Clinical trial results:
A Phase 1 Study Of Ramucirumab, a Human Monoclonal Antibody Against the Vascular Endothelial Growth Factor-2 (VEGFR-2) Receptor in Children With Refractory Solid Tumors, Including CNS Tumors

Summary

EudraCT number	2021-000364-30
Trial protocol	Outside EU/EEA
Global end of trial date	16 July 2019

Results information

Result version number	v1
This version publication date	30 June 2021
First version publication date	30 June 2021

Trial information

Trial identification

Sponsor protocol code	I4T-MC-JVDA

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02564198
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 15542

Notes:

Sponsors

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, IN, United States, 46285
Public contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 877CTLilly,
Scientific contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 8772854559,

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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 July 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this study is to evaluate the safety of the study drug known as ramucirumab in children with recurrent or refractory solid tumors including central nervous system (CNS) tumors.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 December 2015
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	United States: 29
Worldwide total number of subjects	29
EEA total number of subjects	0

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)	1
Children (2-11 years)	10
Adolescents (12-17 years)	14
Adults (18-64 years)	4
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

No Text Available

Pre-assignment

Screening details:

Completers included participants who had progressive disease, death due to any cause or alive and on study at conclusion, but off treatment.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	8 mg/kg Ramucirumab (Part A)

Arm description:

Participants received 8 milligram per kilogram [mg/kg] Ramucirumab administered as an intravenous infusion every 2 weeks (Q2W) with 3 doses per 42 day cycle.

Arm type	Experimental
Investigational medicinal product name	Ramucirumab
Investigational medicinal product code	
Other name	IMC-1121B, Cyramza, LY3009806
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received 8 mg/kg Ramucirumab administered as an intravenous infusion.

Arm title	12 mg/kg Ramucirumab (Part A)

Arm description:

Participants received 12 mg/kg Ramucirumab as an intravenous injection Q2W with 3 doses per cycle.

Arm type	Experimental
Investigational medicinal product name	Ramucirumab
Investigational medicinal product code	
Other name	IMC-1121B, Cyramza, LY3009806
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received 12 mg/kg Ramucirumab administered as an intravenous infusion.

Arm title	12 mg/kg Ramucirumab (Part B)

Arm description:

Participants received 12 mg/kg Ramucirumab as an intravenous injection Q2W with 3 doses per cycle.

Arm type	Experimental
Investigational medicinal product name	Ramucirumab
Investigational medicinal product code	
Other name	IMC-1121B, Cyramza, LY3009806
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received 12 mg/kg Ramucirumab administered as an intravenous infusion.

Number of subjects in period 1	8 mg/kg Ramucirumab (Part A)	12 mg/kg Ramucirumab (Part A)	12 mg/kg Ramucirumab (Part B)
Started	8	15	6
Received at least 1 dose of study drug	8	15	6
Completed	6	10	6
Not completed	2	5	0
Consent withdrawn by subject	2	4	-
Adverse event, non-fatal	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	8 mg/kg Ramucirumab (Part A)
Reporting group description:	
Participants received 8 milligram per kilogram [mg/kg] Ramucirumab administered as an intravenous infusion every 2 weeks (Q2W) with 3 doses per 42 day cycle.	
Reporting group title	12 mg/kg Ramucirumab (Part A)
Reporting group description:	
Participants received 12 mg/kg Ramucirumab as an intravenous injection Q2W with 3 doses per cycle.	
Reporting group title	12 mg/kg Ramucirumab (Part B)
Reporting group description:	
Participants received 12 mg/kg Ramucirumab as an intravenous injection Q2W with 3 doses per cycle.	

Reporting group values	8 mg/kg Ramucirumab (Part A)	12 mg/kg Ramucirumab (Part A)	12 mg/kg Ramucirumab (Part B)
Number of subjects	8	15	6
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	15.8	11.9	9.7
standard deviation	± 3.33	± 5.59	± 5.9
Gender categorical Units: Subjects			
Female	4	6	2
Male	4	9	4
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	2	2
Not Hispanic or Latino	6	12	4
Unknown or Not Reported	0	1	0
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	2	1

White	7	12	4
More than one race	0	0	0
Unknown or Not Reported	1	1	1
Region of Enrollment Units: Subjects			
United States	8	15	6

Reporting group values	Total		
Number of subjects	29		
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)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	12		
Male	17		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	6		
Not Hispanic or Latino	22		
Unknown or Not Reported	1		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	0		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	3		
White	23		
More than one race	0		
Unknown or Not Reported	3		
Region of Enrollment Units: Subjects			
United States	29		

End points

End points reporting groups

Reporting group title	8 mg/kg Ramucirumab (Part A)
Reporting group description:	
Participants received 8 milligram per kilogram [mg/kg] Ramucirumab administered as an intravenous infusion every 2 weeks (Q2W) with 3 doses per 42 day cycle.	
Reporting group title	12 mg/kg Ramucirumab (Part A)
Reporting group description:	
Participants received 12 mg/kg Ramucirumab as an intravenous injection Q2W with 3 doses per cycle.	
Reporting group title	12 mg/kg Ramucirumab (Part B)
Reporting group description:	
Participants received 12 mg/kg Ramucirumab as an intravenous injection Q2W with 3 doses per cycle.	
Subject analysis set title	8 mg/kg Ramucirumab
Subject analysis set type	Per protocol
Subject analysis set description:	
Participants received 8 mg/kg Ramucirumab administered as an intravenous infusion Q2W with 3 doses per 42 day cycle.	
Subject analysis set title	12 mg/kg Ramucirumab
Subject analysis set type	Per protocol
Subject analysis set description:	
Participants received 12 mg/kg Ramucirumab as an intravenous injection Q2W with 3 doses per cycle.	

Primary: Number of participants with Dose Limiting Toxicities (DLTs): Maximum Tolerated Dose of Ramucirumab

End point title	Number of participants with Dose Limiting Toxicities (DLTs): Maximum Tolerated Dose of Ramucirumab[1][2]
End point description:	
A DLT is defined as an Adverse Event (AE) that is likely related to the study medication or combination, and fulfills any one of the following criteria, graded according to the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0: 1. Any death not clearly due to the underlying disease or extraneous causes 2. Neutropenic fever 2. Any Grade ≥3 non-hematologic toxicity 3. Grade ≥4 neutropenia or thrombocytopenia >7 days 4. Grade ≥3 thrombocytopenia with bleeding 5. Grade ≥3 nausea/vomiting or diarrhea>72 hours with adequate antiemetic and other supportive care 6. Grade ≥3 fatigue ≥1 week 7. Grade ≥3 electrolyte abnormality that lasts>72 hours, unless the Participant has clinical symptoms, in which case all Grade 3+electrolyte abnormality regardless of duration should count as a DLT. Analysis Population Description (APD): All randomized participants who received at least one dose of study drug.	
End point type	Primary
End point timeframe:	
Baseline to Study Completion (Up to 42 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: No inferential statistics were planned for this endpoint.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No inferential statistics were planned for this endpoint.

End point values	8 mg/kg Ramucirumab (Part A)	12 mg/kg Ramucirumab (Part A)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	15		
Units: Participants				
number (not applicable)	1	1		

Statistical analyses

No statistical analyses for this end point

Primary: Population Pharmacokinetics (PK): Minimum Concentration (Cmin) of Ramucirumab

End point title	Population Pharmacokinetics (PK): Minimum Concentration (Cmin) of Ramucirumab[3]

End point description:

Population Pharmacokinetics (PK): Minimum observed plasma concentration of Ramucirumab.

APD: All randomized participants who received at least one dose of study drug and had evaluable PK data.

End point type	Primary

End point timeframe:

Predose, Cycle 1 Day 1 (end of infusion (EOI), 1 hour after EOI) and Cycle 1 Day 43 (1 hour after EOI)

Notes:

[3] - 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: No inferential statistics were planned for this endpoint.

End point values	8 mg/kg Ramucirumab	12 mg/kg Ramucirumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8[4]	19[5]		
Units: microgram per milliliter (µg/mL)				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1	30.0 (± 32)	48.3 (± 41)		
Cycle 1 Day 43	53.6 (± 31)	80.2 (± 44)		

Notes:

[4] - Cycle 1 Day 1: 8 participants
Cycle 1 Day 43: 4 participants
[5] - Cycle 1 Day 1: 19 participants
Cycle 1 Day 43: 16 participants

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with Anti-Ramucirumab Antibodies

End point title	Number of Participants with Anti-Ramucirumab Antibodies[6]

End point description:

Number of participants with positive treatment emergent anti-ramucirumab antibodies was summarized by treatment group. A treatment-emergent anti-drug antibodies (TEADA) sample was defined as: a post

treatment sample with at least a 4-fold increase in titer from pre treatment sample; or 1:20 post treatment titer for participants that had no detectable ADA titer at baseline.

APD: All randomized participants who received at least one dose of study drug.

End point type	Primary

End point timeframe:

Predose Cycle 1 Day 1 through Follow-Up (Up to 42 Months)

Notes:

[6] - 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: No inferential statistics were planned for this endpoint.

End point values	8 mg/kg Ramucirumab (Part A)	12 mg/kg Ramucirumab (Part A)	12 mg/kg Ramucirumab (Part B)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	15	6	
Units: participants				
number (not applicable)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR): Percentage of Participants Who Achieve Complete Response (CR) or Partial Response (PR)

End point title	Overall Response Rate (ORR): Percentage of Participants Who Achieve Complete Response (CR) or Partial Response (PR)

End point description:

ORR is the best response of complete response (CR) or partial response (PR) as classified by the independent central review according to the Response Evaluation Criteria In Solid Tumors (RECIST v1.1). CR is a disappearance of all target and non-target lesions and normalization of tumor marker level. PR is an at least 30% decrease in the sum of the diameters of target lesions (taking as reference the baseline sum diameter) without progression of non-target lesions or appearance of new lesions. Overall response rate is calculated as a total number of participants with CR or PR divided by the total number of participants per cohort with at least 1 measurable lesion, multiplied by 100. Progressive Disease (PD) was at least a 20% increase in the sum of the diameters of target lesions, with reference being the smallest sum on study and an absolute increase of at least 5 mm, or unequivocal progression of non-target lesions, or 1 or more new lesions.
APD: All randomized participants.

End point type	Secondary

End point timeframe:

Baseline to Date of Objective Disease Progression (Up to 42 Months)

End point values	8 mg/kg Ramucirumab (Part A)	12 mg/kg Ramucirumab (Part A)	12 mg/kg Ramucirumab (Part B)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	15	6	
Units: Percentage of participants				
number (confidence interval 95%)	0 (0.0 to 41.0)	0 (0.0 to 23.2)	0 (0.0 to 45.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With a Best Overall Response of Complete Response (CR), Partial Response (PR) or Stable Disease (SD): Disease Control Rate (DCR)

End point title	Percentage of Participants With a Best Overall Response of Complete Response (CR), Partial Response (PR) or Stable Disease (SD): Disease Control Rate (DCR)

End point description:

Disease Control Rate (DCR) was the percentage of participants with a best overall response of CR, PR, or Stable Disease (SD) as per Response using RECIST v1.1 criteria. CR defined as the disappearance of all target and non-target lesions and no appearance of new lesions. PR defined as at least a 30% decrease in the sum of the LD of target lesions (taking as reference the baseline sum LD), no progression of non-target lesions, and no appearance of new lesions. SD was neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD for target lesions, no progression of non-target lesions, and no appearance of new lesions. PD was at least a 20% increase in the sum of the diameters of target lesions, with reference being the smallest sum on study and an absolute increase of at least 5 mm, or unequivocal progression of non-target lesions, or 1 or more new lesions.

APD: All randomized participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Baseline to Date of Objective Disease Progression (Up to 42 Months)

End point values	8 mg/kg Ramucirumab (Part A)	12 mg/kg Ramucirumab (Part A)	12 mg/kg Ramucirumab (Part B)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	15	6	
Units: Percentage of participants				
number (confidence interval 95%)	62.5 (29.0 to 96.3)	40.0 (17.7 to 71.1)	33.3 (4.3 to 77.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

DOR was the time from the date of first evidence of complete response or partial response to the date of objective progression or the date of death due to any cause, whichever is earlier. CR and PR were

defined using the RECIST v1.1. CR defined as the disappearance of all target and non-target lesions and no appearance of new lesions. PR defined as at least a 30% decrease in the sum of the LD of target lesions (taking as reference the baseline sum LD), no progression of non-target lesions, and no appearance of new lesions. If a responder was not known to have died or have objective progression as of the data inclusion cutoff date, duration of response was censored at the last adequate tumor assessment date.
APD: Zero participants analyzed. Duration of response was not evaluable, as there were no participants with CR or PR.

End point type	Secondary

End point timeframe:

Date of Complete Response (CR) or Partial Response (PR) to Date of Objective Disease Progression or Death Due to Any Cause (Up to 42 Months)

End point values	8 mg/kg Ramucirumab (Part A)	12 mg/kg Ramucirumab (Part A)	12 mg/kg Ramucirumab (Part B)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[7]	0[8]	0[9]	
Units: Months				
median (confidence interval 95%)	(to)	(to)	(to)	

Notes:

[7] - Writer To Revise

[8] - Writer To Revise

[9] - Writer To Revise

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival is defined as the time from date of randomization to the date of death (due to any cause). For participants whose last known status is alive at the data cutoff date for the analysis, time will be censored as the last contact date prior to the data cutoff date.

APD: Zero participants analyzed. Overall survival was not evaluable, as there were no deaths observed in this study.

End point type	Secondary

End point timeframe:

Baseline to Date of Death from Any Cause (Up to 42 Months)

End point values	8 mg/kg Ramucirumab (Part A)	12 mg/kg Ramucirumab (Part A)	12 mg/kg Ramucirumab (Part B)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[10]	0[11]	0[12]	
Units: Months				
median (confidence interval 95%)	(to)	(to)	(to)	

Notes:
[10] - Writer To Revise
[11] - Writer To Revise
[12] - Writer To Revise

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline, up to 4 years 8 months	
Adverse event reporting additional description:	
I4T-MC-JVDA	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups	
Reporting group title	8 mg/kg Ramucirumab (Part A)
Reporting group description: -	
Reporting group title	12 mg/kg Ramucirumab (Part A)
Reporting group description: -	
Reporting group title	12 mg/kg Ramucirumab (Part B)
Reporting group description: -	

Serious adverse events	8 mg/kg Ramucirumab (Part A)	12 mg/kg Ramucirumab (Part A)	12 mg/kg Ramucirumab (Part B)
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 8 (37.50%)	7 / 15 (46.67%)	2 / 6 (33.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
tumour pain			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (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
Injury, poisoning and procedural complications			
fracture			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (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
Vascular disorders			

hypertension			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	0 / 15 (0.00%)	0 / 6 (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
hypotension			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
headache			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	0 / 15 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
paraesthesia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (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
peripheral motor neuropathy			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (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
seizure			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	0 / 15 (0.00%)	1 / 6 (16.67%)
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 disorders and administration site conditions			
pyrexia			

alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	3 / 15 (20.00%)	0 / 6 (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
Gastrointestinal disorders			
abdominal pain			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
dyspnoea			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	2 / 15 (13.33%)	0 / 6 (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
hypoxia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	2 / 15 (13.33%)	0 / 6 (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
pulmonary haemorrhage			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (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 and urinary disorders			
urinary tract obstruction			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (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
Musculoskeletal and connective tissue disorders			

bone pain			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (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			
infection			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (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
kidney infection			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	0 / 15 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pneumonia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (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	8 mg/kg Ramucirumab (Part A)	12 mg/kg Ramucirumab (Part A)	12 mg/kg Ramucirumab (Part B)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)	15 / 15 (100.00%)	6 / 6 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
tumour haemorrhage			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
tumour pain			
alternative dictionary used:			

MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	0 / 15 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Vascular disorders			
flushing			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	2 / 15 (13.33%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
hypertension			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 8 (25.00%)	6 / 15 (40.00%)	2 / 6 (33.33%)
occurrences (all)	2	13	3
hypotension			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	3 / 15 (20.00%)	1 / 6 (16.67%)
occurrences (all)	0	8	2
General disorders and administration site conditions			
chills			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
face oedema			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	2 / 15 (13.33%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
facial pain			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
fatigue			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	8 / 15 (53.33%)	1 / 6 (16.67%)
occurrences (all)	1	9	1
impaired healing			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	1 / 8 (12.50%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
localised oedema			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
malaise			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
non-cardiac chest pain			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
pain			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
pyrexia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	6 / 15 (40.00%)	1 / 6 (16.67%)
occurrences (all)	1	6	1
swelling			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
hypersensitivity			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	2 / 15 (13.33%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Respiratory, thoracic and mediastinal disorders			
aphonia			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	0 / 8 (0.00%)	0 / 15 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
aspiration			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
atelectasis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
cough			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	7 / 15 (46.67%)	2 / 6 (33.33%)
occurrences (all)	1	10	3
dyspnoea			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	2 / 15 (13.33%)	1 / 6 (16.67%)
occurrences (all)	1	2	2
epistaxis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	2 / 15 (13.33%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
nasal congestion			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	5 / 15 (33.33%)	1 / 6 (16.67%)
occurrences (all)	1	5	1
oropharyngeal pain			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	4 / 15 (26.67%)	1 / 6 (16.67%)
occurrences (all)	0	4	1
productive cough			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1

rhinitis allergic			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
rhinorrhoea			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	2 / 15 (13.33%)	2 / 6 (33.33%)
occurrences (all)	0	3	2
upper respiratory tract congestion			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
wheezing			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
anxiety			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	0 / 15 (0.00%)	2 / 6 (33.33%)
occurrences (all)	1	0	2
confusional state			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	0 / 15 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
depression			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
insomnia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
personality change			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Investigations			
activated partial thromboplastin time prolonged			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
alanine aminotransferase increased			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	6 / 15 (40.00%)	3 / 6 (50.00%)
occurrences (all)	1	7	3
anion gap increased			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
aspartate aminotransferase increased			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	12 / 15 (80.00%)	2 / 6 (33.33%)
occurrences (all)	1	14	2
bacterial test positive			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
blood alkaline phosphatase increased			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	4 / 15 (26.67%)	0 / 6 (0.00%)
occurrences (all)	1	5	0
blood bicarbonate decreased			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
blood bilirubin increased			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
blood cholesterol increased			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	2	1	0
blood creatinine increased			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	2 / 15 (13.33%)	1 / 6 (16.67%)
occurrences (all)	0	3	2
c-reactive protein increased			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	0 / 15 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
ejection fraction decreased			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
haemoglobin increased			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	1 / 15 (6.67%)	3 / 6 (50.00%)
occurrences (all)	2	6	5
international normalised ratio decreased			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
international normalised ratio increased			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	2 / 15 (13.33%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
lipase increased			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
lymphocyte count decreased			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	4 / 8 (50.00%)	2 / 15 (13.33%)	4 / 6 (66.67%)
occurrences (all)	7	2	5
neutrophil count decreased			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	5 / 15 (33.33%)	2 / 6 (33.33%)
occurrences (all)	2	6	2
platelet count decreased			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 8 (25.00%)	3 / 15 (20.00%)	2 / 6 (33.33%)
occurrences (all)	3	4	3
prothrombin time shortened			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
weight decreased			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
weight increased			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	1 / 6 (16.67%)
occurrences (all)	0	5	2
white blood cell count decreased			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 8 (25.00%)	6 / 15 (40.00%)	2 / 6 (33.33%)
occurrences (all)	2	7	2
Injury, poisoning and procedural complications			
arthropod bite			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
contusion			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
gastrostomy tube site complication			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
infusion related reaction			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
post procedural discharge			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
skin laceration			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
vascular access complication			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	0 / 15 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Cardiac disorders			
sinus bradycardia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
sinus tachycardia			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	2 / 8 (25.00%)	5 / 15 (33.33%)	2 / 6 (33.33%)
occurrences (all)	2	7	3
Nervous system disorders			
ataxia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	0 / 15 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
disturbance in attention			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
dizziness			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 8 (25.00%)	1 / 15 (6.67%)	1 / 6 (16.67%)
occurrences (all)	2	1	1
headache			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 8 (25.00%)	7 / 15 (46.67%)	0 / 6 (0.00%)
occurrences (all)	2	8	0
hemiparesis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	0 / 15 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
hypersomnia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
hypoaesthesia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	0 / 15 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
memory impairment			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	0 / 8 (0.00%)	0 / 15 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
sinus headache			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
somnolence			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 8 (25.00%)	9 / 15 (60.00%)	2 / 6 (33.33%)
occurrences (all)	4	9	3
eosinophilia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
ear pain			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	0 / 15 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
hypoacusis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
eye pain			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	2 / 15 (13.33%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
photophobia			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	1 / 8 (12.50%)	0 / 15 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
vision blurred			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	0 / 15 (0.00%)	2 / 6 (33.33%)
occurrences (all)	1	0	2
Gastrointestinal disorders			
abdominal pain			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 8 (25.00%)	5 / 15 (33.33%)	1 / 6 (16.67%)
occurrences (all)	2	6	2
abdominal pain upper			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
constipation			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	2 / 15 (13.33%)	2 / 6 (33.33%)
occurrences (all)	0	2	3
diarrhoea			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	1 / 15 (6.67%)	2 / 6 (33.33%)
occurrences (all)	1	1	2
dysphagia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	0 / 15 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
gastrooesophageal reflux disease			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	0 / 15 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
mouth ulceration			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
nausea			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	4 / 8 (50.00%)	7 / 15 (46.67%)	1 / 6 (16.67%)
occurrences (all)	5	7	1
oral disorder			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
periodontal disease			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
stomatitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
tongue geographic			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
vomiting			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	3 / 8 (37.50%)	7 / 15 (46.67%)	2 / 6 (33.33%)
occurrences (all)	4	7	3
Skin and subcutaneous tissue disorders			
alopecia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
dermatitis acneiform			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	0 / 8 (0.00%)	2 / 15 (13.33%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
dry skin			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	2 / 15 (13.33%)	0 / 6 (0.00%)
occurrences (all)	0	3	0
eczema asteatotic			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
erythema multiforme			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
onychomadesis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
pain of skin			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
petechiae			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
pruritus			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 8 (25.00%)	2 / 15 (13.33%)	1 / 6 (16.67%)
occurrences (all)	2	2	1
rash maculo-papular			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	3 / 15 (20.00%)	1 / 6 (16.67%)
occurrences (all)	1	3	1

skin ulcer			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Renal and urinary disorders			
chromaturia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	0 / 15 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
haematuria			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 8 (25.00%)	4 / 15 (26.67%)	1 / 6 (16.67%)
occurrences (all)	2	4	1
pollakiuria			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
proteinuria			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 8 (25.00%)	6 / 15 (40.00%)	1 / 6 (16.67%)
occurrences (all)	4	8	1
urinary hesitation			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
urinary tract pain			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
hyperthyroidism			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			

back pain			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	1 / 15 (6.67%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
flank pain			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
muscular weakness			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
musculoskeletal chest pain			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
musculoskeletal pain			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
myalgia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
neck pain			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 8 (25.00%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
osteoporosis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
pain in extremity			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	3 / 8 (37.50%)	2 / 15 (13.33%)	0 / 6 (0.00%)
occurrences (all)	3	5	0
Infections and infestations			
coxsackie viral infection			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
mucosal infection			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
skin infection			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	0 / 15 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
soft tissue infection			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
upper respiratory tract infection			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	3 / 15 (20.00%)	0 / 6 (0.00%)
occurrences (all)	1	3	0
urinary tract infection			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	0 / 15 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	1
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	7 / 15 (46.67%)	1 / 6 (16.67%)
occurrences (all)	1	9	2
dehydration			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	0 / 8 (0.00%)	2 / 15 (13.33%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
hypercalcaemia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	1 / 6 (16.67%)
occurrences (all)	0	3	1
hyperglycaemia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	5 / 15 (33.33%)	1 / 6 (16.67%)
occurrences (all)	1	8	2
hyperkalaemia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 8 (25.00%)	2 / 15 (13.33%)	1 / 6 (16.67%)
occurrences (all)	3	4	1
hypermagnesaemia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	4 / 15 (26.67%)	3 / 6 (50.00%)
occurrences (all)	0	4	4
hypernatraemia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
hyperphosphataemia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	0 / 15 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
hypoalbuminaemia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 8 (25.00%)	4 / 15 (26.67%)	1 / 6 (16.67%)
occurrences (all)	2	6	1
hypocalcaemia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	7 / 15 (46.67%)	2 / 6 (33.33%)
occurrences (all)	1	7	3

hypochloraemia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
hypoglycaemia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	4 / 15 (26.67%)	0 / 6 (0.00%)
occurrences (all)	0	5	0
hypokalaemia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 8 (25.00%)	2 / 15 (13.33%)	1 / 6 (16.67%)
occurrences (all)	2	2	1
hyponatraemia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	7 / 15 (46.67%)	1 / 6 (16.67%)
occurrences (all)	1	12	1
hypophosphataemia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 8 (12.50%)	5 / 15 (33.33%)	2 / 6 (33.33%)
occurrences (all)	1	5	3
vitamin d deficiency			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 8 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported