Clinical trial results:
A PHASE 1/2 OPEN-LABEL MULTICENTER STUDY OF AVADOMIDE (CC-122) IN COMBINATION WITH R-CHOP-21 FOR PREVIOUSLY UNTREATED POOR-RISK (IPI 3) DIFFUSE LARGE B-CELL LYMPHOMA

Summary

EudraCT number	2016-003778-42
Trial protocol	ES BE
Global end of trial date	16 December 2020

Results information

Result version number	v1 (current)
This version publication date	07 May 2022
First version publication date	07 May 2022

Trial information

Trial identification

Sponsor protocol code	CC-122-DLBCL-002

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	16 December 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase 1: The primary objective of the Phase 1 portion of the study is to evaluate the safety and tolerability of avadomide (CC-122) in combination with R-CHOP-21 for first-line treatment of patients with poor-risk (IPI ≥ 3) diffuse large B-cell lymphoma (DLBCL) in order to identify an appropriate dose and schedule for further investigation in Phase 2. Phase 2: The primary objective of the Phase 2 portion of the study is to evaluate the rate of complete response when adding avadomide (CC-122) to the standard R-CHOP-21 regimen in first-line treatment of patients with poor-risk DLBCL

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	17 September 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	United States: 16
Worldwide total number of subjects	35
EEA total number of subjects	15

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	20
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

35 Participants Enrolled

Period 1

Period 1 title	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
Arm title	Arm 1

Arm description:

CC-122 1 mg, Days 1-5 and Days 8-12 (2 weeks out of 3) + R-CHOP-21

Arm type	Experimental
Investigational medicinal product name	CC-122
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

1mg

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use

Dosage and administration details:

375mg/m²

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	CHOP
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use

Dosage and administration details:

750mg/m²

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	CHOP
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use

Dosage and administration details:

50mg/m²

Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	CHOP

Pharmaceutical forms	Infusion
Routes of administration	Intravascular use
Dosage and administration details: 1.4mg/m² (max 2.0mg total)	
Investigational medicinal product name	Prednisone/Prednisolone
Investigational medicinal product code	
Other name	CHOP
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use
Dosage and administration details: 100mg	
Investigational medicinal product name	Pegylated Granulocyte Colony-Stimulating Factor
Investigational medicinal product code	
Other name	Peg-G-CSF
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use
Dosage and administration details: NA	
Arm title	Arm 2
Arm description: CC-122 2 mg, Days 1-5 and Days 8-12 (2 weeks out of 3) + R-CHOP-21	
Arm type	Experimental
Investigational medicinal product name	CC-122
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 2mg	
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use
Dosage and administration details: 375mg/m²	
Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	CHOP
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use
Dosage and administration details: 750mg/m²	
Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	CHOP
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use
Dosage and administration details: 50mg/m²	

Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	CHOP
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use
Dosage and administration details: 1.4mg/m² (max 2.0mg total)	
Investigational medicinal product name	Prednisone/Prednisolone
Investigational medicinal product code	
Other name	CHOP
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use
Dosage and administration details: 100mg	
Arm title	Arm 3
Arm description: CC-122 3 mg, Days 1-5 and Days 8-12 (2 weeks out of 3) + R-CHOP-21	
Arm type	Experimental
Investigational medicinal product name	CC-122
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 3mg	
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use
Dosage and administration details: 375mg/m²	
Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	CHOP
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use
Dosage and administration details: 750mg/m²	
Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	CHOP
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use
Dosage and administration details: 50mg/m²	
Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	CHOP
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use

Dosage and administration details: 1.4mg/m² (max 2.0mg total)	
Investigational medicinal product name	Prednisone/Prednisolone
Investigational medicinal product code	
Other name	CHOP
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use
Dosage and administration details: 100mg	
Arm title	Arm 4
Arm description: CC-122 3 mg, Days 1-5, Days 8-12, and Days 15-19 (3 weeks out of 3) + R-CHOP-21	
Arm type	Experimental
Investigational medicinal product name	CC-122
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 3mg	
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use
Dosage and administration details: 375mg/m²	
Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	CHOP
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use
Dosage and administration details: 750mg/m²	
Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	CHOP
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use
Dosage and administration details: 50mg/m²	
Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	CHOP
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use
Dosage and administration details: 1.4mg/m² (max 2.0mg total)	
Investigational medicinal product name	Prednisone/Prednisolone
Investigational medicinal product code	
Other name	CHOP

Pharmaceutical forms	Infusion
Routes of administration	Intravascular use

Dosage and administration details:
100mg

Number of subjects in period 1	Arm 1	Arm 2	Arm 3
Started	4	11	12
Completed	4	10	11
Not completed	0	1	1
Other Reasons	-	-	1
Death	-	1	-
Progressive Disease	-	-	-

Number of subjects in period 1	Arm 4
Started	8
Completed	7
Not completed	1
Other Reasons	-
Death	-
Progressive Disease	1

Baseline characteristics

Reporting groups	
Reporting group title	Arm 1
Reporting group description:	
CC-122 1 mg, Days 1-5 and Days 8-12 (2 weeks out of 3) + R-CHOP-21	
Reporting group title	Arm 2
Reporting group description:	
CC-122 2 mg, Days 1-5 and Days 8-12 (2 weeks out of 3) + R-CHOP-21	
Reporting group title	Arm 3
Reporting group description:	
CC-122 3 mg, Days 1-5 and Days 8-12 (2 weeks out of 3) + R-CHOP-21	
Reporting group title	Arm 4
Reporting group description:	
CC-122 3 mg, Days 1-5, Days 8-12, and Days 15-19 (3 weeks out of 3) + R-CHOP-21	

Reporting group values	Arm 1	Arm 2	Arm 3
Number of subjects	4	11	12
Age Categorical Units: Subjects			
Adults (18-64 years)	3	4	4
From 65-84 years	1	7	8
Age Continuous Units: years			
arithmetic mean	63.3	64.7	62.6
standard deviation	± 6.18	± 8.56	± 15.29
Gender Categorical Units: Subjects			
Female	4	5	6
Male	0	6	6
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Black or African American	0	0	2
Native Hawaiian or Other Pacific Islander	0	0	0
White	4	9	9
Not Collected or Reported	0	1	1
Other	0	1	0
Ethnicity Units: Subjects			
Hispanic of Latino	0	1	0
Not Hispanic or Latino	3	10	11
Not Reported	1	0	1
Unknown	0	0	0

Reporting group values	Arm 4	Total	
Number of subjects	8	35	

Age Categorical Units: Subjects			
Adults (18-64 years)	4	15	
From 65-84 years	4	20	
Age Continuous Units: years			
arithmetic mean	59.3		
standard deviation	± 13.81	-	
Gender Categorical Units: Subjects			
Female	2	17	
Male	6	18	
Race Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Black or African American	0	2	
Native Hawaiian or Other Pacific Islander	0	0	
White	8	30	
Not Collected or Reported	0	2	
Other	0	1	
Ethnicity Units: Subjects			
Hispanic of Latino	2	3	
Not Hispanic or Latino	6	30	
Not Reported	0	2	
Unknown	0	0	

Subject analysis sets	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description: Safety Population	
Subject analysis set title	DL/T Evaluable
Subject analysis set type	Sub-group analysis
Subject analysis set description: DLT Evaluable Population	

Reporting group values	Safety Population	DL/T Evaluable	
Number of subjects	35	35	
Age Categorical Units: Subjects			
Adults (18-64 years)	15	15	
From 65-84 years	20	20	
Age Continuous Units: years			
arithmetic mean	62.6	62.6	
standard deviation	± 12.00	± 12.0	

Gender Categorical Units: Subjects			
Female	17	17	
Male	18	18	
Race Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Black or African American	2	2	
Native Hawaiian or Other Pacific Islander	0	0	
White	30	30	
Not Collected or Reported	2	2	
Other	1	1	
Ethnicity Units: Subjects			
Hispanic of Latino	3	3	
Not Hispanic or Latino	30	30	
Not Reported	2	2	
Unknown	0	0	

End points

End points reporting groups

Reporting group title	Arm 1
Reporting group description: CC-122 1 mg, Days 1-5 and Days 8-12 (2 weeks out of 3) + R-CHOP-21	
Reporting group title	Arm 2
Reporting group description: CC-122 2 mg, Days 1-5 and Days 8-12 (2 weeks out of 3) + R-CHOP-21	
Reporting group title	Arm 3
Reporting group description: CC-122 3 mg, Days 1-5 and Days 8-12 (2 weeks out of 3) + R-CHOP-21	
Reporting group title	Arm 4
Reporting group description: CC-122 3 mg, Days 1-5, Days 8-12, and Days 15-19 (3 weeks out of 3) + R-CHOP-21	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description: Safety Population	
Subject analysis set title	DL/T Evaluable
Subject analysis set type	Sub-group analysis
Subject analysis set description: DLT Evaluable Population	

Primary: Rate of Dose Limiting Toxicities (DLTs)

End point title	Rate of Dose Limiting Toxicities (DLTs)[1]
End point description: Dose limiting toxicity (DLT) is defined as an event related to CC-122 or its combination with R-CHOP-21 and meeting at least one of non-hematologic DLTs or Hematologic DLTs criteria.	
End point type	Primary
End point timeframe: Up to six 21-day cycles	

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 analysis planned for this endpoint in Phase I.

End point values	Arm 1	Arm 2	Arm 3	Arm 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	11	12	8
Units: Percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 60.2)	18.2 (2.3 to 51.8)	16.7 (2.1 to 48.4)	25.0 (3.2 to 65.1)

End point values	DL/T Evaluable			
Subject group type	Subject analysis set			
Number of subjects analysed	35			
Units: Percentage of participants				

number (confidence interval 95%)	17.1 (6.6 to 33.6)			

Statistical analyses

No statistical analyses for this end point

Primary: Complete Response Rate (CRR)

End point title	Complete Response Rate (CRR)[2]

End point description:

Complete response rate (CRR) is the percentage of participants experiencing positron emission tomography (PET)-negative complete response (CR); Score 1, 2, or 3a with or without a residual mass on 5PSb. Uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.

End point type	Primary

End point timeframe:

6-8 weeks after completion of treatment

Notes:

[2] - 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 analysis planned for this endpoint in Phase I.

End point values	Arm 1	Arm 2	Arm 3	Arm 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	11	12	8
Units: Percentage of participants				
number (confidence interval 95%)	75.0 (19.41 to 99.37)	81.8 (48.22 to 97.72)	91.7 (61.52 to 99.79)	75.0 (34.91 to 96.81)

End point values	Safety Population			
Subject group type	Subject analysis set			
Number of subjects analysed	35			
Units: Percentage of participants				
number (confidence interval 95%)	82.9 (66.35 to 93.44)			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

Objective response rate (ORR) is defined as the percentage of participants with partial response (PR); ≥

50% decrease in sum of perpendicular diameters (SPD) of up to 6 target measurable nodes and extranodal sites or complete response (CR); Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi.

End point type	Secondary

End point timeframe:

After 4 and 6 treatment cycles, and at 6, 12, 18 and 24 months after enrollment

End point values	Arm 1	Arm 2	Arm 3	Arm 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	11	12	8
Units: Percentage of participants				
number (confidence interval 95%)	100.0 (39.76 to 100.00)	81.8 (48.22 to 97.72)	91.7 (61.52 to 99.79)	87.5 (47.35 to 99.68)

End point values	Safety Population			
Subject group type	Subject analysis set			
Number of subjects analysed	35			
Units: Percentage of participants				
number (confidence interval 95%)	88.6 (73.26 to 96.80)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)

End point description:

Progression-free survival (PFS) is defined as the time from the start of treatment to the first documented disease progression or death due to any cause, whichever occurs first. Progression is defined per Lugano Classification criteria.
99999=NA

End point type	Secondary

End point timeframe:

Up to 24 months after last subject is enrolled

End point values	Arm 1	Arm 2	Arm 3	Arm 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	11	12	8
Units: Months				
median (confidence interval 95%)	18.2 (5.09 to 99999)	99999 (5.55 to 99999)	99999 (99999 to 99999)	99999 (0.76 to 99999)

End point values	Safety Population			
Subject group type	Subject analysis set			
Number of subjects analysed	35			
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Event-Free Survival (EFS)

End point title	Event-Free Survival (EFS)

End point description:

Event-free survival (EFS) is defined as the time from the first dosing date of any study drug to the first event of relapse or progression, unplanned re-treatment of lymphoma after initial immunochemotherapy, or death from any cause, whichever occurs first.
99999=NA

End point type	Secondary

End point timeframe:

12 and 24 months after enrollment

End point values	Arm 1	Arm 2	Arm 3	Arm 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	11	12	8
Units: Months				
median (confidence interval 95%)	18.2 (5.09 to 99999)	99999 (5.55 to 99999)	99999 (99999 to 99999)	99999 (0.76 to 99999)

End point values	Safety Population			
Subject group type	Subject analysis set			
Number of subjects analysed	35			
Units: Months				
median (confidence interval 95%)	99999 (99999			

	to 99999)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival (OS) is defined as the time from the first dosing date to death from any cause. OS will be censored at the last date that the participant was known to be alive for participants who were alive at the time of analysis and for participants who were lost to follow-up before death was documented.
99999=NA

End point type	Secondary

End point timeframe:

24 months after enrollment (Cycle 1, Day 1)

End point values	Arm 1	Arm 2	Arm 3	Arm 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	11	12	8
Units: Months				
median (confidence interval 95%)	99999 (14.13 to 99999)	99999 (9.23 to 99999)	99999 (99999 to 99999)	99999 (2.07 to 99999)

End point values	Safety Population			
Subject group type	Subject analysis set			
Number of subjects analysed	35			
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)			

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)

End point description:

Number of Participants with any grade, grade 3-4, and grade 5 Treatment Emergent Adverse Events (TEAEs) including their attribution to treatment with investigational products

End point type	Secondary

End point timeframe:

From first dose until 28 days post last dose

End point values	Arm 1	Arm 2	Arm 3	Arm 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	11	12	8
Units: Participants				
Any Grade TEAE	4	11	11	8
Any Grade TEAE related to CC-122/R-CHOP	4	11	11	8
Grade 3-4 TEAE	3	9	9	7
Grade 3-4 TEAE related to CC-122/R-CHOP	3	9	8	6
Grade 5 TEAE	0	1	0	0
Grade 5 TEAE related to CC-122/R-CHOP	0	1	0	0

End point values	Safety Population			
Subject group type	Subject analysis set			
Number of subjects analysed	35			
Units: Participants				
Any Grade TEAE	34			
Any Grade TEAE related to CC-122/R-CHOP	34			
Grade 3-4 TEAE	28			
Grade 3-4 TEAE related to CC-122/R-CHOP	26			
Grade 5 TEAE	1			
Grade 5 TEAE related to CC-122/R-CHOP	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: SAEs and AEs are collected from first dose to 28 days post last dose Death is collected up from first patient first visit to last patient last visit	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups	
Reporting group title	Arm 1
Reporting group description: mg (Days 1-5 and Days 8-12 (5/7 days; 2 out of 3 weeks)	
Reporting group title	Arm 4
Reporting group description: 3 mg (Days 1-5, Days 8-12, and Days 15-19 (5/7 days; 3 out of 3 weeks)	
Reporting group title	Arm 3
Reporting group description: 3 mg (Days 1-5 and Days 8-12 (5/7 days; 2 out of weeks)	
Reporting group title	Arm 2
Reporting group description: 2 mg (Days 1-5 and Days 8-12 (5/7 days; 2 out of 3 weeks)	

Serious adverse events	Arm 1	Arm 4	Arm 3
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 4 (25.00%)	3 / 8 (37.50%)	4 / 12 (33.33%)
number of deaths (all causes)	1	1	1
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure			

subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 12 (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
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	2 / 12 (16.67%)
occurrences causally related to treatment / all	0 / 0	1 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
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 failure			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteoarthritis			

subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Hepatic infection bacterial			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes virus infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 12 (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
Skin infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Arm 2		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 11 (27.27%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	1		

Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			

subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	1 / 1			
Musculoskeletal and connective tissue disorders				
Osteoarthritis				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pathological fracture				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Hepatic infection bacterial				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes virus infection				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin infection				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Upper respiratory tract infection			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Arm 1	Arm 4	Arm 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	8 / 8 (100.00%)	11 / 12 (91.67%)
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Deep vein thrombosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Hot flush			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Hypertension			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Hypotension			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	3 / 12 (25.00%)
occurrences (all)	0	0	3
Phlebitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 4 (50.00%)	1 / 8 (12.50%)	0 / 12 (0.00%)
occurrences (all)	2	1	0
Chills			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2

Device related thrombosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Early satiety			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Malaise			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Fatigue			
subjects affected / exposed	1 / 4 (25.00%)	2 / 8 (25.00%)	4 / 12 (33.33%)
occurrences (all)	2	2	8
Non-cardiac chest pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	1 / 4 (25.00%)	1 / 8 (12.50%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
Pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Performance status decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Peripheral swelling			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	1 / 4 (25.00%)	2 / 8 (25.00%)	1 / 12 (8.33%)
occurrences (all)	1	3	1
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			

Vulvovaginal pruritus			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Vulvovaginal dryness			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	2 / 12 (16.67%)
occurrences (all)	0	1	4
Dyspnoea			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Dysphonia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Emphysema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Nasal congestion			
subjects affected / exposed	1 / 4 (25.00%)	1 / 8 (12.50%)	3 / 12 (25.00%)
occurrences (all)	2	1	3
Epistaxis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Pneumonitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Productive cough			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	2 / 12 (16.67%)
occurrences (all)	2	0	2
Rhinorrhoea			

subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Sinus congestion			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 4 (25.00%)	1 / 8 (12.50%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Insomnia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Confusional state			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	2 / 12 (16.67%)
occurrences (all)	1	0	3
Blood creatinine increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	4	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	3
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Blood glucose increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Blood pressure decreased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Brain natriuretic peptide increased			

subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	1
C-reactive protein increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	1	0	2
Eosinophil count increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	3 / 12 (25.00%)
occurrences (all)	2	0	5
Neutrophil count decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Transaminases increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Red blood cell count decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Troponin T increased			
subjects affected / exposed	1 / 4 (25.00%)	1 / 8 (12.50%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Weight decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Troponin increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Allergic transfusion reaction			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Procedural complication			

subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Fall			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Infusion related reaction			
subjects affected / exposed	1 / 4 (25.00%)	2 / 8 (25.00%)	1 / 12 (8.33%)
occurrences (all)	1	2	1
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Atrial tachycardia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Cardiac failure			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Palpitations			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Supraventricular tachycardia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 4 (0.00%)	2 / 8 (25.00%)	2 / 12 (16.67%)
occurrences (all)	0	2	2
Dysgeusia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	2 / 12 (16.67%)
occurrences (all)	0	1	2
Drooling			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Headache			

subjects affected / exposed	0 / 4 (0.00%)	3 / 8 (37.50%)	1 / 12 (8.33%)
occurrences (all)	0	3	1
Hypoaesthesia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Paraesthesia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 8 (25.00%)	1 / 12 (8.33%)
occurrences (all)	0	2	1
Peripheral motor neuropathy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 4 (0.00%)	3 / 8 (37.50%)	3 / 12 (25.00%)
occurrences (all)	0	5	3
Sudden onset of sleep			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 4 (50.00%)	4 / 8 (50.00%)	4 / 12 (33.33%)
occurrences (all)	4	4	14
Febrile neutropenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Leukopenia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	5 / 12 (41.67%)
occurrences (all)	0	1	11
Lymphopenia			
subjects affected / exposed	1 / 4 (25.00%)	2 / 8 (25.00%)	2 / 12 (16.67%)
occurrences (all)	1	7	2
Neutropenia			
subjects affected / exposed	3 / 4 (75.00%)	4 / 8 (50.00%)	6 / 12 (50.00%)
occurrences (all)	10	9	12
Thrombocytopenia			
subjects affected / exposed	3 / 4 (75.00%)	0 / 8 (0.00%)	3 / 12 (25.00%)
occurrences (all)	3	0	6

Thrombocytosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Lacrimation increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Abdominal distension			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Abdominal pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Abdominal pain lower			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Abdominal pain upper			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Anal fissure			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Ascites			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Colitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	2 / 4 (50.00%)	5 / 8 (62.50%)	5 / 12 (41.67%)
occurrences (all)	2	5	5
Diarrhoea			

subjects affected / exposed	1 / 4 (25.00%)	1 / 8 (12.50%)	2 / 12 (16.67%)
occurrences (all)	1	1	2
Dry mouth			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Dyspepsia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Flatulence			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Gingival swelling			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	5 / 12 (41.67%)
occurrences (all)	0	0	7
Oral pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Rectal haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	3 / 4 (75.00%)	0 / 8 (0.00%)	2 / 12 (16.67%)
occurrences (all)	5	0	2
Vomiting			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0

Erythema			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Nail discolouration			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Rash erythematous			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Rash maculo-papular			
subjects affected / exposed	0 / 4 (0.00%)	2 / 8 (25.00%)	2 / 12 (16.67%)
occurrences (all)	0	2	5
Skin induration			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Skin fissures			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Urticaria			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Arthralgia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Bone pain			

subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Muscle spasms			
subjects affected / exposed	1 / 4 (25.00%)	1 / 8 (12.50%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
Muscular weakness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Musculoskeletal pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Myalgia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	1 / 12 (8.33%)
occurrences (all)	0	3	1
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Conjunctivitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Diverticulitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Folliculitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Furuncle			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Herpes simplex			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0

Influenza			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Oesophageal infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Oral candidiasis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	2 / 12 (16.67%)
occurrences (all)	0	1	4
Oral fungal infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Rhinovirus infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Sepsis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Staphylococcal infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Streptococcal infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Tooth infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	1 / 12 (8.33%)
occurrences (all)	0	1	1

Urinary tract infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Varicella zoster virus infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Hypermagnesaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Hyperkalaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Hypernatraemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Hyperphosphataemia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	1 / 12 (8.33%)
occurrences (all)	2	0	1
Hyperuricaemia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Hypocalcaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Hypokalaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	6
Hypomagnesaemia			

subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Hyponatraemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 8 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Hypophosphataemia			
subjects affected / exposed	1 / 4 (25.00%)	2 / 8 (25.00%)	2 / 12 (16.67%)
occurrences (all)	1	2	2
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 4 (25.00%)	1 / 8 (12.50%)	0 / 12 (0.00%)
occurrences (all)	3	1	0

Non-serious adverse events	Arm 2		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 11 (100.00%)		
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Deep vein thrombosis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Hot flush			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Hypertension			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Hypotension			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Phlebitis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			

Asthenia				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Chills				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Device related thrombosis				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Early satiety				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Malaise				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Fatigue				
subjects affected / exposed	2 / 11 (18.18%)			
occurrences (all)	2			
Non-cardiac chest pain				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Oedema peripheral				
subjects affected / exposed	3 / 11 (27.27%)			
occurrences (all)	4			
Pain				
subjects affected / exposed	2 / 11 (18.18%)			
occurrences (all)	3			
Performance status decreased				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Peripheral swelling				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Pyrexia				
subjects affected / exposed	3 / 11 (27.27%)			
occurrences (all)	4			

Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Vulvovaginal pruritus			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Vulvovaginal dryness			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Dyspnoea			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Dysphonia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Emphysema			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Nasal congestion			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Pneumonitis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		

Productive cough subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0		
Rhinorrhoea subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0		
Sinus congestion subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Insomnia subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0		
Confusional state subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0		
Blood creatinine increased subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0		
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Blood lactate dehydrogenase increased subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0		
Blood glucose increased subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Blood pressure decreased			

subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Brain natriuretic peptide increased			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
C-reactive protein increased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Eosinophil count increased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Neutrophil count decreased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Transaminases increased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Red blood cell count decreased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Troponin T increased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Weight decreased			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Troponin increased			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			

Allergic transfusion reaction subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0		
Procedural complication subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0		
Fall subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0		
Infusion related reaction subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0		
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	2 / 11 (18.18%) 2		
Atrial tachycardia subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Cardiac failure subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Palpitations subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1		
Supraventricular tachycardia subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	3 / 11 (27.27%) 3		
Dysgeusia subjects affected / exposed occurrences (all)	2 / 11 (18.18%) 2		
Drooling			

subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Hypoaesthesia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Paraesthesia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Peripheral motor neuropathy			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Peripheral sensory neuropathy			
subjects affected / exposed	7 / 11 (63.64%)		
occurrences (all)	11		
Sudden onset of sleep			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 11 (54.55%)		
occurrences (all)	19		
Febrile neutropenia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Leukopenia			
subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	6		
Lymphopenia			
subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	3		
Neutropenia			
subjects affected / exposed	8 / 11 (72.73%)		
occurrences (all)	14		

Thrombocytopenia			
subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	5		
Thrombocytosis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Eye disorders			
Lacrimation increased			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Abdominal distension			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Abdominal pain			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Abdominal pain lower			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Anal fissure			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Ascites			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Colitis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Constipation			

subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	3		
Diarrhoea			
subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	3		
Dry mouth			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Dyspepsia			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Flatulence			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Gingival swelling			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	5 / 11 (45.45%)		
occurrences (all)	5		
Oral pain			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Rectal haemorrhage			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	3 / 11 (27.27%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			

Alopecia			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	3		
Erythema			
subjects affected / exposed	2 / 11 (18.18%)		
occurrences (all)	2		
Nail discolouration			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	2		
Rash erythematous			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Rash maculo-papular			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Skin induration			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Skin fissures			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Urticaria			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Arthralgia			

subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Bone pain			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Muscle spasms			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Muscular weakness			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Musculoskeletal pain			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Conjunctivitis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Diverticulitis			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Folliculitis			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Furuncle			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		

Herpes simplex				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Influenza				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Nasopharyngitis				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Oesophageal infection				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Oral candidiasis				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Oral fungal infection				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Pneumonia				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Rhinovirus infection				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Sepsis				
subjects affected / exposed	0 / 11 (0.00%)			
occurrences (all)	0			
Staphylococcal infection				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Streptococcal infection				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			
Tooth infection				
subjects affected / exposed	1 / 11 (9.09%)			
occurrences (all)	1			

Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0			
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0			
Varicella zoster virus infection subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0			
Vulvovaginal candidiasis subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0			
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0			
Hypermagnesaemia subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0			
Hyperkalaemia subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0			
Hypernatraemia subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0			
Hyperphosphataemia subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0			
Hyperuricaemia subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0			
Hypocalcaemia subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1			
Hypokalaemia				

subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Hypomagnesaemia			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		
Hyponatraemia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	2		
Hypophosphataemia			
subjects affected / exposed	1 / 11 (9.09%)		
occurrences (all)	1		
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 11 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 April 2017	References to the generic drug name were deleted. This generic name was not yet approved outside the US and was not appropriate to reference in a multinational study. It was clarified that Grade 5 AEs would be tabulated and listed separately from Grade 3 or 4 AEs.
12 June 2017	The definition of DLT was updated according to feedback from the US Food and Drug Administration.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported