



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
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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
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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
Arm title	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.

Arm title	TD-4208 22 µg
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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.

Arm title	TD-4208 44 µg
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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.

Arm title	TD-4208 88 µg
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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.

Arm title	TD-4208 175 µg
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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.

Arm title	TD-4208 350 µg
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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.

Arm title	TD-4208 700 µg
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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.

Number of subjects in period 1	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

Number of subjects in period 1	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

Number of subjects in period 1	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
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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: 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.	

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: 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	
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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

Statistical analysis title	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 ^[1]
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

Statistical analysis title	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 ^[2]
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

Statistical analysis title	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 ^[3]
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

Statistical analysis title	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 ^[4]
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

Statistical analysis title	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 ^[5]
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

Statistical analysis title	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 ^[6]
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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.1
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Participants received placebo once daily for 7 days.

Reporting group title	TD-4208 22 µg
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Reporting group description:

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

Reporting group title	TD-4208 44 µg
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Reporting group description:

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

Reporting group title	TD-4208 88 µg
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Reporting group description:

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

Reporting group title	TD-4208 175 µg
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Reporting group description:

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

Reporting group title	TD-4208 350 µg
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Reporting group description:

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

Reporting group title	TD-4208 700 µg
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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

Serious adverse events	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

Serious adverse events	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 %

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

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

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

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

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

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

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported