



Clinical trial results:

A Phase 2 Multicenter, Open-label Study to Determine the Efficacy and Safety of Pomalidomide (CC-4047) in Combination With Low-Dose Dexamethasone in Subjects With Relapsed or Refractory Multiple Myeloma and Moderate or Severe Renal Impairment Including Subjects Undergoing Hemodialysis

Summary

EudraCT number	2013-001903-36
Trial protocol	IT GR ES GB NL AT FR
Global end of trial date	28 July 2021

Results information

Result version number	v1
This version publication date	13 August 2022
First version publication date	13 August 2022

Trial information

Trial identification

Sponsor protocol code	CC-4047-MM-013
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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	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, 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	03 September 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	28 July 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate efficacy of the combination of pomalidomide and low-dose dexamethasone (LD-DEX) in subjects with relapsed or refractory multiple myeloma (RRMM) and impaired renal function.

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	05 March 2014
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	Australia: 3
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Greece: 13
Country: Number of subjects enrolled	Italy: 17
Country: Number of subjects enrolled	Netherlands: 11
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	United Kingdom: 16
Worldwide total number of subjects	81
EEA total number of subjects	62

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)	15
From 65 to 84 years	64
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

81 participants treated

Period 1

Period 1 title	Treatment Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
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Arm title	Cohort A
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Arm description:

Participants with moderate renal impairment of $30 \leq \text{eGFR} < 45 \text{ mL/min/1.73 m}^2$ are treated with 4 mg/day Pomalidomide on days 1-21 of a 28-day cycle + 40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old) Dexamethasone on days 1, 8, 15, 22 of a 28-day cycle

Arm type	Experimental
Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old)

Investigational medicinal product name	Pomalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

4 mg

Arm title	Cohort B
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Arm description:

Participant with severe renal impairment of $\text{eGFR} < 30 \text{ mL/min/1.73 m}^2$ not requiring hemodialysis are treated with 4 mg/day Pomalidomide on days 1-21 of a 28-day cycle + 40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old) Dexamethasone on days 1, 8, 15, 22 of a 28-day cycle

Arm type	Experimental
Investigational medicinal product name	Pomalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

4 mg

Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

40 mg/day (\leq 75 years old) or 20 mg/day ($>$ 75 years old)

Arm title	Cohort C
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Arm description:

Participant with severe renal impairment Participant with severe renal impairment of eGFR $<$ 30 mL/min/1.73 m² requiring hemodialysis are treated with 4 mg/day Pomalidomide on days 1-21 of a 28-day cycle + 40 mg/day (\leq 75 years old) or 20 mg/day ($>$ 75 years old) Dexamethasone on days 1, 8, 15, 22 of a 28-day cycle

Arm type	Experimental
Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

40 mg/day (\leq 75 years old) or 20 mg/day ($>$ 75 years old)

Investigational medicinal product name	Pomalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

4 mg

Number of subjects in period 1	Cohort A	Cohort B	Cohort C
Started	33	34	14
Completed	0	0	0
Not completed	33	34	14
Adverse event, serious fatal	1	8	5
Consent withdrawn by subject	1	1	1
Adverse event, non-fatal	6	8	4
Progressive Disease	22	17	4
Other reasons	3	-	-

Baseline characteristics

Reporting groups

Reporting group title	Cohort A
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Reporting group description:

Participants with moderate renal impairment of $30 \leq \text{eGFR} < 45 \text{ mL/min/1.73 m}^2$ are treated with 4 mg/day Pomalidomide on days 1-21 of a 28-day cycle + 40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old) Dexamethasone on days 1, 8, 15, 22 of a 28-day cycle

Reporting group title	Cohort B
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Reporting group description:

Participant with severe renal impairment of $\text{eGFR} < 30 \text{ mL/min/1.73 m}^2$ not requiring hemodialysis are treated with 4 mg/day Pomalidomide on days 1-21 of a 28-day cycle + 40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old) Dexamethasone on days 1, 8, 15, 22 of a 28-day cycle

Reporting group title	Cohort C
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Reporting group description:

Participant with severe renal impairment Participant with severe renal impairment of $\text{eGFR} < 30 \text{ mL/min/1.73 m}^2$ requiring hemodialysis are treated with 4 mg/day Pomalidomide on days 1-21 of a 28-day cycle + 40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old) Dexamethasone on days 1, 8, 15, 22 of a 28-day cycle

Reporting group values	Cohort A	Cohort B	Cohort C
Number of subjects	33	34	14
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)	7	4	4
From 65-84 years	24	30	10
85 years and over	2	0	0
Age Continuous			
Units: Years			
arithmetic mean	71.4	71.6	68.2
standard deviation	± 8.77	± 7.56	± 7.20
Sex: Female, Male			
Units: Participants			
Female	9	18	5
Male	24	16	9
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	0	0
White	33	33	14
More than one race	0	0	0

Unknown or Not Reported	0	1	0
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	2	0	0
Not Hispanic or Latino	31	34	14
Unknown or Not Reported	0	0	0

Reporting group values	Total		
Number of subjects	81		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	15		
From 65-84 years	64		
85 years and over	2		
Age Continuous			
Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units: Participants			
Female	32		
Male	49		
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	0		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	0		
White	80		
More than one race	0		
Unknown or Not Reported	1		
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	2		
Not Hispanic or Latino	79		
Unknown or Not Reported	0		

End points

End points reporting groups

Reporting group title	Cohort A
Reporting group description: Participants with moderate renal impairment of $30 \leq \text{eGFR} < 45 \text{ mL/min/1.73 m}^2$ are treated with 4 mg/day Pomalidomide on days 1-21 of a 28-day cycle + 40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old) Dexamethasone on days 1, 8, 15, 22 of a 28-day cycle	
Reporting group title	Cohort B
Reporting group description: Participant with severe renal impairment of $\text{eGFR} < 30 \text{ mL/min/1.73 m}^2$ not requiring hemodialysis are treated with 4 mg/day Pomalidomide on days 1-21 of a 28-day cycle + 40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old) Dexamethasone on days 1, 8, 15, 22 of a 28-day cycle	
Reporting group title	Cohort C
Reporting group description: Participant with severe renal impairment Participant with severe renal impairment of $\text{eGFR} < 30 \text{ mL/min/1.73 m}^2$ requiring hemodialysis are treated with 4 mg/day Pomalidomide on days 1-21 of a 28-day cycle + 40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old) Dexamethasone on days 1, 8, 15, 22 of a 28-day cycle	

Primary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR) ^[1]
End point description: Overall response rate (ORR) is defined as the percentage of participants with a best overall response (BOR) of complete response (CR) or partial response (PR) using the following international myeloma working group (IMWG) uniform response criteria: Complete response (CR): Negative immunofixation of serum and urine, and disappearance of any soft tissue plasmacytomas, and $< 5\%$ plasma cells in bone marrow Partial response (PR): $\geq 50\%$ reduction of serum M-protein and reduction in 24-hour urinary M-protein by $\geq 90\%$ or to $< 200 \text{ mg}$ per 24 hours	
End point type	Primary
End point timeframe: Up to 34 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 planned for this endpoints	

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	33	34	14	
Units: Percentage of Participants				
number (confidence interval 95%)	39.4 (22.9 to 57.9)	32.4 (17.4 to 50.5)	14.3 (1.8 to 42.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Renal Response

End point title	Renal Response
End point description:	
Renal response is defined as the percentage of confirmed responders of renal complete response (CRrenal), or renal partial response (PRrenal), or renal minor response (MRrenal) according to the following criteria defined by Ludwig and Dimopoulos: Renal Complete Response (CRrenal): Sustained (ie, at least 2 months) improvement of baseline GFR from < 50 mL/min/1.73 m ² to ≥ 60 mL/min/1.73 m ² (stage ≥ 3 to stage 1/2 chronic kidney disease) Renal Partial Response (PRrenal): Sustained improvement of baseline eGFR from < 15 mL/min/1.73 m ² to 30-59 mL/min/1.73 m ² Renal Minor Response (MRrenal): Sustained improvement of baseline eGFR of < 15 mL/min/1.73 m ² to 15-29 mL/min/1.73 m ²	
End point type	Secondary
End point timeframe:	
Up to 88 months	

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	33	34	14	
Units: Percentage of participants				
number (confidence interval 95%)	18.2 (7.0 to 35.5)	35.3 (19.7 to 53.5)	7.1 (0.2 to 33.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response (TTR)

End point title	Time to Response (TTR)
End point description:	
Time to response (TTR) is assessed as the time from start of treatment to the first documented response (partial response or better) based on international myeloma working group criteria (IMWG) Partial Response (PR): ≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hours 99999=NA because of inconsistent mean and median values with respect to range of values	
End point type	Secondary
End point timeframe:	
Up to 88 months	

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	11	2	
Units: Months				
median (full range (min-max))	99999 (99999 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Renal Response (TTRR)

End point title | Time to Renal Response (TTRR)

End point description:

Time to Renal Response (TTRR) is assessed as the time from start of treatment until the date when criteria defined by Ludwig and Dimopoulos for renal response will be first met

Renal Complete Response (CR_{renal}): Sustained (ie, at least 2 months) improvement of baseline GFR from < 50 mL/min/1.73 m² to ≥ 60 mL/min/1.73 m² (stage ≥ 3 to stage 1/2 chronic kidney disease)

Renal Partial Response (PR_{renal}): Sustained improvement of baseline eGFR from < 15 mL/min/1.73 m² to 30-59 mL/min/1.73 m²

Renal Minor Response (MR_{renal}): Sustained improvement of baseline eGFR of < 15 mL/min/1.73 m² to 15-29 mL/min/1.73 m²

99999=NA because of inconsistent mean and median values with respect to range of values

End point type | Secondary

End point timeframe:

Up to 88 months

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	12	1	
Units: Months				
median (full range (min-max))	99999 (99999 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DoR)

End point title | Duration of Response (DoR)

End point description:

Duration of response (DoR) is defined as time from the first response (partial response or better) to the first documented progressive disease

Partial response (PR): ≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hours

99999= Not estimable

End point type | Secondary

End point timeframe:

Up to 88 months

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	11	2	
Units: Months				
median (confidence interval 95%)	10.5 (4.60 to 19.20)	4.6 (2.79 to 12.53)	99999 (1.45 to 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)
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End point description:

PFS is assessed as the time from start of treatment until the time of progressive disease (PD) or death from any cause on study treatment, whichever comes first. Participants not experiencing a documented progression will be censored at the time of their last tumor assessment

PD: Increase of 25% from lowest response value in any one or more of the following:

- Serum M-component
- Urine M-component
- Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/L)
- Bone marrow plasma cell percentage (absolute % must be ≥ 10%)
- Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas
- Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder

End point type	Secondary
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End point timeframe:

Up to 88 months

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	33	34	14	
Units: Months				
median (confidence interval 95%)	6.9 (4.60 to 9.30)	4.1 (2.79 to 6.51)	2.4 (0.95 to 6.41)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP)

End point title	Time to Progression (TTP)
End point description:	
<p>Time to progression (TTP) is assessed as the time from study treatment start until progressive disease. Deaths due to causes other than progression will be censored. Participants not experiencing a documented progression will be censored at the time of their last tumor assessment</p> <p>PD: Increase of 25% from lowest response value in any one or more of the following:</p> <ul style="list-style-type: none"> - Serum M-component - Urine M-component - Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/L) - Bone marrow plasma cell percentage (absolute % must be ≥ 10%) - Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas - Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder <p>99999= Not Estimable</p>	
End point type	Secondary
End point timeframe:	
Up to 88 months	

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	33	34	14	
Units: Months				
median (confidence interval 95%)	7.4 (4.60 to 14.50)	4.6 (3.09 to 6.67)	4.0 (0.95 to 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
<p>Overall survival (OS) is assessed as the time from start of treatment until the time of death from any cause. If no death is recorded, the participant will be censored at the time the participant was last known to be alive</p>	
End point type	Secondary
End point timeframe:	
Up to 88 months	

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	33	34	14	
Units: Months				
median (confidence interval 95%)	16.4 (7.79 to 31.59)	11.8 (6.35 to 14.27)	5.2 (1.81 to 9.67)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Treatment Emergent Adverse Events (TEAEs)

End point title	Number of Participants with Treatment Emergent Adverse Events (TEAEs)
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End point description:

Treatment Emergent Adverse Event (TEAE) is defined as an adverse event (AE) occurring or worsening on or after the first treatment of study medication graded by the national cancer institute common terminology criteria (version 4.0)

Grade 3 = Severe event

Grade 4 = Life threatening event

End point type	Secondary
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End point timeframe:

From first dose to 28 days after last dose (Up to approximately 10 months)

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	33	34	14	
Units: Percentage of participants				
number (not applicable)				
TEAE	100	100	100	
TEAE related to Pomalidomide	90.9	85.3	92.9	
TEAE related to low dose Dexamethasone	63.6	50.0	50.0	
Grade 3-4 TEAE	93.9	91.2	92.9	
Grade 3-4 TEAE related to Pomalidomide	75.8	67.6	85.7	
Grade 3-4 TEAE related to low dose Dexamethasone	27.3	26.5	35.7	
Serious TEAE	57.6	67.6	85.7	
Serious TEAE related to Pomalidomide	21.2	35.3	28.6	
Serious TEAE related to low dose Dexamethasone	24.2	17.6	21.4	

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-Time Curve from Time Zero to the

Last Measured Time Point (AUC(0-t))

End point title	Area Under the Plasma Concentration-Time Curve from Time Zero to the Last Measured Time Point (AUC(0-t))
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End point description:

Area under the Pomalidomide plasma concentration-time curve from time zero to the last measured time point (AUC(0-t))

End point type	Secondary
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End point timeframe:

Pre-dose, 1, 2, 3, 4, 6, and 8 hours post-dose on cycle 1 day 8

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	5	7	
Units: h*ug/L				
geometric mean (geometric coefficient of variation)	899.84 (\pm 38.7)	944.93 (\pm 84.5)	427.49 (\pm 140.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-Time Curve from Time Zero to infinity (AUC(0-inf))

End point title	Area Under the Plasma Concentration-Time Curve from Time Zero to infinity (AUC(0-inf))
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End point description:

Area under the Pomalidomide plasma concentration-time curve from time zero to infinity (AUC(0-inf))

End point type	Secondary
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End point timeframe:

Pre-dose, 1, 2, 3, 4, 6, and 8 hours post-dose on cycle 1 day 8

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	2	4	
Units: h*ug/L				
geometric mean (geometric coefficient of variation)	1581.54 (\pm 212.0)	1570.07 (\pm 206.8)	834.13 (\pm 50.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax)

End point title	Maximum Observed Plasma Concentration (Cmax)
End point description:	Maximum observed Pomalidomide plasma concentration (Cmax)
End point type	Secondary
End point timeframe:	Pre-dose, 1, 2, 3, 4, 6, and 8 hours post-dose on cycle 1 day 8

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	5	7	
Units: ug/L				
geometric mean (geometric coefficient of variation)	75.64 (\pm 24.8)	111.02 (\pm 48.3)	61.82 (\pm 74.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time of Maximum Observed Plasma Concentration (Tmax)

End point title	Time of Maximum Observed Plasma Concentration (Tmax)
End point description:	Time of maximum observed Pomalidomide plasma concentration (Tmax)
End point type	Secondary
End point timeframe:	Pre-dose, 1, 2, 3, 4, 6, and 8 hours post-dose on cycle 1 day 8

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	5	7	
Units: Hours				
geometric mean (geometric coefficient of variation)	3.35 (\pm 24.6)	3.52 (\pm 55.2)	2.33 (\pm 51.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Terminal Half-life (t1/2)

End point title	Apparent Terminal Half-life (t1/2)
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End point description:

Pomalidomide terminal half-life (t_{1/2})

End point type Secondary

End point timeframe:

Pre-dose, 1, 2, 3, 4, 6, and 8 hours post-dose on cycle 1 day 8

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	2	4	
Units: Hours				
geometric mean (geometric coefficient of variation)	11.81 (± 268.5)	8.34 (± 75.7)	7.16 (± 45.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Clearance (CL/F)

End point title Apparent Clearance (CL/F)

End point description:

Pomalidomide plasma apparent clearance (CL/F)

End point type Secondary

End point timeframe:

Pre-dose, 1, 2, 3, 4, 6, and 8 hours post-dose on cycle 1 day 8

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	2	4	
Units: L/h				
geometric mean (geometric coefficient of variation)	2.53 (± 212.0)	2.55 (± 206.8)	4.80 (± 50.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Terminal Volume of Distribution (V_z/F)

End point title Apparent Terminal Volume of Distribution (V_z/F)

End point description:

Pomalidomide apparent terminal volume of distribution (V_z/F)

End point type Secondary

End point timeframe:

Pre-dose, 1, 2, 3, 4, 6, and 8 hours post-dose on cycle 1 day 8

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	2	4	
Units: (L)				
geometric mean (geometric coefficient of variation)	43.10 (\pm 31.1)	30.67 (\pm 68.0)	49.51 (\pm 106.7)	

Statistical analyses

No statistical analyses for this end point

Post-hoc: Overall Response Rate (ORR) Post-hoc

End point title Overall Response Rate (ORR) Post-hoc

End point description:

Overall response rate (ORR) is defined as the percentage of participants with a best overall response (BOR) of complete response (CR) or partial response (PR) using the following international myeloma working group (IMWG) uniform response criteria:

Complete response (CR): Negative immunofixation of serum and urine, and disappearance of any soft tissue plasmacytomas, and < 5% plasma cells in bone marrow

Partial response (PR): \geq 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by \geq 90% or to < 200 mg per 24 hours

End point type Post-hoc

End point timeframe:

Up to 88 months

End point values	Cohort A	Cohort B	Cohort C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	33	34	14	
Units: Percentage of participants				
number (confidence interval 95%)	42.4 (25.5 to 60.8)	32.4 (17.4 to 50.5)	14.3 (1.8 to 42.8)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events and Serious Adverse Events were monitored from first dose to 28 days post last dose (Up to 10 months). Participants were assessed for All Cause Mortality from their first dose until the study was completed (up to 88 months)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	MedDRA24.0

Reporting groups

Reporting group title	Cohort A
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Reporting group description:

Participants with moderate renal impairment of $30 \leq \text{eGFR} < 45 \text{ mL/min/1.73 m}^2$ are treated with 4 mg/day Pomalidomide on days 1-21 of a 28-day cycle + 40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old) Dexamethasone on days 1, 8, 15, 22 of a 28-day cycle

Reporting group title	Cohort B
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Reporting group description:

Participant with severe renal impairment of $\text{eGFR} < 30 \text{ mL/min/1.73 m}^2$ not requiring hemodialysis are treated with 4 mg/day Pomalidomide on days 1-21 of a 28-day cycle + 40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old) Dexamethasone on days 1, 8, 15, 22 of a 28-day cycle

Reporting group title	Cohort C
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Reporting group description:

Participant with severe renal impairment Participant with severe renal impairment of $\text{eGFR} < 30 \text{ mL/min/1.73 m}^2$ requiring hemodialysis are treated with 4 mg/day Pomalidomide on days 1-21 of a 28-day cycle + 40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old) Dexamethasone on days 1, 8, 15, 22 of a 28-day cycle

Serious adverse events	Cohort A	Cohort B	Cohort C
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 33 (57.58%)	23 / 34 (67.65%)	12 / 14 (85.71%)
number of deaths (all causes)	25	31	13
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bowen's disease			
subjects affected / exposed	1 / 33 (3.03%)	0 / 34 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningioma			
subjects affected / exposed	1 / 33 (3.03%)	0 / 34 (0.00%)	0 / 14 (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
Pancreatic carcinoma			

subjects affected / exposed	0 / 33 (0.00%)	0 / 34 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Plasma cell leukaemia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 34 (2.94%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Plasma cell myeloma			
subjects affected / exposed	1 / 33 (3.03%)	1 / 34 (2.94%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Squamous cell carcinoma of lung			
subjects affected / exposed	1 / 33 (3.03%)	0 / 34 (0.00%)	0 / 14 (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	0 / 33 (0.00%)	1 / 34 (2.94%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoperfusion			
subjects affected / exposed	0 / 33 (0.00%)	1 / 34 (2.94%)	0 / 14 (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
Hypotension			
subjects affected / exposed	0 / 33 (0.00%)	1 / 34 (2.94%)	0 / 14 (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			
Asthenia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 34 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

General physical health deterioration			
subjects affected / exposed	1 / 33 (3.03%)	2 / 34 (5.88%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hyperthermia			
subjects affected / exposed	1 / 33 (3.03%)	0 / 34 (0.00%)	0 / 14 (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
Pyrexia			
subjects affected / exposed	2 / 33 (6.06%)	3 / 34 (8.82%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	1 / 2	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypogammaglobulinaemia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 34 (2.94%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	0 / 33 (0.00%)	0 / 34 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 33 (3.03%)	0 / 34 (0.00%)	0 / 14 (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
Dyspnoea			
subjects affected / exposed	1 / 33 (3.03%)	2 / 34 (5.88%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercapnia			

subjects affected / exposed	0 / 33 (0.00%)	0 / 34 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 33 (3.03%)	0 / 34 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 33 (0.00%)	1 / 34 (2.94%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 33 (0.00%)	3 / 34 (8.82%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Arteriovenous fistula thrombosis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 34 (2.94%)	0 / 14 (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
Fall			
subjects affected / exposed	1 / 33 (3.03%)	0 / 34 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	1 / 33 (3.03%)	0 / 34 (0.00%)	0 / 14 (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
Hip fracture			
subjects affected / exposed	0 / 33 (0.00%)	0 / 34 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Humerus fracture			
subjects affected / exposed	0 / 33 (0.00%)	0 / 34 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural hypotension			
subjects affected / exposed	0 / 33 (0.00%)	0 / 34 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	1 / 33 (3.03%)	0 / 34 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	0 / 33 (0.00%)	1 / 34 (2.94%)	0 / 14 (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
Subdural haemorrhage			
subjects affected / exposed	1 / 33 (3.03%)	0 / 34 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 33 (0.00%)	1 / 34 (2.94%)	0 / 14 (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	1 / 33 (3.03%)	0 / 34 (0.00%)	0 / 14 (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
Atrial fibrillation			
subjects affected / exposed	0 / 33 (0.00%)	0 / 34 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			

subjects affected / exposed	0 / 33 (0.00%)	0 / 34 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac failure			
subjects affected / exposed	1 / 33 (3.03%)	1 / 34 (2.94%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 1	0 / 0
Pericardial disease			
subjects affected / exposed	1 / 33 (3.03%)	0 / 34 (0.00%)	0 / 14 (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
Ventricular fibrillation			
subjects affected / exposed	0 / 33 (0.00%)	0 / 34 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 33 (0.00%)	1 / 34 (2.94%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	1 / 33 (3.03%)	0 / 34 (0.00%)	0 / 14 (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
Ischaemic stroke			
subjects affected / exposed	0 / 33 (0.00%)	1 / 34 (2.94%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 33 (0.00%)	1 / 34 (2.94%)	0 / 14 (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
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	0 / 33 (0.00%)	3 / 34 (8.82%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 34 (2.94%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 33 (3.03%)	1 / 34 (2.94%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 33 (0.00%)	5 / 34 (14.71%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	3 / 5	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	1 / 33 (3.03%)	0 / 34 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 33 (3.03%)	0 / 34 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Colitis ischaemic			
subjects affected / exposed	0 / 33 (0.00%)	1 / 34 (2.94%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Diarrhoea			
subjects affected / exposed	2 / 33 (6.06%)	1 / 34 (2.94%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0

Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 33 (3.03%)	0 / 34 (0.00%)	0 / 14 (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
Intestinal ischaemia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 34 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	1 / 33 (3.03%)	0 / 34 (0.00%)	0 / 14 (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
Skin and subcutaneous tissue disorders			
Pyoderma gangrenosum			
subjects affected / exposed	0 / 33 (0.00%)	1 / 34 (2.94%)	0 / 14 (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
Stevens-Johnson syndrome			
subjects affected / exposed	0 / 33 (0.00%)	1 / 34 (2.94%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 33 (0.00%)	2 / 34 (5.88%)	0 / 14 (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
Renal failure			
subjects affected / exposed	2 / 33 (6.06%)	2 / 34 (5.88%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 2	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Urinary retention			
subjects affected / exposed	0 / 33 (0.00%)	0 / 34 (0.00%)	1 / 14 (7.14%)
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 and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 33 (3.03%)	0 / 34 (0.00%)	0 / 14 (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
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 33 (3.03%)	0 / 34 (0.00%)	0 / 14 (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
Cytomegalovirus infection			
subjects affected / exposed	0 / 33 (0.00%)	1 / 34 (2.94%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 33 (0.00%)	0 / 34 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 33 (3.03%)	0 / 34 (0.00%)	0 / 14 (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
Endophthalmitis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 34 (2.94%)	0 / 14 (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
Enterococcal bacteraemia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 34 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterococcal sepsis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 34 (2.94%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0

Gastroenteritis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 34 (2.94%)	0 / 14 (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
Gastrointestinal infection			
subjects affected / exposed	0 / 33 (0.00%)	1 / 34 (2.94%)	0 / 14 (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
Hepatitis E			
subjects affected / exposed	1 / 33 (3.03%)	0 / 34 (0.00%)	0 / 14 (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
Influenza			
subjects affected / exposed	1 / 33 (3.03%)	0 / 34 (0.00%)	0 / 14 (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
Large intestine infection			
subjects affected / exposed	1 / 33 (3.03%)	0 / 34 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Leishmaniasis			
subjects affected / exposed	1 / 33 (3.03%)	0 / 34 (0.00%)	0 / 14 (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
Lower respiratory tract infection			
subjects affected / exposed	1 / 33 (3.03%)	1 / 34 (2.94%)	0 / 14 (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
Parainfluenzae virus infection			
subjects affected / exposed	0 / 33 (0.00%)	1 / 34 (2.94%)	0 / 14 (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
Parotitis			

subjects affected / exposed	1 / 33 (3.03%)	0 / 34 (0.00%)	0 / 14 (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
Peritonitis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 34 (2.94%)	0 / 14 (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			
subjects affected / exposed	8 / 33 (24.24%)	4 / 34 (11.76%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	3 / 8	1 / 5	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 33 (0.00%)	1 / 34 (2.94%)	0 / 14 (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 cytomegaloviral			
subjects affected / exposed	1 / 33 (3.03%)	0 / 34 (0.00%)	0 / 14 (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 haemophilus			
subjects affected / exposed	1 / 33 (3.03%)	0 / 34 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pneumococcal			
subjects affected / exposed	0 / 33 (0.00%)	1 / 34 (2.94%)	0 / 14 (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
Pyelonephritis acute			
subjects affected / exposed	0 / 33 (0.00%)	1 / 34 (2.94%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			

subjects affected / exposed	0 / 33 (0.00%)	0 / 34 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Respiratory tract infection fungal			
subjects affected / exposed	0 / 33 (0.00%)	0 / 34 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection viral			
subjects affected / exposed	0 / 33 (0.00%)	1 / 34 (2.94%)	0 / 14 (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
Sepsis			
subjects affected / exposed	0 / 33 (0.00%)	2 / 34 (5.88%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Septic shock			
subjects affected / exposed	0 / 33 (0.00%)	2 / 34 (5.88%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Sinusitis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 34 (2.94%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal bacteraemia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 34 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 33 (0.00%)	2 / 34 (5.88%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	0 / 33 (0.00%)	1 / 34 (2.94%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection pseudomonal			
subjects affected / exposed	0 / 33 (0.00%)	1 / 34 (2.94%)	0 / 14 (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
Metabolism and nutrition disorders			
Electrolyte imbalance			
subjects affected / exposed	1 / 33 (3.03%)	0 / 34 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Fluid overload			
subjects affected / exposed	1 / 33 (3.03%)	0 / 34 (0.00%)	0 / 14 (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
Hyperkalaemia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 34 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Hypoalbuminaemia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 34 (2.94%)	0 / 14 (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
Hypocalcaemia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 34 (2.94%)	0 / 14 (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
Hypoglycaemia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 34 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			

subjects affected / exposed	0 / 33 (0.00%)	1 / 34 (2.94%)	0 / 14 (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: 5 %

Non-serious adverse events	Cohort A	Cohort B	Cohort C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 33 (100.00%)	34 / 34 (100.00%)	14 / 14 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 33 (0.00%)	1 / 34 (2.94%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 33 (0.00%)	2 / 34 (5.88%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
Haemorrhage			
subjects affected / exposed	0 / 33 (0.00%)	0 / 34 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Hypertension			
subjects affected / exposed	0 / 33 (0.00%)	2 / 34 (5.88%)	1 / 14 (7.14%)
occurrences (all)	0	2	1
Hypotension			
subjects affected / exposed	0 / 33 (0.00%)	4 / 34 (11.76%)	3 / 14 (21.43%)
occurrences (all)	0	4	4
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	8 / 33 (24.24%)	5 / 34 (14.71%)	5 / 14 (35.71%)
occurrences (all)	11	6	5
Catheter site pain			
subjects affected / exposed	0 / 33 (0.00%)	0 / 34 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Chills			

subjects affected / exposed	0 / 33 (0.00%)	1 / 34 (2.94%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Fatigue			
subjects affected / exposed	10 / 33 (30.30%)	9 / 34 (26.47%)	4 / 14 (28.57%)
occurrences (all)	11	12	5
General physical health deterioration			
subjects affected / exposed	2 / 33 (6.06%)	0 / 34 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Hypothermia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 34 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Oedema peripheral			
subjects affected / exposed	5 / 33 (15.15%)	7 / 34 (20.59%)	4 / 14 (28.57%)
occurrences (all)	5	10	4
Pyrexia			
subjects affected / exposed	9 / 33 (27.27%)	8 / 34 (23.53%)	3 / 14 (21.43%)
occurrences (all)	17	13	3
Immune system disorders			
Immunosuppression			
subjects affected / exposed	0 / 33 (0.00%)	0 / 34 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	3 / 33 (9.09%)	0 / 34 (0.00%)	0 / 14 (0.00%)
occurrences (all)	3	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 33 (15.15%)	8 / 34 (23.53%)	2 / 14 (14.29%)
occurrences (all)	8	12	2
Dysphonia			
subjects affected / exposed	2 / 33 (6.06%)	1 / 34 (2.94%)	0 / 14 (0.00%)
occurrences (all)	2	1	0
Dyspnoea			
subjects affected / exposed	7 / 33 (21.21%)	6 / 34 (17.65%)	1 / 14 (7.14%)
occurrences (all)	8	7	1
Dyspnoea exertional			

subjects affected / exposed	0 / 33 (0.00%)	0 / 34 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Epistaxis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 34 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Nasal congestion			
subjects affected / exposed	0 / 33 (0.00%)	0 / 34 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Oropharyngeal pain			
subjects affected / exposed	0 / 33 (0.00%)	3 / 34 (8.82%)	0 / 14 (0.00%)
occurrences (all)	0	3	0
Productive cough			
subjects affected / exposed	1 / 33 (3.03%)	2 / 34 (5.88%)	0 / 14 (0.00%)
occurrences (all)	1	2	0
Rhinorrhoea			
subjects affected / exposed	2 / 33 (6.06%)	1 / 34 (2.94%)	0 / 14 (0.00%)
occurrences (all)	2	1	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	2 / 33 (6.06%)	0 / 34 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Anxiety			
subjects affected / exposed	0 / 33 (0.00%)	1 / 34 (2.94%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Confusional state			
subjects affected / exposed	1 / 33 (3.03%)	2 / 34 (5.88%)	1 / 14 (7.14%)
occurrences (all)	1	2	1
Depressed mood			
subjects affected / exposed	2 / 33 (6.06%)	0 / 34 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Insomnia			
subjects affected / exposed	5 / 33 (15.15%)	5 / 34 (14.71%)	1 / 14 (7.14%)
occurrences (all)	6	5	1
Sleep disorder			
subjects affected / exposed	2 / 33 (6.06%)	0 / 34 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0

Investigations			
Blood calcium decreased			
subjects affected / exposed	0 / 33 (0.00%)	0 / 34 (0.00%)	2 / 14 (14.29%)
occurrences (all)	0	0	2
Blood creatinine increased			
subjects affected / exposed	0 / 33 (0.00%)	3 / 34 (8.82%)	2 / 14 (14.29%)
occurrences (all)	0	4	4
Blood potassium increased			
subjects affected / exposed	0 / 33 (0.00%)	0 / 34 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
C-reactive protein increased			
subjects affected / exposed	2 / 33 (6.06%)	4 / 34 (11.76%)	1 / 14 (7.14%)
occurrences (all)	4	4	1
Glomerular filtration rate decreased			
subjects affected / exposed	0 / 33 (0.00%)	0 / 34 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	2
Procalcitonin increased			
subjects affected / exposed	0 / 33 (0.00%)	0 / 34 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Weight decreased			
subjects affected / exposed	1 / 33 (3.03%)	0 / 34 (0.00%)	2 / 14 (14.29%)
occurrences (all)	1	0	2
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 33 (6.06%)	0 / 34 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Fall			
subjects affected / exposed	2 / 33 (6.06%)	2 / 34 (5.88%)	0 / 14 (0.00%)
occurrences (all)	9	2	0
Procedural hypotension			
subjects affected / exposed	0 / 33 (0.00%)	0 / 34 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 33 (0.00%)	1 / 34 (2.94%)	3 / 14 (21.43%)
occurrences (all)	0	1	5

Tachycardia subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	1 / 34 (2.94%) 1	2 / 14 (14.29%) 3
Nervous system disorders			
Cognitive disorder subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	0 / 34 (0.00%) 0	0 / 14 (0.00%) 0
Dizziness subjects affected / exposed occurrences (all)	4 / 33 (12.12%) 4	4 / 34 (11.76%) 5	0 / 14 (0.00%) 0
Headache subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	3 / 34 (8.82%) 3	0 / 14 (0.00%) 0
Monoplegia subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 34 (0.00%) 0	1 / 14 (7.14%) 1
Paraesthesia subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 34 (0.00%) 0	1 / 14 (7.14%) 1
Peripheral sensorimotor neuropathy subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 34 (0.00%) 0	1 / 14 (7.14%) 1
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	6 / 34 (17.65%) 6	3 / 14 (21.43%) 5
Transient ischaemic attack subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	2 / 34 (5.88%) 3	0 / 14 (0.00%) 0
Tremor subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	3 / 34 (8.82%) 3	0 / 14 (0.00%) 0
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	26 / 33 (78.79%) 46	15 / 34 (44.12%) 23	9 / 14 (64.29%) 20
Leukopenia			

subjects affected / exposed occurrences (all)	6 / 33 (18.18%) 7	8 / 34 (23.53%) 20	5 / 14 (35.71%) 10
Lymphopenia subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	2 / 34 (5.88%) 3	0 / 14 (0.00%) 0
Neutropenia subjects affected / exposed occurrences (all)	26 / 33 (78.79%) 67	21 / 34 (61.76%) 43	9 / 14 (64.29%) 25
Thrombocytopenia subjects affected / exposed occurrences (all)	19 / 33 (57.58%) 23	16 / 34 (47.06%) 21	9 / 14 (64.29%) 21
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 34 (0.00%) 0	1 / 14 (7.14%) 1
Eye disorders Cataract subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	2 / 34 (5.88%) 2	0 / 14 (0.00%) 0
Conjunctival haemorrhage subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	3 / 34 (8.82%) 3	0 / 14 (0.00%) 0
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	1 / 34 (2.94%) 1	1 / 14 (7.14%) 1
Abdominal pain subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	1 / 34 (2.94%) 1	1 / 14 (7.14%) 1
Constipation subjects affected / exposed occurrences (all)	7 / 33 (21.21%) 8	7 / 34 (20.59%) 8	1 / 14 (7.14%) 1
Diarrhoea subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 11	6 / 34 (17.65%) 6	1 / 14 (7.14%) 1
Dyspepsia			

subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	1 / 34 (2.94%) 1	0 / 14 (0.00%) 0
Dysphagia subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	1 / 34 (2.94%) 1	0 / 14 (0.00%) 0
Haematochezia subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 34 (0.00%) 0	1 / 14 (7.14%) 1
Nausea subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	6 / 34 (17.65%) 7	2 / 14 (14.29%) 2
Vomiting subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	2 / 34 (5.88%) 2	1 / 14 (7.14%) 1
Skin and subcutaneous tissue disorders			
Decubitus ulcer subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	2 / 34 (5.88%) 2	1 / 14 (7.14%) 1
Dry skin subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	0 / 34 (0.00%) 0	1 / 14 (7.14%) 1
Hyperhidrosis subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	1 / 34 (2.94%) 1	0 / 14 (0.00%) 0
Pruritus subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	2 / 34 (5.88%) 2	1 / 14 (7.14%) 1
Rash maculo-papular subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	2 / 34 (5.88%) 2	0 / 14 (0.00%) 0
Seborrhoeic dermatitis subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 34 (0.00%) 0	1 / 14 (7.14%) 1
Renal and urinary disorders			
Dysuria			

subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	2 / 34 (5.88%) 2	0 / 14 (0.00%) 0
Haematuria subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 34 (0.00%) 0	1 / 14 (7.14%) 1
Renal failure subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	0 / 34 (0.00%) 0	0 / 14 (0.00%) 0
Endocrine disorders Adrenal insufficiency subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 34 (0.00%) 0	1 / 14 (7.14%) 1
Hypothyroidism subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	1 / 34 (2.94%) 1	1 / 14 (7.14%) 1
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	4 / 34 (11.76%) 5	0 / 14 (0.00%) 0
Back pain subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 4	3 / 34 (8.82%) 3	1 / 14 (7.14%) 1
Bone pain subjects affected / exposed occurrences (all)	4 / 33 (12.12%) 4	4 / 34 (11.76%) 7	1 / 14 (7.14%) 1
Muscle spasms subjects affected / exposed occurrences (all)	6 / 33 (18.18%) 6	4 / 34 (11.76%) 6	1 / 14 (7.14%) 1
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	0 / 34 (0.00%) 0	1 / 14 (7.14%) 2
Neck pain subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	2 / 34 (5.88%) 2	0 / 14 (0.00%) 0
Pain in extremity			

subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	2 / 34 (5.88%) 2	1 / 14 (7.14%) 1
Spinal pain subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	2 / 34 (5.88%) 2	0 / 14 (0.00%) 0
Infections and infestations			
Bronchitis subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	3 / 34 (8.82%) 3	0 / 14 (0.00%) 0
Cellulitis subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	0 / 34 (0.00%) 0	0 / 14 (0.00%) 0
Escherichia infection subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 34 (0.00%) 0	1 / 14 (7.14%) 1
Herpes virus infection subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	2 / 34 (5.88%) 2	1 / 14 (7.14%) 1
Influenza subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 2	2 / 34 (5.88%) 2	0 / 14 (0.00%) 0
Localised infection subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	2 / 34 (5.88%) 2	0 / 14 (0.00%) 0
Lower respiratory tract infection subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 2	4 / 34 (11.76%) 5	0 / 14 (0.00%) 0
Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 3	4 / 34 (11.76%) 7	1 / 14 (7.14%) 1
Oral candidiasis subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	2 / 34 (5.88%) 2	0 / 14 (0.00%) 0
Pneumonia subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	3 / 34 (8.82%) 3	3 / 14 (21.43%) 3

Pneumonia respiratory syncytial viral subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 34 (0.00%) 0	1 / 14 (7.14%) 1
Respiratory tract infection subjects affected / exposed occurrences (all)	6 / 33 (18.18%) 6	2 / 34 (5.88%) 2	1 / 14 (7.14%) 1
Sepsis subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 34 (0.00%) 0	1 / 14 (7.14%) 1
Skin infection subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 34 (0.00%) 0	1 / 14 (7.14%) 1
Upper respiratory tract infection subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 4	2 / 34 (5.88%) 2	1 / 14 (7.14%) 2
Urinary tract infection subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 3	8 / 34 (23.53%) 11	0 / 14 (0.00%) 0
Metabolism and nutrition disorders			
Acidosis subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	0 / 34 (0.00%) 0	1 / 14 (7.14%) 1
Decreased appetite subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	5 / 34 (14.71%) 7	0 / 14 (0.00%) 0
Fluid overload subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	2 / 34 (5.88%) 2	0 / 14 (0.00%) 0
Hypercalcaemia subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	1 / 34 (2.94%) 1	0 / 14 (0.00%) 0
Hyperglycaemia subjects affected / exposed occurrences (all)	0 / 33 (0.00%) 0	2 / 34 (5.88%) 2	2 / 14 (14.29%) 4
Hyperkalaemia			

subjects affected / exposed	1 / 33 (3.03%)	4 / 34 (11.76%)	3 / 14 (21.43%)
occurrences (all)	3	6	4
Hyperphosphataemia			
subjects affected / exposed	0 / 33 (0.00%)	2 / 34 (5.88%)	1 / 14 (7.14%)
occurrences (all)	0	2	1
Hyperuricaemia			
subjects affected / exposed	1 / 33 (3.03%)	0 / 34 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Hypoalbuminaemia			
subjects affected / exposed	1 / 33 (3.03%)	2 / 34 (5.88%)	2 / 14 (14.29%)
occurrences (all)	1	2	2
Hypocalcaemia			
subjects affected / exposed	1 / 33 (3.03%)	6 / 34 (17.65%)	2 / 14 (14.29%)
occurrences (all)	1	7	2
Hypokalaemia			
subjects affected / exposed	0 / 33 (0.00%)	3 / 34 (8.82%)	1 / 14 (7.14%)
occurrences (all)	0	4	1
Hypomagnesaemia			
subjects affected / exposed	1 / 33 (3.03%)	0 / 34 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 November 2013	Clarification about concomitant medications and additional assessments
24 June 2014	Updating biopsy assessments during screening and updated inclusion criteria

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported