Clinical trial results:
A Randomized Multicenter Pivotal Study of CDX-011 (CR011-vcMMAE) in Patients with Metastatic, GPNMB Over-Expressing, Triple-Negative Breast Cancer

Summary

EudraCT number	2015-003693-33
Trial protocol	GB ES DE AT BE IT
Global end of trial date	07 August 2018

Results information

Result version number	v1 (current)
This version publication date	14 February 2019
First version publication date	14 February 2019
Summary attachment (see zip file)	CDX011-04 CSR Synopsis (CDX011-04_Synposis_Abbrev_CSR_dated_09Nov18.pdf)

Trial information

Trial identification

Sponsor protocol code	CDX011-04

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01997333
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Celldex Therapeutics, Inc.
Sponsor organisation address	53 Frontage Road, Suite 200, Hampton, United States, 08827
Public contact	Director of Regulatory Affairs, Celldex Therapeutics, Inc., info@celldex.com
Scientific contact	Director of Regulatory Affairs, 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	22 May 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 November 2017
Global end of trial reached?	Yes
Global end of trial date	07 August 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the anti-cancer activity of CDX-011 in metastatic, GPNMB over-expressing, triple-negative breast cancer as measured by the duration of progression-free survival (PFS).

Protection of trial subjects:

Safety assessments occurred at every 21-day cycle including 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. The EORTC Core Quality of Life Questionnaire (QLQ-30) was completed at screening, at first dose of study drug, and at every other dosing cycle until end of treatment by patients who were fluent in a language in which the questionnaires were validated.

An independent data monitoring committee (IDMC) was convened for this study and acted in an advisory capacity to the sponsor with respect to safeguarding the interests of patients, assessing interim safety data, and for monitoring the overall conduct of the study.

Background therapy: -

Evidence for comparator:

Capecitabine was selected as the comparator as it represented a standard of care option for patients with triple negative breast cancer.

Actual start date of recruitment	19 February 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 18
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	France: 18
Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	Australia: 18
Country: Number of subjects enrolled	Canada: 12
Country: Number of subjects enrolled	Italy: 13
Country: Number of subjects enrolled	United States: 215
Worldwide total number of subjects	327
EEA total number of subjects	82

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)	258
From 65 to 84 years	67
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

1531 patients were screened between December 2013 and July 2017.

Pre-assignment

Screening details:

1531 patients screened to randomize 327 patients. Most common reasons for screen failure were tumor tissue inadequate/gpNMB negative (697), failure to meet other eligibility (256), and refusal to participate (77).

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

As this was an open-label study, there was no masking of trial participants or investigators. The imaging review committee and biostatistical team at the study sponsor were masked to treatment assignments until after study closure.

Arms

Are arms mutually exclusive?	Yes
Arm title	CDX-011

Arm description:

CDX-011 administered on Day 1 of each 21 day cycle until disease progression, discontinuation due to toxicity, withdrawal of consent or end of study.

Arm type	Experimental
Investigational medicinal product name	Glembatumumab vedotin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Glembatumumab vedotin solution (injection concentrate); 1.88 mg/kg; intravenous infusion on Day 1 of repeated 21-day cycles

Arm title	Capecitabine

Arm description:

Capecitabine administered on days 1 through 14 of each 21 day cycle until disease progression, discontinuation due to toxicity, withdrawal of consent, or end of study.

Arm type	Active comparator
Investigational medicinal product name	capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Capecitabine administered orally; starting dose was 1250 mg/m2 twice daily (equivalent to 2500 mg/m2 total daily dose) per the package insert, days 1-14 of repeated 21 day cycles; subsequent treatment was dictated by tolerance and institutional practice.

Number of subjects in period 1	CDX-011	Capecitabine
Started	218	109
Completed	199	76
Not completed	19	33
Consent withdrawn by subject	6	15
Various	2	1
Lost to follow-up	6	-
Did not receive treatment	5	17

Baseline characteristics

Reporting groups	
Reporting group title	CDX-011
Reporting group description:	
CDX-011 administered on Day 1 of each 21 day cycle until disease progression, discontinuation due to toxicity, withdrawal of consent or end of study.	
Reporting group title	Capecitabine
Reporting group description:	
Capecitabine administered on days 1 through 14 of each 21 day cycle until disease progression, discontinuation due to toxicity, withdrawal of consent, or end of study.	

Reporting group values	CDX-011	Capecitabine	Total
Number of subjects	218	109	327
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	177	81	258
From 65-84 years	40	27	67
85 years and over	1	1	2
Age continuous			
Units: years			
median	55	55	
full range (min-max)	28 to 85	31 to 85	-
Gender categorical			
Units: Subjects			
Female	218	109	327
Male	0	0	0

End points

End points reporting groups

Reporting group title	CDX-011
Reporting group description:	
CDX-011 administered on Day 1 of each 21 day cycle until disease progression, discontinuation due to toxicity, withdrawal of consent or end of study.	
Reporting group title	Capecitabine
Reporting group description:	
Capecitabine administered on days 1 through 14 of each 21 day cycle until disease progression, discontinuation due to toxicity, withdrawal of consent, or end of study.	

Primary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)
End point description:	
PFS is defined as the time from randomization to the earlier of disease progression or death due to any cause. The primary analysis of PFS was based on PFS events determined retrospectively by the central independent review committee, blinded to treatment assignment and investigator assessments according to RECIST 1.1 criteria.	
End point type	Primary
End point timeframe:	
Evaluated every 6-9 weeks following treatment initiation.	

End point values	CDX-011	Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218	109		
Units: months				
median (confidence interval 95%)	2.9 (2.8 to 3.5)	2.8 (1.6 to 3.2)		

Statistical analyses

Statistical analysis title	PFS
Comparison groups	CDX-011 v Capecitabine
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Logrank

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

ORR is defined as the percentage of patients who achieve best overall response of complete or partial response. The analysis of ORR was based on ORR events determined retrospectively by the central independent review committee, blinded to treatment assignment and investigator assessments according to RECIST 1.1 criteria. Per Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.1), Complete Response (CR) = Disappearance of all target lesions and nontarget lesions, Partial Response (PR), >= 30% decrease in the sum of the longest diameter of target lesions with no progression in non-target lesions and no new lesions.

End point type	Secondary

End point timeframe:

Evaluated every 6-9 weeks following treatment initiation

End point values	CDX-011	Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	100		
Units: Percentage				
median (confidence interval 95%)	26 (20 to 33)	21 (14 to 30)		

Statistical analyses

Statistical analysis title	ORR
Comparison groups	CDX-011 v Capecitabine
Number of subjects included in analysis	279
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Cochran-Mantel-Haenszel

Secondary: Duration of Response

End point title	Duration of Response

End point description:

Duration of response (DOR) is the number of months from the time criteria are first met for either CR or PR, until the first date that PD is objectively documented. The analysis of DOR was determined retrospectively by the central independent review committee,blinded to treatment assignment and investigator assessments according to RECIST 1.1 criteria. Per Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.1), Complete Response (CR) = Disappearance of all target lesions and non-target lesions, Partial Response (PR), >= 30% decrease in the sum of the longest diameter of target lesions with no progression in non-target lesions and no new lesions.

End point type	Secondary

End point timeframe:

Evaluated every 6-9 weeks following treatment initiation.

End point values	CDX-011	Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	21		
Units: months				
median (confidence interval 95%)	2.8 (2.3 to 5.5)	4.2 (2.7 to 5.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall Survival (OS) is defined as the number of months from randomization to the date of death due to any cause.

End point type	Secondary

End point timeframe:

During treatment and 3 months from end of treatment through end of study or approximately up to 5 years.

End point values	CDX-011	Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	218	109		
Units: months				
median (confidence interval 95%)	8.9 (7.9 to 10.5)	8.7 (6.9 to 10.8)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the time a subject took their first dose of study treatment (CDX-011 or Capecitabine) through (whichever occurs first) either a) 28 calendar days after the last administration of study treatment, or b) initiation of alternate anticancer therapy.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

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

Reporting group description: -

Serious adverse events	Active Study Drug	Control	
Total subjects affected by serious adverse events			
subjects affected / exposed	71 / 213 (33.33%)	19 / 92 (20.65%)	
number of deaths (all causes)	134	65	
number of deaths resulting from adverse events	4	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to central nervous system			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Embolism			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			

subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Axillary pain			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	2 / 213 (0.94%)	3 / 92 (3.26%)	
occurrences causally related to treatment / all	1 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	2 / 213 (0.94%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			

subjects affected / exposed	3 / 213 (1.41%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyserositis			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (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	7 / 213 (3.29%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	2 / 8	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	0 / 213 (0.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	6 / 213 (2.82%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 8	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal oedema			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pleural effusion			
subjects affected / exposed	3 / 213 (1.41%)	2 / 92 (2.17%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 213 (0.94%)	2 / 92 (2.17%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 213 (0.94%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination			
subjects affected / exposed	1 / 213 (0.47%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 213 (0.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Blood bilirubin increased			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine increased			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 213 (0.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stoma complication			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma site haemorrhage			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	2 / 213 (0.94%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain oedema			
subjects affected / exposed	0 / 213 (0.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	2 / 213 (0.94%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	2 / 213 (0.94%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	0 / 213 (0.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	2 / 213 (0.94%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	3 / 213 (1.41%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 213 (0.94%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract nuclear			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 213 (2.82%)	2 / 92 (2.17%)	
occurrences causally related to treatment / all	2 / 6	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	4 / 213 (1.88%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	6 / 213 (2.82%)	5 / 92 (5.43%)	
occurrences causally related to treatment / all	4 / 6	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 213 (0.00%)	2 / 92 (2.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	2 / 213 (0.94%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 213 (0.47%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Megacolon			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	8 / 213 (3.76%)	3 / 92 (3.26%)	
occurrences causally related to treatment / all	6 / 9	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			

subjects affected / exposed	1 / 213 (0.47%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 213 (0.47%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	3 / 213 (1.41%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	7 / 213 (3.29%)	4 / 92 (4.35%)	
occurrences causally related to treatment / all	5 / 8	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 213 (0.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	2 / 213 (0.94%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Drug eruption			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain of skin			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pruritus			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash erythematous			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash generalised			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	3 / 213 (1.41%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic epidermal necrolysis			

subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (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			
Arthralgia			
subjects affected / exposed	2 / 213 (0.94%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	2 / 213 (0.94%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
bone pain			
subjects affected / exposed	1 / 213 (0.47%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest wall mass			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 213 (0.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 213 (0.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pain in extremity			
subjects affected / exposed	2 / 213 (0.94%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacterascites			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cellulitis			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest wall abscess			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 213 (0.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	0 / 213 (0.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastitis			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			

subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (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	5 / 213 (2.35%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	1 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	5 / 213 (2.35%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	2 / 5	1 / 1	
deaths causally related to treatment / all	1 / 2	0 / 0	
Sepsis syndrome			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic shock			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary tract infection			
subjects affected / exposed	4 / 213 (1.88%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			

subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 213 (0.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 213 (0.47%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	3 / 213 (1.41%)	2 / 92 (2.17%)	
occurrences causally related to treatment / all	2 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 213 (0.47%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	2 / 213 (0.94%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	0 / 213 (0.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Active Study Drug	Control	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	211 / 213 (99.06%)	91 / 92 (98.91%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	23 / 213 (10.80%)	3 / 92 (3.26%)	
occurrences (all)	40	7	
Aspartate aminotransferase increased			
subjects affected / exposed	25 / 213 (11.74%)	6 / 92 (6.52%)	
occurrences (all)	47	11	
Blood alkaline phosphatase increased			
subjects affected / exposed	18 / 213 (8.45%)	2 / 92 (2.17%)	
occurrences (all)	27	2	
Lymphocyte count decreased			
subjects affected / exposed	12 / 213 (5.63%)	3 / 92 (3.26%)	
occurrences (all)	25	4	
Neutrophil count decreased			
subjects affected / exposed	38 / 213 (17.84%)	1 / 92 (1.09%)	
occurrences (all)	73	5	
Weight decreased			
subjects affected / exposed	37 / 213 (17.37%)	5 / 92 (5.43%)	
occurrences (all)	54	5	
White blood cell count decreased			
subjects affected / exposed	24 / 213 (11.27%)	2 / 92 (2.17%)	
occurrences (all)	47	4	
Nervous system disorders			
Dizziness			
subjects affected / exposed	19 / 213 (8.92%)	4 / 92 (4.35%)	
occurrences (all)	21	4	
Dysgeusia			

subjects affected / exposed	23 / 213 (10.80%)	2 / 92 (2.17%)	
occurrences (all)	26	2	
Headache			
subjects affected / exposed	39 / 213 (18.31%)	5 / 92 (5.43%)	
occurrences (all)	53	5	
Neuropathy peripheral			
subjects affected / exposed	28 / 213 (13.15%)	4 / 92 (4.35%)	
occurrences (all)	48	4	
Paraesthesia			
subjects affected / exposed	12 / 213 (5.63%)	5 / 92 (5.43%)	
occurrences (all)	14	7	
Peripheral sensory neuropathy			
subjects affected / exposed	47 / 213 (22.07%)	4 / 92 (4.35%)	
occurrences (all)	68	6	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	33 / 213 (15.49%)	9 / 92 (9.78%)	
occurrences (all)	48	15	
Neutropenia			
subjects affected / exposed	49 / 213 (23.00%)	5 / 92 (5.43%)	
occurrences (all)	101	12	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	14 / 213 (6.57%)	5 / 92 (5.43%)	
occurrences (all)	21	5	
Chills			
subjects affected / exposed	14 / 213 (6.57%)	4 / 92 (4.35%)	
occurrences (all)	17	6	
Fatigue			
subjects affected / exposed	101 / 213 (47.42%)	37 / 92 (40.22%)	
occurrences (all)	160	57	
Non-cardiac chest pain			
subjects affected / exposed	4 / 213 (1.88%)	5 / 92 (5.43%)	
occurrences (all)	4	5	
Oedema peripheral			

subjects affected / exposed	13 / 213 (6.10%)	10 / 92 (10.87%)	
occurrences (all)	16	13	
Pain			
subjects affected / exposed	21 / 213 (9.86%)	4 / 92 (4.35%)	
occurrences (all)	25	4	
Pyrexia			
subjects affected / exposed	37 / 213 (17.37%)	12 / 92 (13.04%)	
occurrences (all)	46	16	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	12 / 213 (5.63%)	3 / 92 (3.26%)	
occurrences (all)	17	3	
Abdominal pain			
subjects affected / exposed	22 / 213 (10.33%)	16 / 92 (17.39%)	
occurrences (all)	27	25	
Abdominal pain upper			
subjects affected / exposed	17 / 213 (7.98%)	6 / 92 (6.52%)	
occurrences (all)	18	6	
Constipation			
subjects affected / exposed	61 / 213 (28.64%)	13 / 92 (14.13%)	
occurrences (all)	82	14	
Diarrhoea			
subjects affected / exposed	55 / 213 (25.82%)	44 / 92 (47.83%)	
occurrences (all)	88	81	
Dry mouth			
subjects affected / exposed	10 / 213 (4.69%)	5 / 92 (5.43%)	
occurrences (all)	10	5	
Dyspepsia			
subjects affected / exposed	22 / 213 (10.33%)	4 / 92 (4.35%)	
occurrences (all)	27	4	
Dysphagia			
subjects affected / exposed	12 / 213 (5.63%)	0 / 92 (0.00%)	
occurrences (all)	15	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	16 / 213 (7.51%)	4 / 92 (4.35%)	
occurrences (all)	16	4	

Nausea			
subjects affected / exposed	91 / 213 (42.72%)	39 / 92 (42.39%)	
occurrences (all)	142	54	
Oral pain			
subjects affected / exposed	11 / 213 (5.16%)	2 / 92 (2.17%)	
occurrences (all)	12	2	
Stomatitis			
subjects affected / exposed	37 / 213 (17.37%)	24 / 92 (26.09%)	
occurrences (all)	56	43	
Vomiting			
subjects affected / exposed	46 / 213 (21.60%)	17 / 92 (18.48%)	
occurrences (all)	68	24	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	24 / 213 (11.27%)	10 / 92 (10.87%)	
occurrences (all)	32	13	
Dyspnoea			
subjects affected / exposed	32 / 213 (15.02%)	11 / 92 (11.96%)	
occurrences (all)	37	11	
Oropharyngeal pain			
subjects affected / exposed	15 / 213 (7.04%)	2 / 92 (2.17%)	
occurrences (all)	18	2	
Pleural effusion			
subjects affected / exposed	5 / 213 (2.35%)	5 / 92 (5.43%)	
occurrences (all)	17	5	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	88 / 213 (41.31%)	1 / 92 (1.09%)	
occurrences (all)	101	1	
Dry skin			
subjects affected / exposed	8 / 213 (3.76%)	5 / 92 (5.43%)	
occurrences (all)	9	5	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	10 / 213 (4.69%)	40 / 92 (43.48%)	
occurrences (all)	15	132	
Pruritus			

subjects affected / exposed	69 / 213 (32.39%)	4 / 92 (4.35%)	
occurrences (all)	124	5	
Pruritus generalised			
subjects affected / exposed	12 / 213 (5.63%)	0 / 92 (0.00%)	
occurrences (all)	21	0	
Rash			
subjects affected / exposed	29 / 213 (13.62%)	3 / 92 (3.26%)	
occurrences (all)	65	4	
Rash erythematous			
subjects affected / exposed	15 / 213 (7.04%)	1 / 92 (1.09%)	
occurrences (all)	23	1	
Rash macular			
subjects affected / exposed	11 / 213 (5.16%)	0 / 92 (0.00%)	
occurrences (all)	23	0	
Rash maculo-papular			
subjects affected / exposed	40 / 213 (18.78%)	5 / 92 (5.43%)	
occurrences (all)	103	13	
Rash pruritic			
subjects affected / exposed	18 / 213 (8.45%)	0 / 92 (0.00%)	
occurrences (all)	48	0	
Skin hyperpigmentation			
subjects affected / exposed	19 / 213 (8.92%)	3 / 92 (3.26%)	
occurrences (all)	21	3	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	15 / 213 (7.04%)	5 / 92 (5.43%)	
occurrences (all)	22	5	
Insomnia			
subjects affected / exposed	24 / 213 (11.27%)	6 / 92 (6.52%)	
occurrences (all)	24	6	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	38 / 213 (17.84%)	3 / 92 (3.26%)	
occurrences (all)	50	4	
Back pain			

subjects affected / exposed	21 / 213 (9.86%)	12 / 92 (13.04%)	
occurrences (all)	23	12	
Bone pain			
subjects affected / exposed	24 / 213 (11.27%)	3 / 92 (3.26%)	
occurrences (all)	29	5	
Muscle spasms			
subjects affected / exposed	12 / 213 (5.63%)	1 / 92 (1.09%)	
occurrences (all)	13	1	
Muscular weakness			
subjects affected / exposed	12 / 213 (5.63%)	3 / 92 (3.26%)	
occurrences (all)	14	3	
Musculoskeletal chest pain			
subjects affected / exposed	9 / 213 (4.23%)	11 / 92 (11.96%)	
occurrences (all)	10	12	
Musculoskeletal pain			
subjects affected / exposed	10 / 213 (4.69%)	8 / 92 (8.70%)	
occurrences (all)	14	9	
Myalgia			
subjects affected / exposed	27 / 213 (12.68%)	4 / 92 (4.35%)	
occurrences (all)	39	4	
Pain in extremity			
subjects affected / exposed	25 / 213 (11.74%)	9 / 92 (9.78%)	
occurrences (all)	36	17	
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	18 / 213 (8.45%)	1 / 92 (1.09%)	
occurrences (all)	20	1	
Urinary tract infection			
subjects affected / exposed	18 / 213 (8.45%)	3 / 92 (3.26%)	
occurrences (all)	29	3	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	63 / 213 (29.58%)	17 / 92 (18.48%)	
occurrences (all)	79	17	
Dehydration			

subjects affected / exposed	15 / 213 (7.04%)	6 / 92 (6.52%)	
occurrences (all)	21	8	
Hyperglycaemia			
subjects affected / exposed	15 / 213 (7.04%)	0 / 92 (0.00%)	
occurrences (all)	26	0	
Hypoalbuminaemia			
subjects affected / exposed	11 / 213 (5.16%)	5 / 92 (5.43%)	
occurrences (all)	24	6	
Hypokalaemia			
subjects affected / exposed	24 / 213 (11.27%)	8 / 92 (8.70%)	
occurrences (all)	38	10	
Hypophosphataemia			
subjects affected / exposed	14 / 213 (6.57%)	5 / 92 (5.43%)	
occurrences (all)	22	9	

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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported

Notes: