



Clinical trial results:

A Phase 2, Randomized, Double-Blind Study of Ipilimumab Administered at 3 mg/kg vs 10 mg/kg in Adult Subjects with Metastatic Chemotherapy-Naïve Castration Resistant Prostate Cancer Who are Asymptomatic or Minimally Symptomatic

Summary

EudraCT number	2014-002987-34
Trial protocol	DE GB IT ES NL
Global end of trial date	15 December 2016

Results information

Result version number	v1 (current)
This version publication date	31 December 2017
First version publication date	31 December 2017

Trial information

Trial identification

Sponsor protocol code	CA184-437
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.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	15 December 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the rate of severe immune-related adverse events (irAEs). To assess the safety profile of subjects with chemotherapy-naïve mCRPC randomized to ipilimumab 3 mg/kg and 10 mg/kg.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 December 2014
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	Australia: 2
Country: Number of subjects enrolled	Chile: 8
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Germany: 21
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	United States: 21
Worldwide total number of subjects	82
EEA total number of subjects	51

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)	27
From 65 to 84 years	51
85 years and over	4

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

82 subjects were enrolled; 53 were randomized; 51 were treated with study drug. 29 were not randomized due to screening failures. 2 were randomized and not treated due to administrative reason by sponsor and "other" reason

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ipilimumab 3 mg/kg

Arm description:

Ipilimumab at 3 mg/kg was administered by intravenous (IV) infusion over a time period of 60-100 minutes, based on body weight. Induction Phase dosing consisted of a single dose every 3 weeks (Q3W) for 4 doses. This was followed by Maintenance Phase dosing of a single dose every 12 weeks (Q12W). Treatment was for a maximum treatment period of 3 years from the first induction dose of blinded study therapy, or until subject met treatment stopping criteria.

Arm type	Experimental
Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	
Other name	Yervoy, BMS-734016
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ipilimumab, at either 3 mg/kg or 10 mg/kg, was administered by intravenous (IV) infusion over a time period of 60-100 minutes, based on subject body weight. Induction Phase dosing consisted of a single dose every 3 weeks (Q3W) for 4 doses. This was followed by Maintenance Phase dosing of a single dose every 12 weeks (Q12W). Treatment was for a maximum treatment period of 3 years from the first induction dose of blinded study therapy, or until subject met treatment stopping criteria.

Arm title	Ipilimumab 10 mg/kg
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Arm description:

Ipilimumab at 10 mg/kg was administered by intravenous (IV) infusion over a time period of 60-100 minutes, based on body weight. Induction Phase dosing consisted of a single dose every 3 weeks (Q3W) for 4 doses. This was followed by Maintenance Phase dosing of a single dose every 12 weeks (Q12W). Treatment was for a maximum treatment period of 3 years from the first induction dose of blinded study therapy, or until subject met treatment stopping criteria.

Arm type	Experimental
Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	
Other name	Yervoy, BMS-734016
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ipilimumab, at either 3 mg/kg or 10 mg/kg, was administered by intravenous (IV) infusion over a time period of 60-100 minutes, based on subject body weight. Induction Phase dosing consisted of a single dose every 3 weeks (Q3W) for 4 doses. This was followed by Maintenance Phase dosing of a single dose

every 12 weeks (Q12W). Treatment was for a maximum treatment period of 3 years from the first induction dose of blinded study therapy, or until subject met treatment stopping criteria.

Number of subjects in period 1^[1]	Ipilimumab 3 mg/kg	Ipilimumab 10 mg/kg
Started	25	26
Completed	0	2
Not completed	25	24
Disease progression	5	2
Study closed by sponsor	16	13
Study drug toxicity	3	6
Other	-	1
No longer meets criteria	-	1
Withdrawal by Subject	1	-
Administrative reason by sponsor	-	1

Notes:

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

Justification: 82 subjects were enrolled; 53 were randomized; 51 were treated with study drug. 29 were not randomized due to screening failures. 2 were randomized and not treated due to administrative reason by sponsor and "other" reason

Baseline characteristics

Reporting groups

Reporting group title	Ipilimumab 3 mg/kg
Reporting group description:	
Ipilimumab at 3 mg/kg was administered by intravenous (IV) infusion over a time period of 60-100 minutes, based on body weight. Induction Phase dosing consisted of a single dose every 3 weeks (Q3W) for 4 doses. This was followed by Maintenance Phase dosing of a single dose every 12 weeks (Q12W). Treatment was for a maximum treatment period of 3 years from the first induction dose of blinded study therapy, or until subject met treatment stopping criteria.	
Reporting group title	Ipilimumab 10 mg/kg
Reporting group description:	
Ipilimumab at 10 mg/kg was administered by intravenous (IV) infusion over a time period of 60-100 minutes, based on body weight. Induction Phase dosing consisted of a single dose every 3 weeks (Q3W) for 4 doses. This was followed by Maintenance Phase dosing of a single dose every 12 weeks (Q12W). Treatment was for a maximum treatment period of 3 years from the first induction dose of blinded study therapy, or until subject met treatment stopping criteria.	

Reporting group values	Ipilimumab 3 mg/kg	Ipilimumab 10 mg/kg	Total
Number of subjects	25	26	51
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	10	9	19
From 65-84 years	14	15	29
85 years and over	1	2	3
Age Continuous Units: years			
median	66.00	66.50	
full range (min-max)	50.00 to 85.00	49.00 to 87.00	-
Gender, Male/Female Units: Subjects			
Female	0	0	0
Male	25	26	51
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	1	1
White	25	24	49
More than one race	0	0	0
Unknown or Not Reported	0	1	1

End points

End points reporting groups

Reporting group title	Ipilimumab 3 mg/kg
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Reporting group description:

Ipilimumab at 3 mg/kg was administered by intravenous (IV) infusion over a time period of 60-100 minutes, based on body weight. Induction Phase dosing consisted of a single dose every 3 weeks (Q3W) for 4 doses. This was followed by Maintenance Phase dosing of a single dose every 12 weeks (Q12W). Treatment was for a maximum treatment period of 3 years from the first induction dose of blinded study therapy, or until subject met treatment stopping criteria.

Reporting group title	Ipilimumab 10 mg/kg
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Reporting group description:

Ipilimumab at 10 mg/kg was administered by intravenous (IV) infusion over a time period of 60-100 minutes, based on body weight. Induction Phase dosing consisted of a single dose every 3 weeks (Q3W) for 4 doses. This was followed by Maintenance Phase dosing of a single dose every 12 weeks (Q12W). Treatment was for a maximum treatment period of 3 years from the first induction dose of blinded study therapy, or until subject met treatment stopping criteria.

Primary: Radiographic progression-free survival (rPFS)

End point title	Radiographic progression-free survival (rPFS) ^[1]
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End point description:

rPFS was defined as the time from the date of randomization until the date of disease progression based on radiographic evidence and/or death from any cause, whichever occurs first. Radiographic disease progression is defined as: Confirmed bone disease progression according to criteria adapted from the Prostate Cancer Clinical Trials Working Group 2 (PCWG2), OR Non-bone disease progression according to the modified Response Evaluation Criteria In Solid Tumors (RECIST) 1.1

End point type	Primary
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End point timeframe:

From date of randomization until disease progression or death (assessed up to December 2016, approximately 24 months)

Notes:

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

Justification: Only summary statistics were planned for this endpoint

End point values	Ipilimumab 3 mg/kg	Ipilimumab 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	26		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects who experienced immune-related adverse events (irAEs)

End point title	Number of subjects who experienced immune-related adverse events (irAEs)
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End point description:

The total number of subjects with immune-related adverse events of any grade is reported for each arm.

End point type	Secondary
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End point timeframe:

From first dose of ipilimumab to last dose plus 90 days

End point values	Ipilimumab 3 mg/kg	Ipilimumab 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	26		
Units: Subjects	13	18		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
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End point description:

OS was defined as the time from the date of randomization until the date of death. For those subjects who have not died, OS was censored at the last date the subject was known to be alive.

End point type	Secondary
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End point timeframe:

From randomization to death from any cause (assessed up to December 2016, approximately 24 months)

End point values	Ipilimumab 3 mg/kg	Ipilimumab 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	26		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Prostate Specific Antigen Progression-free Survival (PSA PFS)

End point title	Prostate Specific Antigen Progression-free Survival (PSA PFS)
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End point description:

Prostate specific antigen progression-free survival (PSA PFS) was defined as the time from

randomization to the earliest date of PSA progression or death, whichever occurs earlier. Subjects who did not progress or die were censored at the last PSA assessment date.

End point type	Secondary
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End point timeframe:

From randomization to the earliest date of PSA progression or death, whichever comes earlier (assessed up to December 2016, approximately 24 months)

End point values	Ipilimumab 3 mg/kg	Ipilimumab 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	26		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Pain Progression

End point title	Time to Pain Progression
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End point description:

Pain progression was defined as the earliest of the following: 1) Increase in BPI-SF pain Item #3 score of ≥ 2 point from baseline maintained over 2 consecutive time periods. 2) Initiation of opioid analgesic (excluding codeine or dextropropoxyphene) as: - Subjects with no opioid analgesic use at baseline: initiation of opioid analgesic for palliation of disease related pain - Subjects with baseline opioid analgesic use: increase in opioid analgesic use ≥ 3 days (consecutive or not) over a 14-day period. 3) Initiation of palliative radiotherapy for prostate cancer 4) Increase in mean analgesic score (AS): - Subjects with baseline AS > 10 : an increase in AS of $\geq 25\%$ from baseline - Subjects with baseline AS ≤ 10 : an increase in AS of ≥ 10 points from baseline.

End point type	Secondary
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End point timeframe:

From randomization until pain progression (assessed up to December 2016, approximately 24 months)

End point values	Ipilimumab 3 mg/kg	Ipilimumab 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	26		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Prostate specific antigen response rate

End point title	Prostate specific antigen response rate
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End point description:

PSA response rate was defined as the proportion of subjects with a 50% or greater decrease from baseline to the lowest post-baseline PSA result (confirmed 3 weeks later) for each randomized arm.

End point type	Secondary
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End point timeframe:

From baseline to PSA response (assessed up to December 2016, approximately 48 months)

End point values	Ipilimumab 3 mg/kg	Ipilimumab 10 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	26		
Units: percentage				
number (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-study adverse events: events reported between first dose and 90 days after last dose of study therapy.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	10 MG/KG IPILIMUMAB
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Reporting group description:

10 MG/KG IPILIMUMAB- was administered by intravenous (IV) infusion over a time period of 60-100 minutes, based on subject body weight. Induction Phase dosing consisted of a single dose every 3 weeks (Q3W) for 4 doses. This was followed by Maintenance Phase dosing of a single dose every 12 weeks (Q12W). Treatment was for a maximum treatment period of 3 years from the first induction dose of blinded study therapy, or until subject met treatment stopping criteria.

Reporting group title	3 MG/KG IPILIMUMAB
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Reporting group description:

3 MG/KG IPILIMUMAB-was administered by intravenous (IV) infusion over a time period of 60-100 minutes, based on subject body weight. Induction Phase dosing consisted of a single dose every 3 weeks (Q3W) for 4 doses. This was followed by Maintenance Phase dosing of a single dose every 12 weeks (Q12W). Treatment was for a maximum treatment period of 3 years from the first induction dose of blinded study therapy, or until subject met treatment stopping criteria.

Serious adverse events	10 MG/KG IPILIMUMAB	3 MG/KG IPILIMUMAB	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 26 (57.69%)	6 / 25 (24.00%)	
number of deaths (all causes)	2	1	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	0 / 26 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 26 (3.85%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

General physical health deterioration			
subjects affected / exposed	2 / 26 (7.69%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 26 (7.69%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Autoimmune colitis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	4 / 26 (15.38%)	3 / 25 (12.00%)	
occurrences causally related to treatment / all	5 / 5	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	7 / 26 (26.92%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	10 / 10	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			

subjects affected / exposed	1 / 26 (3.85%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 26 (3.85%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 26 (3.85%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 26 (3.85%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophysitis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacterial diarrhoea			

subjects affected / exposed	0 / 26 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic shock			
subjects affected / exposed	1 / 26 (3.85%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 26 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	10 MG/KG IPILIMUMAB	3 MG/KG IPILIMUMAB	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 26 (84.62%)	22 / 25 (88.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 26 (3.85%)	4 / 25 (16.00%)	
occurrences (all)	1	4	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 26 (7.69%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Fatigue			
subjects affected / exposed	9 / 26 (34.62%)	4 / 25 (16.00%)	
occurrences (all)	9	4	
Mucosal inflammation			

subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	0 / 25 (0.00%) 0	
Pain subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	1 / 25 (4.00%) 1	
Pyrexia subjects affected / exposed occurrences (all)	6 / 26 (23.08%) 8	3 / 25 (12.00%) 3	
Reproductive system and breast disorders Pelvic pain subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	2 / 25 (8.00%) 2	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	2 / 25 (8.00%) 2	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	3 / 26 (11.54%) 3	0 / 25 (0.00%) 0	
Investigations Weight decreased subjects affected / exposed occurrences (all)	3 / 26 (11.54%) 3	0 / 25 (0.00%) 0	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	0 / 25 (0.00%) 0	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	3 / 25 (12.00%) 3	
Gastrointestinal disorders Colitis subjects affected / exposed occurrences (all) Diarrhoea	4 / 26 (15.38%) 4	3 / 25 (12.00%) 3	

subjects affected / exposed occurrences (all)	15 / 26 (57.69%) 20	11 / 25 (44.00%) 12	
Nausea subjects affected / exposed occurrences (all)	3 / 26 (11.54%) 3	2 / 25 (8.00%) 2	
Vomiting subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	0 / 25 (0.00%) 0	
Skin and subcutaneous tissue disorders			
Eczema subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	0 / 25 (0.00%) 0	
Hyperhidrosis subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	2 / 25 (8.00%) 2	
Pruritus subjects affected / exposed occurrences (all)	5 / 26 (19.23%) 5	4 / 25 (16.00%) 4	
Rash subjects affected / exposed occurrences (all)	9 / 26 (34.62%) 10	5 / 25 (20.00%) 5	
Rash maculo-papular subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 3	1 / 25 (4.00%) 1	
Urticaria subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	2 / 25 (8.00%) 2	
Skin lesion subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	2 / 25 (8.00%) 2	
Renal and urinary disorders			
Nocturia subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	0 / 25 (0.00%) 0	
Haematuria			

subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	0 / 25 (0.00%) 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 26 (11.54%)	3 / 25 (12.00%)	
occurrences (all)	3	4	
Back pain			
subjects affected / exposed	1 / 26 (3.85%)	3 / 25 (12.00%)	
occurrences (all)	2	3	
Pain in extremity			
subjects affected / exposed	2 / 26 (7.69%)	2 / 25 (8.00%)	
occurrences (all)	1	2	
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	0 / 26 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Systemic infection			
subjects affected / exposed	0 / 26 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 26 (15.38%)	1 / 25 (4.00%)	
occurrences (all)	4	1	
Dehydration			
subjects affected / exposed	2 / 26 (7.69%)	1 / 25 (4.00%)	
occurrences (all)	2	1	
Hypokalaemia			
subjects affected / exposed	2 / 26 (7.69%)	0 / 25 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported