Clinical trial results:
An International, Randomized, Double-Blind, Controlled Study of Rindopepimut/GM-CSF with Adjuvant Temozolomide in Patients with Newly Diagnosed, Surgically Resected, EGFRvIII-positive Glioblastoma (The “ACT IV” Study)

Summary

EudraCT number	2011-006068-32
Trial protocol	HU GR GB DE AT BE ES NL IT FR
Global end of trial date	15 April 2016

Results information

Result version number	v1 (current)
This version publication date	22 September 2018
First version publication date	22 September 2018
Summary attachment (see zip file)	ACT IV Abb CSR Synopsis (ACT IV Abb CSR Synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	CDX110-04

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01480479
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Celldex Therapeutics, Inc.
Sponsor organisation address	119 Fourth Ave, Needham, United States, 02494
Public contact	Celldex Therapeutics, Celldex Therapeutics. Inc. , info@celldex.com
Scientific contact	Celldex Therapeutics, Celldex Therapeutics. Inc., info@celldex.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	29 April 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 March 2016
Global end of trial reached?	Yes
Global end of trial date	15 April 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to confirm that the addition of rindopepimut/GM-CSF to adjuvant temozolomide improved overall survival in patients with newly diagnosed, resected, EGFRvIII positive glioblastoma who had undergone gross-total resection.

Protection of trial subjects:

Safety assessments included monthly physical examination, vital signs, routine hematology, blood chemistry, urinalysis and evaluation of adverse events using NCI Common Terminology Criteria for Adverse Events (CTCAE) v 4.0.
An independent data monitoring committee (DMC) was convened for this study and acted in an advisory capacity to the sponsor with respect to safeguarding the interests of study patients, assessing interim safety and efficacy data, and for monitoring the overall conduct of the study.

Background therapy:

Standard maintenance temozolomide administered orally at a dose of 150–200 mg/m2 on days 1–5 of 28-day cycles, for 6–12 cycles, or longer if consistent with the local standard of care.

Evidence for comparator:

Keyhole limpet haemocyanin (KLH; 100 mcg) was given as a control injection to produce a local reaction similar to that expected with rindopepimut to maintain the treatment blind.

Actual start date of recruitment	29 November 2011
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	Netherlands: 2
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Czech Republic: 6
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Hungary: 21
Country: Number of subjects enrolled	Italy: 17
Country: Number of subjects enrolled	United States: 468
Country: Number of subjects enrolled	Canada: 70
Country: Number of subjects enrolled	Israel: 7
Country: Number of subjects enrolled	Switzerland: 17

Country: Number of subjects enrolled	Australia: 53
Country: Number of subjects enrolled	India: 3
Country: Number of subjects enrolled	New Zealand: 12
Country: Number of subjects enrolled	Taiwan: 7
Country: Number of subjects enrolled	Thailand: 4
Country: Number of subjects enrolled	Brazil: 9
Country: Number of subjects enrolled	Mexico: 2
Country: Number of subjects enrolled	Peru: 1
Worldwide total number of subjects	745
EEA total number of subjects	92

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)	571
From 65 to 84 years	173
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

First patient screened in November 2011. In addition to the above countries listed, Colombia and Belgium screened patients.

Pre-assignment

Screening details:

Patients underwent tissue screening for EGFRvIII at the same time or ahead of screening for other eligibility criteria. EGFRvIII negativity was the largest reason for being ineligible for the trial.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Unblinded Pharmacists who were otherwise not involved in Study conduct, obtained a randomized treatment assignment and managed study treatment via interactive response technology. Prepared Study treatments were blinded prior to delivery to Study staff for administration. KLH was given as a control injection to produce a local reaction similar to what was expected for Rindopepimut. Humoral response was analyzed but only available to laboratory staff until database lock and unblinding.

Arms

Are arms mutually exclusive?	Yes
Arm title	Active Study Drug

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Rindopepimut
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Intradermal use

Dosage and administration details:

Rindopepimut (CDX-110): A vaccine consisting of a 14 amino-acid synthetic peptide (13 amino acids from EGFRvIII plus a cysteine residue; termed EGFRvIII peptide) covalently linked to the carrier protein Keyhole Limpet Hemocyanin (KLH); 0.8 mL containing approximately 500 mcg rindopepimut and 150 mcg GM-CSF administered via intradermal injections. Lots used include A1200126, B0011, B0013, P58605ARG.

Investigational medicinal product name	GM-CSF
Investigational medicinal product code	
Other name	Leukine, sargramostim
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Intradermal use

Dosage and administration details:

GM-CSF: Leukine® (sargramostim); yeast-derived, recombinant human granulocyte-macrophage colony stimulating factor (rhu GM-CSF); administered via intradermal injections. Lots used include B15195, B17684, B19739, B19946, B20641, B21696A.

Investigational medicinal product name	Temozolomide
Investigational medicinal product code	
Other name	TMZ, Temodar
Pharmaceutical forms	Tablet, Concentrate for concentrate for solution for infusion
Routes of administration	Oral use, Intravenous use

Dosage and administration details:

Temozolomide (TMZ): TEMODAR® (Merck); oral or intravenous administration according to the instructions in the product label and per standard practice; typical dose is 150 mg/m2 body surface area per day for the first cycle and may increase to 200 mg/m2 body surface area per day in subsequent cycles.
Commercial supplies were used.

Arm title	Blinded Control
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Keyhole Limpet Hemocyanin
Investigational medicinal product code	
Other name	KLH, VACMUNE
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intradermal use

Dosage and administration details:

Keyhole Limpet Hemocyanin (KLH): VACMUNE® (Biosyn Corporation); a high purity, clinical grade, well-characterized aqueous formulation of a mixture of KLH 1 and KLH 2 immunocyanin subunits purified from native KLH, the high molecular mass hemocyanin of the giant keyhole limpet Megathura Crenulata, which has been reformulated and lyophilized by Celldex; 0.8 mL containing 100 mcg of KLH administered via intradermal injections. Lots used include 1-FIN-1145, 1-FIN-1646, 1-FIN-1947.

Investigational medicinal product name	Temozolomide
Investigational medicinal product code	
Other name	TMZ, Temodar
Pharmaceutical forms	Concentrate for concentrate for solution for infusion, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Temozolomide (TMZ): TEMODAR® (Merck); oral or intravenous administration according to the instructions in the product label and per standard practice; typical dose is 150 mg/m2 body surface area per day for the first cycle and may increase to 200 mg/m2 body surface area per day in subsequent cycles.
Commercial supplies were used.

Number of subjects in period 1	Active Study Drug	Blinded Control
Started	371	374
Completed	362	361
Not completed	9	13
Consent withdrawn by subject	5	7
other, not specified	1	3
Lost to follow-up	3	3

Baseline characteristics

Reporting groups	
Reporting group title	Active Study Drug
Reporting group description: -	
Reporting group title	Blinded Control
Reporting group description: -	

Reporting group values	Active Study Drug	Blinded Control	Total
Number of subjects	371	374	745
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			
median	59	58	
full range (min-max)	25 to 80	19 to 85	-
Gender categorical Units: Subjects			
Female	119	146	265
Male	252	228	480

Subject analysis sets	
Subject analysis set title	MRD Population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Patients with minimal residual disease.	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description: All randomized patients.	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description: All patients who received at least one dose of study treatment.	

Reporting group values	MRD Population	ITT	Safety Population
Number of subjects	405	745	741
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			
median	58	58	58
full range (min-max)	19 to 85	19 to 85	19 to 85
Gender categorical Units: Subjects			
Female	151	265	261
Male	254	480	480

End points

End points reporting groups

Reporting group title	Active Study Drug
Reporting group description: -	
Reporting group title	Blinded Control
Reporting group description: -	
Subject analysis set title	MRD Population
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Patients with minimal residual disease.	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description: All randomized patients.	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description: All patients who received at least one dose of study treatment.	

Primary: Overall survival in the MRD population

End point title	Overall survival in the MRD population
End point description:	
End point type	Primary
End point timeframe: From randomization until death or study closure.	

End point values	Active Study Drug	Blinded Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	195	210		
Units: months				
median (confidence interval 95%)	20.1 (18.5 to 22.1)	20.0 (18.1 to 21.9)		

Statistical analyses

Statistical analysis title	Overall Survival
Comparison groups	Active Study Drug v Blinded Control

Number of subjects included in analysis	405
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.025
Method	Logrank

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time the patient had taken at least one dose of double-blind vaccine through (whichever occurs first) either a) 28 calendar days after the last administration of double-blind vaccine, or b) initiation of alternative anticancer therapy.

Adverse event reporting additional description:

Adverse events and serious adverse events were to be recorded on the CRF. Assessments included monthly physical exams, vital signs, routine hematology, blood chemistry, and urinalysis as well as quality of life questionnaires, MDASI-BT, QLQ-C#) and BN20.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Active Study Drug
Reporting group description: -	
Reporting group title	Blinded Control

Reporting group description: -

Serious adverse events	Active Study Drug	Blinded Control	
Total subjects affected by serious adverse events			
subjects affected / exposed	96 / 369 (26.02%)	102 / 372 (27.42%)	
number of deaths (all causes)	254	269	
number of deaths resulting from adverse events	7	6	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Borderline mucinous tumour of ovary			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain neoplasm benign			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial tumour haemorrhage			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			

subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of the tongue			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	4 / 369 (1.08%)	3 / 372 (0.81%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	0 / 369 (0.00%)	2 / 372 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 369 (0.27%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 369 (0.27%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			

subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Hypotension			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 369 (0.81%)	3 / 372 (0.81%)	
occurrences causally related to treatment / all	0 / 3	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Condition aggravated			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gait disturbance			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection site reaction			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Non-cardiac chest pain			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	3 / 369 (0.81%)	4 / 372 (1.08%)	
occurrences causally related to treatment / all	2 / 3	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Sleep apnoea syndrome			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emphysema			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			

subjects affected / exposed	0 / 369 (0.00%)	4 / 372 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	7 / 369 (1.90%)	4 / 372 (1.08%)	
occurrences causally related to treatment / all	1 / 7	0 / 4	
deaths causally related to treatment / all	1 / 2	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 369 (0.54%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Confusional state			
subjects affected / exposed	7 / 369 (1.90%)	2 / 372 (0.54%)	
occurrences causally related to treatment / all	0 / 7	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			

subjects affected / exposed	1 / 369 (0.27%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug dependence			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	3 / 369 (0.81%)	2 / 372 (0.54%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood bilirubin			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Fall			
subjects affected / exposed	4 / 369 (1.08%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoradionecrosis			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomeningocele			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation necrosis			
subjects affected / exposed	0 / 369 (0.00%)	2 / 372 (0.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Spinal compression fracture			

subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	2 / 369 (0.54%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac arrest			
subjects affected / exposed	1 / 369 (0.27%)	2 / 372 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Tachycardia			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	2 / 369 (0.54%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			

subjects affected / exposed	3 / 369 (0.81%)	2 / 372 (0.54%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ataxia			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	7 / 369 (1.90%)	12 / 372 (3.23%)	
occurrences causally related to treatment / all	4 / 7	4 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haematoma			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 369 (0.27%)	3 / 372 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cognitive disorder			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	1 / 369 (0.27%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			

subjects affected / exposed	1 / 369 (0.27%)	2 / 372 (0.54%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 369 (0.27%)	3 / 372 (0.81%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Epilepsy			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 369 (0.00%)	2 / 372 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	3 / 369 (0.81%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Headache			
subjects affected / exposed	2 / 369 (0.54%)	4 / 372 (1.08%)	
occurrences causally related to treatment / all	0 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	4 / 369 (1.08%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiplegia			

subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	5 / 369 (1.36%)	3 / 372 (0.81%)	
occurrences causally related to treatment / all	1 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial pressure increased			
subjects affected / exposed	1 / 369 (0.27%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	1 / 369 (0.27%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Movement disorder			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures			
subjects affected / exposed	2 / 369 (0.54%)	2 / 372 (0.54%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyramidal tract syndrome			

subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	18 / 369 (4.88%)	22 / 372 (5.91%)	
occurrences causally related to treatment / all	2 / 18	1 / 22	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sensory disturbance			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	1 / 369 (0.27%)	2 / 372 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural hygroma			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	5 / 369 (1.36%)	2 / 372 (0.54%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasogenic cerebral oedema			

subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Febrile neutropenia			
subjects affected / exposed	1 / 369 (0.27%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic anaemia			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spontaneous haematoma			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	5 / 369 (1.36%)	3 / 372 (0.81%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Vision blurred			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 369 (0.00%)	2 / 372 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haemorrhage			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nausea			
subjects affected / exposed	1 / 369 (0.27%)	4 / 372 (1.08%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			

subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal fissure			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Volvulus			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 369 (0.27%)	5 / 372 (1.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection site erythema			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			

subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug eruption			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash generalised			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 369 (0.54%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urinary			
subjects affected / exposed	0 / 369 (0.00%)	2 / 372 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			

subjects affected / exposed	3 / 369 (0.81%)	2 / 372 (0.54%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal tubular necrosis			
subjects affected / exposed	2 / 369 (0.54%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	2 / 369 (0.54%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes insipidus			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Muscular weakness			
subjects affected / exposed	0 / 369 (0.00%)	4 / 372 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Herpes zoster			
subjects affected / exposed	0 / 369 (0.00%)	2 / 372 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 369 (0.00%)	2 / 372 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 369 (0.00%)	2 / 372 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			

subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ophthalmic herpes zoster			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital cellulitis			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 369 (0.81%)	4 / 372 (1.08%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			

subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	1 / 369 (0.27%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 369 (0.54%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 369 (0.27%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tooth infection			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	7 / 369 (1.90%)	2 / 372 (0.54%)	
occurrences causally related to treatment / all	0 / 7	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection pseudomonal			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 369 (0.27%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
West Nile viral infection			

subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	2 / 369 (0.54%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 369 (0.27%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	3 / 369 (0.81%)	2 / 372 (0.54%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperammonaemia			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 369 (0.27%)	2 / 372 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 369 (0.00%)	1 / 372 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	2 / 369 (0.54%)	0 / 372 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Active Study Drug	Blinded Control	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	362 / 369 (98.10%)	353 / 372 (94.89%)	
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	261 / 369 (70.73%)	118 / 372 (31.72%)	
occurrences (all)	71	32	
Injection site oedema			
subjects affected / exposed	35 / 369 (9.49%)	13 / 372 (3.49%)	
occurrences (all)	10	4	
Injection site pruritus			
subjects affected / exposed	146 / 369 (39.57%)	29 / 372 (7.80%)	
occurrences (all)	40	8	
Injection site rash			
subjects affected / exposed	55 / 369 (14.91%)	13 / 372 (3.49%)	
occurrences (all)	15	4	
Injection site swelling			
subjects affected / exposed	42 / 369 (11.38%)	7 / 372 (1.88%)	
occurrences (all)	11	2	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	43 / 369 (11.65%)	64 / 372 (17.20%)	
occurrences (all)	12	17	

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

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28844499