Clinical trial results:
Single-arm phase II study of maintenance therapy with aflibercept after first-line treatment with FOLFIRI plus aflibercept in metastatic colorectal cancer patients

Summary

EudraCT number	2013-002567-26
Trial protocol	GR
Global end of trial date	25 September 2017

Results information

Result version number	v1 (current)
This version publication date	04 October 2019
First version publication date	04 October 2019

Trial information

Trial identification

Sponsor protocol code	HE6A/13

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02129257
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hellenic Cooperative Oncology Group
Sponsor organisation address	Hatzikonstandi 18, Athens, Greece, 11524
Public contact	Clinical Trials, Hellenic Cooperative Oncology Group, 0030 2106912520, hecogoff@otenet.gr
Scientific contact	Clinical Trials, Hellenic Cooperative Oncology Group, 0030 2106912520, hecogoff@otenet.gr

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	26 September 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the 12-month progression-free survival (PFS) rate.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, the Good Clinical Practice guidelines and the local regulatory requirements

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 May 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Greece: 73
Worldwide total number of subjects	73
EEA total number of subjects	73

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)	37
From 65 to 84 years	36
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

participants were enrolled in the study from 26 May 2014 until 27 January 2016 in 11 sites

Pre-assignment

Screening details:

Patients were screened for eligibility before entering the study and signed the informed consent form which was obtained before any study procedure

Period 1

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

Arms

Arm title	FOLFIRI+AFLIBERCEPT & AFLIBERCEPT MAINTENANCE

Arm description:

First line treatment with the combination of FOLFIRI plus Alfibercept for 12 cycles and maintenance therapy with Alfibercept in patients with metastatic colorectal cancer.

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

Dosage and administration details:

The patients received the standard doses of FOLFILI (Leucovorin, 5-Fluorouracil and Irinotecan) combined with Aflibercept (4 mg/KBW i.v) every 2 weeks until disease progression, unacceptable toxicity or completion of 12 weeks, followed by Aflibercept maintenance (4 mg/KBW i.v).

Number of subjects in period 1	FOLFIRI+AFLIBERCEPT & AFLIBERCEPT MAINTENANCE
Started	73
Completed	39
Not completed	34
Physician decision	3
Consent withdrawn by subject	1
Adverse event, non-fatal	10
AE(proteinuria) & 2 weeks without therapy	1
Other illness (COPD)	1
Progression	15
>2 weeks treatment delay	1
Protocol deviation	2

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	73	73	
Age categorical Units: Subjects			
Adults (18-64 years)	37	37	
From 65-84 years	36	36	
85 years and over	0	0	
Age continuous Units: years			
median	63.9		
full range (min-max)	18.2 to 82.8	-	
Gender categorical Units: Subjects			
Female	22	22	
Male	51	51	

End points

End points reporting groups

Reporting group title	FOLFIRI+AFLIBERCEPT & AFLIBERCEPT MAINTENANCE

Reporting group description:

First line treatment with the combination of FOLFIRI plus Alfibercept for 12 cycles and maintenance therapy with Alfibercept in patients with metastatic colorectal cancer.

Subject analysis set title	Response evaluable population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All treated patients, without major protocol deviation, with at least one tumor evaluation while on treatment (except for early disease progression or death) and evaluable for response.

Primary: Progression free survival rate at 1 year

End point title	Progression free survival rate at 1 year[1]

End point description:

The primary efficacy endpoint is progression-free survival rate at 1 year, corresponding to the percentage of patients without any documented progression of the disease after 1 year from registration.

End point type	Primary

End point timeframe:

From the enrollment date up to 1 year

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: Since this was a single arm study and all patients received the same treatment, no comparisons between groups were applicable. The percentage of patients surviving without disease 12 months since study entry and the corresponding 95% confidence intervals were estimated with the Kaplan-Meier product limit method.

End point values	FOLFIRI+AFLIBERCEPT & AFLIBERCEPT MAINTENANCE			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: percentage of patients				
12-month PFS rate (%)	22			

Attachments (see zip file)	Kaplan-Meier curve with respect to PFS/KM_PFS_ITT.tif

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate

End point title	Objective response rate

End point description:

The overall response was determined according to the Response Evaluation Criteria in Solid Tumors (RECIST).

End point type	Secondary

End point timeframe:

CT or MRI scan was performed to assess disease status at baseline and every 8 weeks until the first year from chemotherapy initiation, then every 12 weeks in order to evaluate the response

End point values	FOLFIRI+AFLIBERCEPT & AFLIBERCEPT MAINTENANCE	Response evaluable population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	73	66		
Units: percentage of patients with CR or PR				
Objective response rate (%)	47	52		

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 interval from registration to the date of death (due to any cause) or last contact, whichever occurred first.

End point type	Secondary

End point timeframe:

From registration to the date of death due to any cause assessed up to 60 months.

End point values	FOLFIRI+AFLIBERCEPT & AFLIBERCEPT MAINTENANCE			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: months				
median (confidence interval 95%)	20.9 (16.6 to 29.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival

End point title	Progression free survival

End point description:

PFS is defined as the time interval from registration to the first date of documented tumour progression or death from any cause.

End point type	Secondary

End point timeframe:

From registration to the first date of documented progression or death due to any cause assessed up to 60 months.

End point values	FOLFIRI+AFLIBERCEPT & AFLIBERCEPT MAINTENANCE			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: months				
median (confidence interval 95%)	8.4 (7.4 to 9.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Evaluation of safety

End point title	Evaluation of safety

End point description:

To evaluate the safety of the combination of FOLFIRI with aflibercept followed by aflibercept maintenance treatment.

End point type	Secondary

End point timeframe:

Upon signature of the ICF up to 30 days after the last administration of aflibercept. Following the 30 day EOT visit all ongoing SAEs as well as ongoing related AEs and new related SAEs were collected and followed till resolution/stabilisation.

End point values	FOLFIRI+AFLIBERCEPT & AFLIBERCEPT MAINTENANCE			
Subject group type	Reporting group			
Number of subjects analysed	73[2]			
Units: number of patients				
Any adverse event	71			
Fatal adverse events	0			
Serious adverse events	32			

Notes:

[2] - All enrolled patients received at least one cycle of treatment and were assessed for safety.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Upon signature of the ICF up to 30 days after the last administration of aflibercept. Following the 30 day EOT visit all ongoing SAEs as well as ongoing related AEs and new related SAEs were collected and followed till resolution/stabilisation.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	Aflibercept

Reporting group description: -

Serious adverse events	Aflibercept		
Total subjects affected by serious adverse events			
subjects affected / exposed	32 / 73 (43.84%)		
number of deaths (all causes)	40		
number of deaths resulting from adverse events			
Investigations			
Creatinine urine increased			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Urea urine increased			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Atrial fibrillation			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bradycardia			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fever			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Inflammation			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oedema lower limb			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	3 / 73 (4.11%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Anaemia			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			

subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	7 / 73 (9.59%)		
occurrences causally related to treatment / all	7 / 7		
deaths causally related to treatment / all	0 / 0		
Rectal fistula			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dysphagia			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Mucositis oral			
subjects affected / exposed	4 / 73 (5.48%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ileal obstruction			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			

Hoarseness			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Epistaxis			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute renal failure			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Proteinuria	Additional description: Nephrotic syndrome		
subjects affected / exposed	5 / 73 (6.85%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Sacral pain			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Enterocolitis infectious			

subjects affected / exposed	1 / 73 (1.37%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	2 / 73 (2.74%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Skin infection				
subjects affected / exposed	1 / 73 (1.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	2 / 73 (2.74%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Abdominal infection				
subjects affected / exposed	1 / 73 (1.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Anorectal infection				
subjects affected / exposed	1 / 73 (1.37%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Soft tissue infection				
subjects affected / exposed	1 / 73 (1.37%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Tumour lysis syndrome				
subjects affected / exposed	1 / 73 (1.37%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dehydration				

subjects affected / exposed	2 / 73 (2.74%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Aflibercept		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	68 / 73 (93.15%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	31 / 73 (42.47%)		
occurrences (all)	75		
Hypotension			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Superficial thrombophlebitis			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Thromboembolic event			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	20 / 73 (27.40%)		
occurrences (all)	28		
Fever			
subjects affected / exposed	9 / 73 (12.33%)		
occurrences (all)	21		
Non-cardiac chest pain			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	2 / 73 (2.74%)		
occurrences (all)	3		
Immune system disorders			

Allergic reaction			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Nasal disorder			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Dyspnoea			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	3		
Epistaxis			
subjects affected / exposed	11 / 73 (15.07%)		
occurrences (all)	15		
Hiccups			
subjects affected / exposed	4 / 73 (5.48%)		
occurrences (all)	4		
Nasal congestion			
subjects affected / exposed	2 / 73 (2.74%)		
occurrences (all)	2		
Pharyngeal mucositis			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Nasal ulcer			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Voice alteration			
subjects affected / exposed	3 / 73 (4.11%)		
occurrences (all)	7		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Depression			

subjects affected / exposed	3 / 73 (4.11%)		
occurrences (all)	3		
Insomnia			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	13 / 73 (17.81%)		
occurrences (all)	21		
Alkaline phosphatase increased			
subjects affected / exposed	8 / 73 (10.96%)		
occurrences (all)	9		
Aspartate aminotransferase increased			
subjects affected / exposed	15 / 73 (20.55%)		
occurrences (all)	23		
Blood bilirubin increased			
subjects affected / exposed	7 / 73 (9.59%)		
occurrences (all)	17		
Cholesterol high			
subjects affected / exposed	8 / 73 (10.96%)		
occurrences (all)	10		
Creatinine increased			
subjects affected / exposed	3 / 73 (4.11%)		
occurrences (all)	10		
GGT increased			
subjects affected / exposed	12 / 73 (16.44%)		
occurrences (all)	14		
INR increased			
subjects affected / exposed	2 / 73 (2.74%)		
occurrences (all)	3		
Lymphocyte count decreased			
subjects affected / exposed	6 / 73 (8.22%)		
occurrences (all)	9		
Platelet count decreased			

subjects affected / exposed	8 / 73 (10.96%)		
occurrences (all)	11		
Neutrophil count decreased			
subjects affected / exposed	41 / 73 (56.16%)		
occurrences (all)	116		
Weight loss			
subjects affected / exposed	7 / 73 (9.59%)		
occurrences (all)	7		
White blood cell count decreased			
subjects affected / exposed	32 / 73 (43.84%)		
occurrences (all)	89		
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Nervous system disorders			
Cholinergic syndrome			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Dysgeusia			
subjects affected / exposed	2 / 73 (2.74%)		
occurrences (all)	2		
Headache			
subjects affected / exposed	5 / 73 (6.85%)		
occurrences (all)	5		
Sensory peripheral neuropathy			
subjects affected / exposed	2 / 73 (2.74%)		
occurrences (all)	2		
Seizure			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Syncope			

subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	2		
Burning sensation			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	19 / 73 (26.03%)		
occurrences (all)	31		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Eye disorders			
Blurred vision			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Dry eye			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Periorbital oedema			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Watering eyes			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	8 / 73 (10.96%)		
occurrences (all)	11		
Anal pain			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	10 / 73 (13.70%)		
occurrences (all)	16		
Dental caries			

subjects affected / exposed	2 / 73 (2.74%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	30 / 73 (41.10%)		
occurrences (all)	55		
Dysphagia			
subjects affected / exposed	2 / 73 (2.74%)		
occurrences (all)	3		
Gastritis	Additional description: 1		
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Anal fissure			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Intestinal cutaneous fistula			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Gastrointestinal pain			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Ileus			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Mucositis oral			
subjects affected / exposed	11 / 73 (15.07%)		
occurrences (all)	16		
Nausea			
subjects affected / exposed	12 / 73 (16.44%)		
occurrences (all)	17		
Periodontal disease			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Rectal pain			
subjects affected / exposed	2 / 73 (2.74%)		
occurrences (all)	8		
Toothache			

subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	4 / 73 (5.48%)		
occurrences (all)	8		
Hepatobiliary disorders			
Gallbladder pain			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Hepatic pain			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Portal vein thrombosis			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Hepatobiliary disorder	Additional description: No further information available		
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Alopecia			
subjects affected / exposed	2 / 73 (2.74%)		
occurrences (all)	2		
Erythema multiforme			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	6 / 73 (8.22%)		
occurrences (all)	7		
Pruritus			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Rash acneiform			

subjects affected / exposed	2 / 73 (2.74%)		
occurrences (all)	4		
Rash maculo-papular			
subjects affected / exposed	3 / 73 (4.11%)		
occurrences (all)	3		
Abscess of head and neck			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Onycholysis			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Skin hyperpigmentation			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Skin hypopigmentation			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Renal and urinary disorders			
Cystitis noninfective			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Proteinuria			
subjects affected / exposed	22 / 73 (30.14%)		
occurrences (all)	41		
Musculoskeletal and connective tissue disorders			
Gouty arthritis			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Pain in extremity	Additional description: Upper extremity		
subjects affected / exposed	2 / 73 (2.74%)		
occurrences (all)	2		
Arthralgia			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	2		
Arthritis			

subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	2		
Bone pain			
subjects affected / exposed	2 / 73 (2.74%)		
occurrences (all)	2		
Chest wall pain			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Cramps			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Infections and infestations			
Catheter related infection			
subjects affected / exposed	2 / 73 (2.74%)		
occurrences (all)	2		
Viral infection			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Skin infection			
subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	1		
Tooth infection			
subjects affected / exposed	2 / 73 (2.74%)		
occurrences (all)	2		
Upper respiratory infection			
subjects affected / exposed	3 / 73 (4.11%)		
occurrences (all)	4		
Urinary tract infection			
subjects affected / exposed	3 / 73 (4.11%)		
occurrences (all)	5		
Metabolism and nutrition disorders			
Anorexia			

subjects affected / exposed	10 / 73 (13.70%)			
occurrences (all)	16			
Hypercalcemia				
subjects affected / exposed	1 / 73 (1.37%)			
occurrences (all)	1			
Hyperglycaemia				
subjects affected / exposed	28 / 73 (38.36%)			
occurrences (all)	62			
Hyperkalaemia				
subjects affected / exposed	2 / 73 (2.74%)			
occurrences (all)	12			
Hypermagnesaemia				
subjects affected / exposed	1 / 73 (1.37%)			
occurrences (all)	1			
Hypernatraemia				
subjects affected / exposed	1 / 73 (1.37%)			
occurrences (all)	1			
Hypertriglyceridaemia				
subjects affected / exposed	11 / 73 (15.07%)			
occurrences (all)	12			
Hyperuricaemia				
subjects affected / exposed	6 / 73 (8.22%)			
occurrences (all)	10			
Hypoalbuminaemia				
subjects affected / exposed	9 / 73 (12.33%)			
occurrences (all)	18			
Hypocalcaemia				
subjects affected / exposed	13 / 73 (17.81%)			
occurrences (all)	22			
Hypoglycaemia				
subjects affected / exposed	6 / 73 (8.22%)			
occurrences (all)	8			
Hypokalaemia				
subjects affected / exposed	12 / 73 (16.44%)			
occurrences (all)	23			
Hypomagnesaemia				

subjects affected / exposed	1 / 73 (1.37%)		
occurrences (all)	3		
Hyponatraemia			
subjects affected / exposed	10 / 73 (13.70%)		
occurrences (all)	23		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 February 2015	changes in reporting requirements for Adverse Events of Special Interest

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported