



Clinical trial results:

A Randomized, Double-Blind, Parallel Group, Multi-Center Study to Assess the Efficacy and Safety of PT009 compared to PT005 on COPD Exacerbations over a variable-length (12-52 week) Treatment Period in Subjects With Moderate to Very Severe COPD

Summary

EudraCT number	2016-000155-28
Trial protocol	DK BE GB DE ES AT IT
Global end of trial date	04 April 2018

Results information

Result version number	v1 (current)
This version publication date	21 April 2019
First version publication date	21 April 2019

Trial information

Trial identification

Sponsor protocol code	PT009003
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02727660
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pearl Therapeutics, a Member of the AstraZeneca Group
Sponsor organisation address	200 Cardinal Way, Redwood City, United States, 94063
Public contact	Paul M. Dorinsky, MD, Pearl Therapeutics, a Member of the AstraZeneca Group, 1 6503052600, paul.dorinsky1@astrazeneca.com
Scientific contact	Paul M. Dorinsky, MD, Pearl Therapeutics, a Member of the AstraZeneca Group, 1 6503052600, paul.dorinsky1@astrazeneca.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	04 April 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 April 2018
Global end of trial reached?	Yes
Global end of trial date	04 April 2018
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 assess the effects of BFF MDI relative to FF MDI on lung function.

Protection of trial subjects:

Subjects who are receiving an ICS/LABA will discontinue the ICS/LABA, but continue the ICS component for the remainder of the Screening Period.

Subjects treated with an ICS as part of their inhaled maintenance therapy will continue their ICS for the remainder of the Screening Period.

Sponsor-provided Ventolin HFA to be administered as needed, up to 8 inhalations per day, for control of COPD symptoms.

Subjects receiving phosphodiesterase inhibitors (e.g., roflumilast) at stable doses for at least 4 weeks prior to Visit 1, may continue on these medications throughout the Screening and Randomized Treatment periods.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 April 2016
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	Argentina: 182
Country: Number of subjects enrolled	Austria: 22
Country: Number of subjects enrolled	Belgium: 24
Country: Number of subjects enrolled	Brazil: 62
Country: Number of subjects enrolled	Canada: 34
Country: Number of subjects enrolled	Chile: 41
Country: Number of subjects enrolled	Germany: 49
Country: Number of subjects enrolled	Denmark: 65
Country: Number of subjects enrolled	Spain: 61
Country: Number of subjects enrolled	United Kingdom: 24
Country: Number of subjects enrolled	Italy: 37
Country: Number of subjects enrolled	Mexico: 74
Country: Number of subjects enrolled	Norway: 29
Country: Number of subjects enrolled	Peru: 132
Country: Number of subjects enrolled	Russian Federation: 123
Country: Number of subjects enrolled	Sweden: 23

Country: Number of subjects enrolled	United States: 761
Country: Number of subjects enrolled	South Africa: 100
Worldwide total number of subjects	1843
EEA total number of subjects	334

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)	844
From 65 to 84 years	999
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study screened subjects at 292 study centers in 18 countries and randomized subjects at 259 study centers, from May 2016 to April 2018.

Pre-assignment

Screening details:

Subjects were randomized in a 1:1:1 ratio to BFF MDI 320/9.6 µg, BFF MDI 160/9.6 µg, and FF MDI 9.6 µg treatment groups

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, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
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Arm title	BFF MDI 320/9.6 ug
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Arm description:

Budesonide Formoterol Fumarate Metered dose inhalation 320/9.6 ug

Arm type	Experimental
Investigational medicinal product name	Budesonide Formoterol Fumarate MDI
Investigational medicinal product code	
Other name	BFF MDI 160/4.8 ug
Pharmaceutical forms	Pressurised inhalation, suspension
Routes of administration	Inhalation use

Dosage and administration details:

Taken as 2 inhalations BID

Arm title	BFF MDI 160/9.6 ug
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Arm description:

Budesonide Formoterol Fumarate Metered dose inhalation 160/9.6 ug

Arm type	Experimental
Investigational medicinal product name	Budesonide Formoterol Fumarate MDI
Investigational medicinal product code	
Other name	BFF MDI 80/4.8 ug
Pharmaceutical forms	Pressurised inhalation, suspension
Routes of administration	Inhalation use

Dosage and administration details:

Taken as 2 inhalations BID

Arm title	FF MDI 9.6 ug
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Arm description:

Formoterol Fumarate Metered dose inhalation 9.6 ug

Arm type	Experimental
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Investigational medicinal product name	Formoterol Fumarate MDI
Investigational medicinal product code	
Other name	FF MDI 4.8 ug
Pharmaceutical forms	Pressurised inhalation, suspension
Routes of administration	Inhalation use

Dosage and administration details:

Taken as 2 inhalations BID

Number of subjects in period 1	BFF MDI 320/9.6 ug	BFF MDI 160/9.6 ug	FF MDI 9.6 ug
Started	619	617	607
Completed	503	501	442
Not completed	116	116	165
Administrative Reasons	2	3	4
Consent withdrawn by subject	26	25	30
Physician decision	3	8	14
Adverse event, non-fatal	28	21	32
Protocol Specified Disc. Criteria	5	5	2
Lost to follow-up	5	9	8
Lack of efficacy	40	40	70
Protocol deviation	7	5	5

Baseline characteristics

Reporting groups

Reporting group title	BFF MDI 320/9.6 ug
Reporting group description:	
Budesonide Formoterol Fumarate Metered dose inhalation 320/9.6 ug	
Reporting group title	BFF MDI 160/9.6 ug
Reporting group description:	
Budesonide Formoterol Fumarate Metered dose inhalation 160/9.6 ug	
Reporting group title	FF MDI 9.6 ug
Reporting group description:	
Formoterol Fumarate Metered dose inhalation 9.6 ug	

Reporting group values	BFF MDI 320/9.6 ug	BFF MDI 160/9.6 ug	FF MDI 9.6 ug
Number of subjects	619	617	607
Age categorical			
mITT Population			
Units: Subjects			
Adults (18-64 years)	272	299	273
From 65-84 years	347	318	334
Age Continuous			
mITT Population			
Units: years			
arithmetic mean	65.3	64.5	64.8
standard deviation	± 8.1	± 8.4	± 8.5
Sex: Female, Male			
mITT Population			
Units: Subjects			
Female	252	272	268
Male	367	345	339
Race (NIH/OMB)			
mITT Population			
Units: Subjects			
American Indian or Alaska Native	26	18	24
Asian	1	7	4
Native Hawaiian or Other Pacific Islander	1	0	0
Black or African American	30	22	29
White	514	516	504
More than one race	0	0	0
Unknown or Not Reported	47	54	46
Ethnicity (NIH/OMB)			
mITT Population			
Units: Subjects			
Hispanic or Latino	190	200	190
Not Hispanic or Latino	423	414	412
Unknown or Not Reported	6	3	5
Reporting group values	Total		

Number of subjects	1843		
Age categorical			
mITT Population			
Units: Subjects			
Adults (18-64 years)	844		
From 65-84 years	999		
Age Continuous			
mITT Population			
Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
mITT Population			
Units: Subjects			
Female	792		
Male	1051		
Race (NIH/OMB)			
mITT Population			
Units: Subjects			
American Indian or Alaska Native	68		
Asian	12		
Native Hawaiian or Other Pacific Islander	1		
Black or African American	81		
White	1534		
More than one race	0		
Unknown or Not Reported	147		
Ethnicity (NIH/OMB)			
mITT Population			
Units: Subjects			
Hispanic or Latino	580		
Not Hispanic or Latino	1249		
Unknown or Not Reported	14		

Subject analysis sets

Subject analysis set title	mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The Modified Intent-To-Treat (mITT) Population is defined as all subjects who were randomized to treatment, received any amount of the study treatment, and had post-randomization data obtained prior to discontinuation from treatment.

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Population is defined as all subjects who were randomized to treatment and received at least one dose of the study treatment. Subjects are analyzed according to treatment received rather than randomized.

Reporting group values	mITT	Safety Population	
Number of subjects	1843	1843	

Age categorical			
mITT Population			
Units: Subjects			
Adults (18-64 years)	844	844	
From 65-84 years	999	999	
Age Continuous			
mITT Population			
Units: years			
arithmetic mean	64.9	64.9	
standard deviation	± 8.3	± 8.3	
Sex: Female, Male			
mITT Population			
Units: Subjects			
Female	792	792	
Male	1051	1051	
Race (NIH/OMB)			
mITT Population			
Units: Subjects			
American Indian or Alaska Native	68	68	
Asian	12	12	
Native Hawaiian or Other Pacific Islander	1	1	
Black or African American	81	81	
White	1534	1534	
More than one race	0	0	
Unknown or Not Reported	147	147	
Ethnicity (NIH/OMB)			
mITT Population			
Units: Subjects			
Hispanic or Latino	580	580	
Not Hispanic or Latino	1249	1249	
Unknown or Not Reported	14	14	

End points

End points reporting groups

Reporting group title	BFF MDI 320/9.6 ug
Reporting group description:	
Budesonide Formoterol Fumarate Metered dose inhalation 320/9.6 ug	
Reporting group title	BFF MDI 160/9.6 ug
Reporting group description:	
Budesonide Formoterol Fumarate Metered dose inhalation 160/9.6 ug	
Reporting group title	FF MDI 9.6 ug
Reporting group description:	
Formoterol Fumarate Metered dose inhalation 9.6 ug	
Subject analysis set title	mITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The Modified Intent-To-Treat (mITT) Population is defined as all subjects who were randomized to treatment, received any amount of the study treatment, and had post-randomization data obtained prior to discontinuation from treatment.	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Population is defined as all subjects who were randomized to treatment and received at least one dose of the study treatment. Subjects are analyzed according to treatment received rather than randomized.	

Primary: Morning pre-dose trough FEV1

End point title	Morning pre-dose trough FEV1
End point description:	
Morning pre-dose trough FEV1 (Forced Expiratory Volume in one second) over 24 weeks	
End point type	Primary
End point timeframe:	
over 24 weeks	

End point values	BFF MDI 320/9.6 ug	BFF MDI 160/9.6 ug	FF MDI 9.6 ug	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	578	590	559	
Units: Liter				
least squares mean (confidence interval 95%)	0.063 (0.047 to 0.079)	0.059 (0.044 to 0.074)	0.024 (0.009 to 0.040)	

Statistical analyses

Statistical analysis title	Morning pre-dose trough FEV1
Statistical analysis description:	
Primary endpoint analysis - BFF MDI versus FF MDI	
Comparison groups	BFF MDI 320/9.6 ug v FF MDI 9.6 ug

Number of subjects included in analysis	1137
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≥ 0.05
Method	repeated measures linear mixed model
Parameter estimate	LS Mean Difference
Point estimate	0.039
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.018
upper limit	0.059

Statistical analysis title	Morning pre-dose trough FEV1
Statistical analysis description:	
Primary endpoint analysis - BFF MDI versus FF MDI	
Comparison groups	BFF MDI 160/9.6 ug v FF MDI 9.6 ug
Number of subjects included in analysis	1149
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≥ 0.05
Method	repeated measures linear mixed model
Parameter estimate	LS Mean Difference
Point estimate	0.05
Confidence interval	
level	Other: 0.03 %
sides	2-sided
lower limit	0.014
upper limit	0.055

Secondary: Time to first moderate or severe COPD exacerbation	
End point title	Time to first moderate or severe COPD exacerbation
End point description:	
Time to first moderate or severe COPD (Chronic Obstructive Pulmonary Disease) exacerbation over 52 weeks	
End point type	Secondary
End point timeframe:	
over 52 weeks	

End point values	BFF MDI 320/9.6 ug	BFF MDI 160/9.6 ug	FF MDI 9.6 ug	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	619	617	607	
Units: Participants				
No of subj with ≥ 1 events	220	223	241	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first clinically important deterioration in COPD

End point title	Time to first clinically important deterioration in COPD
End point description:	Time to first clinically important deterioration in COPD over 52 weeks
End point type	Secondary
End point timeframe:	over 52 weeks

End point values	BFF MDI 320/9.6 ug	BFF MDI 160/9.6 ug	FF MDI 9.6 ug	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	619	617	607	
Units: Number	469	462	491	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in average daily rescue Ventolin HFA use

End point title	Change from baseline in average daily rescue Ventolin HFA use
End point description:	Change from baseline in average daily rescue Ventolin HFA use over 24 weeks
End point type	Secondary
End point timeframe:	over 24 weeks

End point values	BFF MDI 320/9.6 ug	BFF MDI 160/9.6 ug	FF MDI 9.6 ug	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	612	610	599	
Units: Puffs per day				
least squares mean (confidence interval 95%)	-1.0 (-1.2 to -0.8)	-1.0 (-1.1 to -0.8)	-0.6 (-0.8 to -0.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects achieving an MCID (Minimal clinically important difference) of 4 units or more in Saint George's Respiratory Questionnaire (SGRQ) total score

End point title	Percentage of subjects achieving an MCID (Minimal clinically important difference) of 4 units or more in Saint George's Respiratory Questionnaire (SGRQ) total score
End point description: Percentage of subjects achieving an MCID (Minimal clinically important difference) of 4 units or more in Saint George's Respiratory Questionnaire (SGRQ) total score over 24 weeks	
End point type	Secondary
End point timeframe: over 24 weeks	

End point values	BFF MDI 320/9.6 ug	BFF MDI 160/9.6 ug	FF MDI 9.6 ug	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	606 ^[1]	613 ^[2]	596 ^[3]	
Units: scores on a scale				
Percent observed	53	53	43	

Notes:

[1] - Observed % (n/N) for Treatment 320/606

[2] - Observed % (n/N) for Treatment 326/613

[3] - Observed % (n/N) for Treatment 254/596

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the Exacerbations of Chronic Pulmonary Disease Tool (EXACT) total score over the treatment period

End point title	Change from baseline in the Exacerbations of Chronic Pulmonary Disease Tool (EXACT) total score over the treatment period
End point description: Change from baseline in the Exacerbations of Chronic Pulmonary Disease Tool (EXACT) total score over the treatment period over 52 weeks	
End point type	Secondary

End point timeframe:
over 52 weeks

End point values	BFF MDI 320/9.6 ug	BFF MDI 160/9.6 ug	FF MDI 9.6 ug	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	614	613	597	
Units: scores on a scale				
least squares mean (confidence interval 95%)	-2.4 (-3.2 to -1.6)	-2.5 (-3.3 to -1.7)	-1.0 (-1.8 to -0.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Transient Dyspnea Index (TDI) focal score

End point title	Transient Dyspnea Index (TDI) focal score
End point description:	Transient Dyspnea Index (TDI) focal score over 24 weeks
End point type	Secondary
End point timeframe:	over 24 weeks

End point values	BFF MDI 320/9.6 ug	BFF MDI 160/9.6 ug	FF MDI 9.6 ug	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	566	578	550	
Units: scores on a scale				
least squares mean (confidence interval 95%)	1.32 (1.10 to 1.53)	1.30 (1.09 to 1.51)	1.06 (0.85 to 1.28)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from the time the subject signed informed consent throughout the treatment period and up to 14 days following the last dose of study drug.

Adverse event reporting additional description:

Serious Adverse Events were collected from the time the subject signed informed consent throughout the treatment period and up to approximately 52 weeks, which includes screening and follow up (14 days after last dose of study drug).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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Reporting groups

Reporting group title	BFF MDI 320/9.6 ug
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Reporting group description:

Budesonide Formoterol Fumarate Metered dose inhalation 320/9.6 ug

Reporting group title	FF MDI 9.6 ug
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Reporting group description:

Formoterol Fumarate Metered dose inhalation 9.6 ug

Reporting group title	BFF MDI 160/9.6 ug
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Reporting group description:

Budesonide Formoterol Fumarate Metered dose inhalation 160/9.6 ug

Serious adverse events	BFF MDI 320/9.6 ug	FF MDI 9.6 ug	BFF MDI 160/9.6 ug
Total subjects affected by serious adverse events			
subjects affected / exposed	60 / 619 (9.69%)	83 / 607 (13.67%)	78 / 617 (12.64%)
number of deaths (all causes)	3	8	4
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm malignant			
subjects affected / exposed	2 / 619 (0.32%)	1 / 607 (0.16%)	1 / 617 (0.16%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma			
subjects affected / exposed	0 / 619 (0.00%)	0 / 607 (0.00%)	1 / 617 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder neoplasm			

subjects affected / exposed	1 / 619 (0.16%)	0 / 607 (0.00%)	0 / 617 (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
Breast cancer			
subjects affected / exposed	0 / 619 (0.00%)	0 / 607 (0.00%)	1 / 617 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervix carcinoma stage III			
subjects affected / exposed	0 / 619 (0.00%)	0 / 607 (0.00%)	1 / 617 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	1 / 619 (0.16%)	0 / 607 (0.00%)	0 / 617 (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
Endometrial cancer			
subjects affected / exposed	0 / 619 (0.00%)	0 / 607 (0.00%)	1 / 617 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic Cancer			
subjects affected / exposed	1 / 619 (0.16%)	0 / 607 (0.00%)	0 / 617 (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
Lung adenocarcinoma			
subjects affected / exposed	1 / 619 (0.16%)	0 / 607 (0.00%)	0 / 617 (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
Lung adenocarcinoma stage III			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	0 / 617 (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
Lung cancer metastatic			

subjects affected / exposed	0 / 619 (0.00%)	0 / 607 (0.00%)	1 / 617 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mantle cell lymphoma			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	0 / 617 (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
Metastatic neoplasm			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	0 / 617 (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
Pancreatic carcinoma			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	0 / 617 (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
Prostate cancer			
subjects affected / exposed	1 / 619 (0.16%)	0 / 607 (0.00%)	0 / 617 (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
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 619 (0.16%)	1 / 607 (0.16%)	0 / 617 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral vascular disease			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	1 / 617 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	0 / 617 (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
Circulatory collapse			

subjects affected / exposed	0 / 619 (0.00%)	0 / 607 (0.00%)	1 / 617 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	1 / 619 (0.16%)	0 / 607 (0.00%)	0 / 617 (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
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 619 (0.16%)	0 / 607 (0.00%)	0 / 617 (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
Peripheral artery aneurysm			
subjects affected / exposed	1 / 619 (0.16%)	0 / 607 (0.00%)	0 / 617 (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
Vasculitis			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	0 / 617 (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 / 619 (0.00%)	0 / 607 (0.00%)	2 / 617 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	2 / 619 (0.32%)	0 / 607 (0.00%)	0 / 617 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	0 / 617 (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
Death			

subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	0 / 617 (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
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	0 / 617 (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
Sudden death			
subjects affected / exposed	0 / 619 (0.00%)	0 / 607 (0.00%)	1 / 617 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	27 / 619 (4.36%)	50 / 607 (8.24%)	30 / 617 (4.86%)
occurrences causally related to treatment / all	0 / 32	0 / 65	0 / 33
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	2 / 619 (0.32%)	6 / 607 (0.99%)	2 / 617 (0.32%)
occurrences causally related to treatment / all	0 / 2	0 / 6	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 619 (0.16%)	1 / 607 (0.16%)	1 / 617 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	2 / 617 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	2 / 617 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercapnia			

subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	0 / 617 (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
Hypoxia			
subjects affected / exposed	1 / 619 (0.16%)	0 / 607 (0.00%)	0 / 617 (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
Pneumonia aspiration			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	0 / 617 (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
Pneumonitis			
subjects affected / exposed	1 / 619 (0.16%)	0 / 607 (0.00%)	0 / 617 (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
Pulmonary alveolar haemorrhage			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	0 / 617 (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
Pulmonary embolism			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	0 / 617 (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
Respiratory distress			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	0 / 617 (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
Psychiatric disorders			
Mental status change			
subjects affected / exposed	1 / 619 (0.16%)	1 / 607 (0.16%)	1 / 617 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alcohol withdrawal syndrome			

subjects affected / exposed	0 / 619 (0.00%)	0 / 607 (0.00%)	1 / 617 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 619 (0.00%)	0 / 607 (0.00%)	1 / 617 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Haemoglobin decreased			
subjects affected / exposed	0 / 619 (0.00%)	0 / 607 (0.00%)	1 / 617 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	1 / 619 (0.16%)	0 / 607 (0.00%)	1 / 617 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal injury			
subjects affected / exposed	1 / 619 (0.16%)	0 / 607 (0.00%)	0 / 617 (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
Ankle fracture			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	0 / 617 (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
Craniocerebral injury			
subjects affected / exposed	0 / 619 (0.00%)	0 / 607 (0.00%)	1 / 617 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 619 (0.16%)	0 / 607 (0.00%)	0 / 617 (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

Fascial rupture			
subjects affected / exposed	1 / 619 (0.16%)	0 / 607 (0.00%)	0 / 617 (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
Femur fracture			
subjects affected / exposed	1 / 619 (0.16%)	0 / 607 (0.00%)	0 / 617 (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
Limb injury			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	0 / 617 (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
Post procedural haemorrhage			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	0 / 617 (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
Road traffic accident			
subjects affected / exposed	1 / 619 (0.16%)	0 / 607 (0.00%)	0 / 617 (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
Spinal compression fracture			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	0 / 617 (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
Toxicity to various agents			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	0 / 617 (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
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 619 (0.00%)	4 / 607 (0.66%)	0 / 617 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			

subjects affected / exposed	1 / 619 (0.16%)	1 / 607 (0.16%)	2 / 617 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 619 (0.00%)	0 / 607 (0.00%)	3 / 617 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	2 / 617 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 619 (0.00%)	2 / 607 (0.33%)	0 / 617 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	0 / 617 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 619 (0.00%)	0 / 607 (0.00%)	1 / 617 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 619 (0.00%)	0 / 607 (0.00%)	1 / 617 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	1 / 619 (0.16%)	0 / 607 (0.00%)	0 / 617 (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
Cardiac failure acute			

subjects affected / exposed	0 / 619 (0.00%)	0 / 607 (0.00%)	1 / 617 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	1 / 619 (0.16%)	0 / 607 (0.00%)	0 / 617 (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
Cor pulmonae			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	0 / 617 (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
Left ventricular failure			
subjects affected / exposed	0 / 619 (0.00%)	0 / 607 (0.00%)	1 / 617 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	1 / 619 (0.16%)	0 / 607 (0.00%)	0 / 617 (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
Nervous system disorders			
Brain injury			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	0 / 617 (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
Carotid artery stenosis			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	0 / 617 (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
Cervical radiculopathy			
subjects affected / exposed	1 / 619 (0.16%)	0 / 607 (0.00%)	0 / 617 (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
Diabetic neuropathy			

subjects affected / exposed	0 / 619 (0.00%)	0 / 607 (0.00%)	1 / 617 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 619 (0.00%)	0 / 607 (0.00%)	1 / 617 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular encephalopathy			
subjects affected / exposed	1 / 619 (0.16%)	0 / 607 (0.00%)	0 / 617 (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
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	0 / 617 (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
Gastrointestinal disorders			
Small intestinal obstruction			
subjects affected / exposed	1 / 619 (0.16%)	2 / 607 (0.33%)	2 / 617 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 619 (0.00%)	2 / 607 (0.33%)	2 / 617 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 619 (0.00%)	0 / 607 (0.00%)	3 / 617 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	1 / 619 (0.16%)	1 / 607 (0.16%)	0 / 617 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal hernia			

subjects affected / exposed	0 / 619 (0.00%)	0 / 607 (0.00%)	1 / 617 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	0 / 617 (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
Colitis			
subjects affected / exposed	1 / 619 (0.16%)	0 / 607 (0.00%)	0 / 617 (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
Gastritis			
subjects affected / exposed	0 / 619 (0.00%)	0 / 607 (0.00%)	1 / 617 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal obstruction			
subjects affected / exposed	0 / 619 (0.00%)	0 / 607 (0.00%)	1 / 617 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	0 / 617 (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
Peptic ulcer			
subjects affected / exposed	1 / 619 (0.16%)	0 / 607 (0.00%)	0 / 617 (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
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 619 (0.00%)	0 / 607 (0.00%)	1 / 617 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			

subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	0 / 617 (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
Cholelithiasis			
subjects affected / exposed	0 / 619 (0.00%)	0 / 607 (0.00%)	1 / 617 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 619 (0.00%)	2 / 607 (0.33%)	1 / 617 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	1 / 619 (0.16%)	0 / 607 (0.00%)	0 / 617 (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
Nephrolithiasis			
subjects affected / exposed	1 / 619 (0.16%)	0 / 607 (0.00%)	0 / 617 (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
Renal tubular acidosis			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	0 / 617 (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
Ureteric obstruction			
subjects affected / exposed	1 / 619 (0.16%)	0 / 607 (0.00%)	0 / 617 (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
Ureterolithiasis			
subjects affected / exposed	1 / 619 (0.16%)	0 / 607 (0.00%)	0 / 617 (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
Musculoskeletal and connective tissue disorders			

Lumbar spinal stenosis			
subjects affected / exposed	1 / 619 (0.16%)	0 / 607 (0.00%)	1 / 617 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	1 / 617 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 619 (0.00%)	0 / 607 (0.00%)	1 / 617 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 619 (0.00%)	0 / 607 (0.00%)	1 / 617 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal osteoarthritis			
subjects affected / exposed	0 / 619 (0.00%)	0 / 607 (0.00%)	1 / 617 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	6 / 619 (0.97%)	9 / 607 (1.48%)	12 / 617 (1.94%)
occurrences causally related to treatment / all	0 / 6	0 / 9	0 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 619 (0.16%)	1 / 607 (0.16%)	1 / 617 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	2 / 617 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	1 / 619 (0.16%)	2 / 607 (0.33%)	0 / 617 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 619 (0.00%)	0 / 607 (0.00%)	2 / 617 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 619 (0.16%)	1 / 607 (0.16%)	0 / 617 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	0 / 617 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess intestinal			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	0 / 617 (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
Appendicitis perforated			
subjects affected / exposed	1 / 619 (0.16%)	0 / 607 (0.00%)	0 / 617 (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
Clostridial infection			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	0 / 617 (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
Clostridium difficile colitis			
subjects affected / exposed	1 / 619 (0.16%)	0 / 607 (0.00%)	0 / 617 (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
Clostridium difficile infection			

subjects affected / exposed	0 / 619 (0.00%)	0 / 607 (0.00%)	1 / 617 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocele male infected			
subjects affected / exposed	0 / 619 (0.00%)	0 / 607 (0.00%)	1 / 617 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	0 / 617 (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
Pneumonia bacterial			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	0 / 617 (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
Pneumonia mycoplasmal			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	0 / 617 (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
Pneumonia streptococcal			
subjects affected / exposed	1 / 619 (0.16%)	0 / 607 (0.00%)	0 / 617 (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
Post procedural infection			
subjects affected / exposed	1 / 619 (0.16%)	0 / 607 (0.00%)	0 / 617 (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
Pyelonephritis			
subjects affected / exposed	1 / 619 (0.16%)	0 / 607 (0.00%)	0 / 617 (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
Septic shock			

subjects affected / exposed	0 / 619 (0.00%)	0 / 607 (0.00%)	1 / 617 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	1 / 619 (0.16%)	0 / 607 (0.00%)	0 / 617 (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
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 619 (0.16%)	0 / 607 (0.00%)	0 / 617 (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
Hyperglycaemia			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	0 / 617 (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
Hypokalaemia			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	0 / 617 (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
Hypovalaemia			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	0 / 617 (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
Type II diabetes mellitus			
subjects affected / exposed	0 / 619 (0.00%)	1 / 607 (0.16%)	0 / 617 (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

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	BFF MDI 320/9.6 ug	FF MDI 9.6 ug	BFF MDI 160/9.6 ug
Total subjects affected by non-serious adverse events			
subjects affected / exposed	266 / 619 (42.97%)	268 / 607 (44.15%)	279 / 617 (45.22%)
Vascular disorders			
Hypertension			
subjects affected / exposed	15 / 619 (2.42%)	14 / 607 (2.31%)	15 / 617 (2.43%)
occurrences (all)	15	14	15
Nervous system disorders			
Headache			
subjects affected / exposed	16 / 619 (2.58%)	18 / 607 (2.97%)	19 / 617 (3.08%)
occurrences (all)	24	20	24
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	13 / 619 (2.10%)	10 / 607 (1.65%)	10 / 617 (1.62%)
occurrences (all)	14	11	11
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	27 / 619 (4.36%)	50 / 607 (8.24%)	30 / 617 (4.86%)
occurrences (all)	32	65	33
Dyspnoea			
subjects affected / exposed	23 / 619 (3.72%)	16 / 607 (2.64%)	16 / 617 (2.59%)
occurrences (all)	23	18	19
Cough			
subjects affected / exposed	14 / 619 (2.26%)	9 / 607 (1.48%)	15 / 617 (2.43%)
occurrences (all)	15	9	17
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	15 / 619 (2.42%)	11 / 607 (1.81%)	17 / 617 (2.76%)
occurrences (all)	21	13	17
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	41 / 619 (6.62%)	36 / 607 (5.93%)	53 / 617 (8.59%)
occurrences (all)	53	43	61
Upper respiratory tract infection			
subjects affected / exposed	28 / 619 (4.52%)	24 / 607 (3.95%)	14 / 617 (2.27%)
occurrences (all)	29	28	18
Pneumonia			

subjects affected / exposed	14 / 619 (2.26%)	15 / 607 (2.47%)	19 / 617 (3.08%)
occurrences (all)	14	15	20
Influenza			
subjects affected / exposed	15 / 619 (2.42%)	10 / 607 (1.65%)	19 / 617 (3.08%)
occurrences (all)	15	10	20
Bronchitis			
subjects affected / exposed	11 / 619 (1.78%)	10 / 607 (1.65%)	13 / 617 (2.11%)
occurrences (all)	11	14	15
Sinusitis			
subjects affected / exposed	9 / 619 (1.45%)	13 / 607 (2.14%)	9 / 617 (1.46%)
occurrences (all)	9	13	11
Acute sinusitis			
subjects affected / exposed	2 / 619 (0.32%)	12 / 607 (1.98%)	6 / 617 (0.97%)
occurrences (all)	2	17	10
Oral candidiasis			
subjects affected / exposed	13 / 619 (2.10%)	7 / 607 (1.15%)	6 / 617 (0.97%)
occurrences (all)	16	8	7
Urinary tract infection			
subjects affected / exposed	10 / 619 (1.62%)	13 / 607 (2.14%)	18 / 617 (2.92%)
occurrences (all)	12	15	20

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 July 2016	Sponsor contact information updated, Clarification to study population, updated inclusion/exclusion criteria, con meds, allowed meds, prohibited meds, and visit schedule.
15 December 2016	Updated study objectives, study design and plan, study duration, exacerbation history, and procedures.
08 January 2018	Clarified synopsis, HCRU endpoints, smoking status, estimands, mITT population. Updated statistical model definition of CID across PT010 & PT009 programs.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported