%) |
| number of deaths (all causes)                     | 0              | 0              | 0              |
| number of deaths resulting from adverse events    | 0              | 0              | 0              |
| Nervous system disorders                          |                |                |                |
| Transient ischemic attack                         |                |                |                |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed                          | 0 / 61 (0.00%) | 1 / 41 (2.44%) | 0 / 39 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| General disorders and administration site conditions |                |                |                |
| Chest pain   |                |                |                |
| subjects affected / exposed                          | 0 / 61 (0.00%) | 1 / 41 (2.44%) | 0 / 39 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                          |                |                |                |
| Pneumonia  |                |                |                |
| subjects affected / exposed                          | 1 / 61 (1.64%) | 0 / 41 (0.00%) | 0 / 39 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |

| <b>Serious adverse events</b>                        | TD-4208 88 µg  | TD-4208 175 µg | TD-4208 350 µg |
|--|----------------|----------------|----------------|
| Total subjects affected by serious adverse events    |                |                |                |
| subjects affected / exposed                          | 0 / 40 (0.00%) | 0 / 37 (0.00%) | 0 / 41 (0.00%) |
| number of deaths (all causes)                        | 0              | 0              | 0              |
| number of deaths resulting from adverse events       | 0              | 0              | 0              |
| Nervous system disorders                             |                |                |                |
| Transient ischemic attack                            |                |                |                |
| subjects affected / exposed                          | 0 / 40 (0.00%) | 0 / 37 (0.00%) | 0 / 41 (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          |
| General disorders and administration site conditions |                |                |                |
| Chest pain   |                |                |                |
| subjects affected / exposed                          | 0 / 40 (0.00%) | 0 / 37 (0.00%) | 0 / 41 (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          |
| Infections and infestations                          |                |                |                |
| Pneumonia  |                |                |                |
| subjects affected / exposed                          | 0 / 40 (0.00%) | 0 / 37 (0.00%) | 0 / 41 (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>                        | TD-4208 700 µg |  |  |
| Total subjects affected by serious adverse events    |                |  |  |
| subjects affected / exposed                          | 0 / 37 (0.00%) |  |  |
| number of deaths (all causes)                        | 0              |  |  |
| number of deaths resulting from adverse events       | 0              |  |  |
| Nervous system disorders                             |                |  |  |
| Transient ischemic attack                            |                |  |  |
| subjects affected / exposed                          | 0 / 37 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| General disorders and administration site conditions |                |  |  |
| Chest pain   |                |  |  |
| subjects affected / exposed                          | 0 / 37 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Infections and infestations                          |                |  |  |
| Pneumonia  |                |  |  |
| subjects affected / exposed                          | 0 / 37 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |

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

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| <b>Non-serious adverse events</b>                     | Placebo          | TD-4208 22 µg    | TD-4208 44 µg    |
| Total subjects affected by non-serious adverse events |                  |                  |                  |
| subjects affected / exposed                           | 33 / 61 (54.10%) | 19 / 41 (46.34%) | 18 / 39 (46.15%) |
| Injury, poisoning and procedural complications        |                  |                  |                  |
| Foot fracture   |                  |                  |                  |
| subjects affected / exposed                           | 0 / 61 (0.00%)   | 0 / 41 (0.00%)   | 2 / 39 (5.13%)   |
| occurrences (all)                                     | 0                | 0                | 2                |
| Vascular disorders                                    |                  |                  |                  |
| Haematoma   |                  |                  |                  |
| subjects affected / exposed                           | 1 / 61 (1.64%)   | 0 / 41 (0.00%)   | 0 / 39 (0.00%)   |
| occurrences (all)                                     | 1                | 0                | 0                |
| Hypotension   |                  |                  |                  |

|  |  |  |  |
|--|--|--|--|
| subjects affected / exposed<br>occurrences (all)   | 0 / 61 (0.00%)<br>0  | 0 / 41 (0.00%)<br>0  | 2 / 39 (5.13%)<br>2  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)   | 9 / 61 (14.75%)<br>10  | 3 / 41 (7.32%)<br>4  | 2 / 39 (5.13%)<br>2  |
| General disorders and administration<br>site conditions<br>Fatigue<br>subjects affected / exposed<br>occurrences (all)<br><br>Catheter site pain<br>subjects affected / exposed<br>occurrences (all)   | 0 / 61 (0.00%)<br>0<br><br>0 / 61 (0.00%)<br>0   | 2 / 41 (4.88%)<br>2<br><br>0 / 41 (0.00%)<br>0   | 2 / 39 (5.13%)<br>3<br><br>2 / 39 (5.13%)<br>2   |
| Ear and labyrinth disorders<br>Vertigo<br>subjects affected / exposed<br>occurrences (all)   | 0 / 61 (0.00%)<br>0  | 0 / 41 (0.00%)<br>0  | 0 / 39 (0.00%)<br>0  |
| Gastrointestinal disorders<br>Nausea<br>subjects affected / exposed<br>occurrences (all)   | 1 / 61 (1.64%)<br>7  | 0 / 41 (0.00%)<br>0  | 2 / 39 (5.13%)<br>2  |
| Respiratory, thoracic and mediastinal<br>disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)<br><br>Dyspnoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Chronic obstructive pulmonary<br>disease<br>subjects affected / exposed<br>occurrences (all)<br><br>Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Rhinorrhoea | 1 / 61 (1.64%)<br>1<br><br>4 / 61 (6.56%)<br>6<br><br>0 / 61 (0.00%)<br>0<br><br>0 / 61 (0.00%)<br>0 | 2 / 41 (4.88%)<br>2<br><br>1 / 41 (2.44%)<br>1<br><br>1 / 41 (2.44%)<br>1<br><br>0 / 41 (0.00%)<br>0 | 1 / 39 (2.56%)<br>1<br><br>1 / 39 (2.56%)<br>2<br><br>0 / 39 (0.00%)<br>0<br><br>1 / 39 (2.56%)<br>1 |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)   | 0 / 61 (0.00%)<br>0 | 0 / 41 (0.00%)<br>0 | 2 / 39 (5.13%)<br>2 |
| Skin and subcutaneous tissue disorders<br>Rash<br>subjects affected / exposed<br>occurrences (all)               | 0 / 61 (0.00%)<br>0 | 1 / 41 (2.44%)<br>1 | 1 / 39 (2.56%)<br>1 |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all) | 0 / 61 (0.00%)<br>0 | 2 / 41 (4.88%)<br>4 | 0 / 39 (0.00%)<br>0 |

| <b>Non-serious adverse events</b>   | TD-4208 88 µg                                  | TD-4208 175 µg                                 | TD-4208 350 µg                                 |
|---|--|--|--|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed  | 19 / 40 (47.50%)                               | 17 / 37 (45.95%)                               | 16 / 41 (39.02%)                               |
| Injury, poisoning and procedural complications<br>Foot fracture<br>subjects affected / exposed<br>occurrences (all)   | 0 / 40 (0.00%)<br>0                            | 0 / 37 (0.00%)<br>0                            | 0 / 41 (0.00%)<br>0                            |
| Vascular disorders<br>Haematoma<br>subjects affected / exposed<br>occurrences (all)<br><br>Hypotension<br>subjects affected / exposed<br>occurrences (all)  | 2 / 40 (5.00%)<br>2<br><br>0 / 40 (0.00%)<br>0 | 0 / 37 (0.00%)<br>0<br><br>0 / 37 (0.00%)<br>0 | 0 / 41 (0.00%)<br>0<br><br>0 / 41 (0.00%)<br>0 |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)  | 3 / 40 (7.50%)<br>6                            | 4 / 37 (10.81%)<br>4                           | 3 / 41 (7.32%)<br>3                            |
| General disorders and administration site conditions<br>Fatigue<br>subjects affected / exposed<br>occurrences (all)<br><br>Catheter site pain<br>subjects affected / exposed<br>occurrences (all) | 0 / 40 (0.00%)<br>0<br><br>0 / 40 (0.00%)<br>0 | 0 / 37 (0.00%)<br>0<br><br>0 / 37 (0.00%)<br>0 | 0 / 41 (0.00%)<br>0<br><br>0 / 41 (0.00%)<br>0 |
| Ear and labyrinth disorders   |  |  |  |



|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| Vertigo<br>subjects affected / exposed<br>occurrences (all)  | 2 / 40 (5.00%)<br>2 | 0 / 37 (0.00%)<br>0 | 0 / 41 (0.00%)<br>0 |
| Gastrointestinal disorders<br>Nausea<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 40 (0.00%)<br>0 | 1 / 37 (2.70%)<br>1 | 0 / 41 (0.00%)<br>0 |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)     | 2 / 40 (5.00%)<br>2 | 2 / 37 (5.41%)<br>2 | 2 / 41 (4.88%)<br>2 |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)   | 1 / 40 (2.50%)<br>1 | 2 / 37 (5.41%)<br>3 | 2 / 41 (4.88%)<br>2 |
| Chronic obstructive pulmonary disease<br>subjects affected / exposed<br>occurrences (all)                        | 3 / 40 (7.50%)<br>3 | 0 / 37 (0.00%)<br>0 | 0 / 41 (0.00%)<br>0 |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)   | 1 / 40 (2.50%)<br>1 | 2 / 37 (5.41%)<br>2 | 0 / 41 (0.00%)<br>0 |
| Rhinorrhoea<br>subjects affected / exposed<br>occurrences (all)  | 0 / 40 (0.00%)<br>0 | 1 / 37 (2.70%)<br>1 | 0 / 41 (0.00%)<br>0 |
| Skin and subcutaneous tissue disorders<br>Rash<br>subjects affected / exposed<br>occurrences (all)               | 0 / 40 (0.00%)<br>0 | 2 / 37 (5.41%)<br>2 | 0 / 41 (0.00%)<br>0 |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all) | 1 / 40 (2.50%)<br>2 | 1 / 37 (2.70%)<br>2 | 1 / 41 (2.44%)<br>2 |

|  |                  |  |  |
|--|------------------|--|--|
| <b>Non-serious adverse events</b>  | TD-4208 700 µg   |  |  |
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed | 14 / 37 (37.84%) |  |  |
| Injury, poisoning and procedural complications                                       |                  |  |  |

|  |                      |  |  |
|--|----------------------|--|--|
| Foot fracture<br>subjects affected / exposed<br>occurrences (all)  | 0 / 37 (0.00%)<br>0  |  |  |
| Vascular disorders<br>Haematoma<br>subjects affected / exposed<br>occurrences (all)                                    | 0 / 37 (0.00%)<br>0  |  |  |
| Hypotension<br>subjects affected / exposed<br>occurrences (all)  | 0 / 37 (0.00%)<br>0  |  |  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)                               | 5 / 37 (13.51%)<br>5 |  |  |
| General disorders and administration<br>site conditions<br>Fatigue<br>subjects affected / exposed<br>occurrences (all) | 0 / 37 (0.00%)<br>0  |  |  |
| Catheter site pain<br>subjects affected / exposed<br>occurrences (all)   | 0 / 37 (0.00%)<br>0  |  |  |
| Ear and labyrinth disorders<br>Vertigo<br>subjects affected / exposed<br>occurrences (all)                             | 0 / 37 (0.00%)<br>0  |  |  |
| Gastrointestinal disorders<br>Nausea<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 37 (0.00%)<br>0  |  |  |
| Respiratory, thoracic and mediastinal<br>disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)        | 2 / 37 (5.41%)<br>2  |  |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)   | 1 / 37 (2.70%)<br>6  |  |  |
| Chronic obstructive pulmonary  |                      |  |  |

|   |                |  |  |
|---|----------------|--|--|
| disease   |                |  |  |
| subjects affected / exposed                     | 0 / 37 (0.00%) |  |  |
| occurrences (all)                               | 0              |  |  |
| Oropharyngeal pain                              |                |  |  |
| subjects affected / exposed                     | 0 / 37 (0.00%) |  |  |
| occurrences (all)                               | 0              |  |  |
| Rhinorrhoea                                     |                |  |  |
| subjects affected / exposed                     | 0 / 37 (0.00%) |  |  |
| occurrences (all)                               | 0              |  |  |
| Skin and subcutaneous tissue disorders          |                |  |  |
| Rash  |                |  |  |
| subjects affected / exposed                     | 1 / 37 (2.70%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Musculoskeletal and connective tissue disorders |                |  |  |
| Back pain                                       |                |  |  |
| subjects affected / exposed                     | 0 / 37 (0.00%) |  |  |
| occurrences (all)                               | 0              |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 06 November 2012 | Changes to the original study protocol reflected in Amendment 1 incorporated additions and changes to the protocol requested by sites participating in the United Kingdom and Germany to comply with local requirements, and to make minor clarifications to the study procedures. |
| 22 January 2013  | Changes to study protocol Amendment 2 incorporated changes requested by the MHRA to require male subjects to continue with contraception for 3 months, rather than 1 month, after the last dose received.  |
| 30 May 2013      | Changes to the original study protocol reflected in Amendment 3 document a change in the Clinical Study Director and Medical Monitor roles from the Sponsor, and correct an editorial discrepancy pertaining to timing of adverse event collection.                                |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported