Clinical trial results:
A Phase II, single-arm clinical trial of administration of Cisplatin and 5-Fluorouracil with Afatinib as first-line therapy in patients with inoperable gastric or gastroesophageal junction cancer

Summary

EudraCT number	2011-006198-25
Trial protocol	GR
Global end of trial date	29 July 2019

Results information

Result version number	v1 (current)
This version publication date	08 August 2020
First version publication date	08 August 2020

Trial information

Trial identification

Sponsor protocol code	HE7/12

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01743365
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hellenic Cooperative Oncology Group
Sponsor organisation address	Messoghion Avenue 41, Athens, Greece, 115 26
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	25 October 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the efficacy and safety of the combination mCisFU-A (modified cisplatin, 5FU, afatinib) as first line therapy iin patients with inoperable, locally advanced or metastatic gastric or gastroesophageal adenocarcinoma in terms of objective response, in accordance with RECIST 1.1.

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	11 February 2013
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: 55
Worldwide total number of subjects	55
EEA total number of subjects	55

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)	26
From 65 to 84 years	29
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled between 11th February 2013 and 29th September 2016 in 12 sites in Greece.

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	Cisplatin, 5FU, Afatinib

Arm description:

The treatment combination was administered in treatment cycles including Cisplatin(75 mgr/m^2) intravenously on Day 1, 5FU (750 mgr/m^2) at 24-hour IV infusion on Days 1-4 and Afatinib (40mg per os) on Days 3-5, 8-12, 15-19 of each cycle. Administration of Afatinib started on Day 3 of each cycle with an administration interval on each weekend ("Weekday on, Weekend off"). In the absence of disease progression or significant toxicity, 6 cycles of combination treatment were administered. Following 6 cycles of the combination treatment, patients continued with Afatinib monotherapy until disease progression,or significant toxicity or withdrawal of consent at the weekday on-weekend off schedule.

Arm type	Experimental
Investigational medicinal product name	Afatinib
Investigational medicinal product code	BIBW 2992
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Afatinib (BIBW 2992) 40 mg film coated tablets were administered orally until disease progression , unacceptable toxicity or patient's consent withdrawal on days 3-5, 8-12, 15-19 of each cycle for 21 days. Administration of Afatinib was started on Day 3 of each cycle with an administration interval on each weekend ("Weekday on, Weekend off"). At the completion of 6 cycles of combination, in the absence of disease progression, the administration of Afatinib, as maintenance monotherapy, will be continued until disease progression, appearance of significant toxicity, or withdrawal of consent at the weekday on weekend off schedule

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cisplatin (75mgr/m^2) was administered in an intravenous infusion on Day 1 until disease progression, unacceptable toxicity, patient's consent withdrawal or completion of six treatment cycles.

Investigational medicinal product name	5 FLUOROURACIL
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

5 FLUOROURACIL was administered (750 mgr/m^2) in a 24-hour intravenous infusion on Days 1-4 until disease progression, unacceptable toxicity, patient's consent withdrawal or completion of six treatment cycles.

Number of subjects in period 1	Cisplatin, 5FU, Afatinib
Started	55
Completed	22
Not completed	33
Resection of measurable disease	1
Physician decision	3
Consent withdrawn by subject	7
Disease progression	16
Adverse event, non-fatal	4
Death	1
Incompliant patient	1

Baseline characteristics

Reporting groups

Reporting group title	Overall trial (overall period)

Reporting group description: -

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	55	55	
Age categorical Units: Subjects			
<=65	30	30	
>65	25	25	
Age continuous Units: years			
median	64.3		
full range (min-max)	20.2 to 77.4	-	
Gender categorical Units: Subjects			
Female	19	19	
Male	36	36	

Subject analysis sets

Subject analysis set title	Per Protocol Population
Subject analysis set type	Per protocol

Subject analysis set description:

The subgroup of patients with gastric adenocarcinoma/carcinoma who received at least one full cycle of the study treatment, and had an initial tumor assessment (Per Protocol, PP population).

Reporting group values	Per Protocol Population		
Number of subjects	42		
Age categorical Units: Subjects			
<=65	23		
>65	19		
Age continuous Units: years			
median	64.4		
full range (min-max)	20.2 to 77.4		
Gender categorical Units: Subjects			
Female	14		
Male	28		

End points

End points reporting groups

Reporting group title	Cisplatin, 5FU, Afatinib

Reporting group description:

The treatment combination was administered in treatment cycles including Cisplatin(75 mgr/m^2) intravenously on Day 1, 5FU (750 mgr/m^2) at 24-hour IV infusion on Days 1-4 and Afatinib (40mg per os) on Days 3-5, 8-12, 15-19 of each cycle. Administration of Afatinib started on Day 3 of each cycle with an administration interval on each weekend ("Weekday on, Weekend off"). In the absence of disease progression or significant toxicity, 6 cycles of combination treatment were administered. Following 6 cycles of the combination treatment, patients continued with Afatinib monotherapy until disease progression,or significant toxicity or withdrawal of consent at the weekday on-weekend off schedule.

Subject analysis set title	Per Protocol Population
Subject analysis set type	Per protocol

Subject analysis set description:

The subgroup of patients with gastric adenocarcinoma/carcinoma who received at least one full cycle of the study treatment, and had an initial tumor assessment (Per Protocol, PP population).

Primary: Objective response rate

End point title	Objective response rate[1]

End point description:

The primary objective of this study was to evaluate the activity of the combination mCisFU-A (modified cisplatin, 5-FU, afatinib) in patients with inoperable, locally advanced or metastatic gastric or gastroesophageal adenocarcinoma in terms of objective response, in accordance with RECIST 1.1. The objective response rate (ORR) was defined as the percentage of patients who had a confirmed complete response (CR) or partial response (PR) according to the evaluation criteria for patients with solid tumours (RECIST 1.1) and was evaluated in (i) all patients included in the trial and ; (ii) patients who have received at least one cycle of the trial medication, who underwent initial evaluation of the disease and who had the correct histologic type of cancer (Per Protocol –PP- population).

End point type	Primary

End point timeframe:

At the average of 6 months per patient. Imaging techniques were applied once every 8 weeks during the administration of mCisFU-A (modified cisplatin, 5-FU, afatinib) (6 cycles), and once every 12 weeks in the maintenance phase with afatinib monotherapy

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: The objective response rate, i.e. the percentage of patients achieving a complete or partial response as the best response was described using descriptive statistics for the entire cohort and the PP population.

End point values	Cisplatin, 5FU, Afatinib	Per Protocol Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	55	42		
Units: percentage of patients				
CR/PR	35	43		
SD	29	36		
PD	18	21		
Treatment discontinuation prior to evaluation	16	0		
Not evaluated due to gastrectomy	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall survival (OS) was calculated from the date of study entry to the date of death from any cause or last contact, whichever occurred first. OS was estimated both in the entire cohort and in the PP population.

End point type	Secondary

End point timeframe:

Patients were followed up for a median of 56 months (95% CI 28.5-NR).

End point values	Cisplatin, 5FU, Afatinib	Per Protocol Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	55	42		
Units: months				
median (confidence interval 95%)	8.7 (6.7 to 11.5)	7.4 (6.6 to 10.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival

End point title	Progression free survival

End point description:

Progression-free survival (PFS) was calculated from the date of study entry to the date of disease progression, death from any cause or last contact. PFS was estimated both in the entire cohort and in the PP population.

End point type	Secondary

End point timeframe:

Patients were followed-up for a median of 56 months (95% CI 28.5-NR).

End point values	Cisplatin, 5FU, Afatinib	Per Protocol Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	55			
Units: months				
median (confidence interval 95%)	5.0 (4.0 to 6.0)	4.8 (4.0 to 5.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety profile

End point title	Safety profile

End point description:

Safety was assessed in the safety population consisting of all patients that received at least one dose of the study drug (s).

End point type	Secondary

End point timeframe:

Assessed up to 36 months. Evaluation of Adverse Events (AEs) was performed on Day 1 and day 10 in cycle 1,on Day 1 in cycles 2-6 (every 21 days) and on Day 1 during maintenance treatment with afatinib (every 4 weeks).

End point values	Cisplatin, 5FU, Afatinib			
Subject group type	Reporting group			
Number of subjects analysed	55			
Units: number of patients				
Any adverse event	54			
Fatal adverse events	0			
Serious adverse event	27			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Evaluation of Adverse Events (AEs) was performed on Day 1, Day 10 in cycle 1, on Day 1 in cycles 2-6 (every 21 days) and on Day 1 during maintenance treatment with afatinib

Adverse event reporting additional description:

The combination of Cisplatin, 5-Fluorouracil with Afatinib was administered as first-line therapy.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23

Reporting groups

Reporting group title	mCisFUA

Reporting group description:

Evaluation of Adverse Events (AEs) was performed on Day 1 and day 10 in cycle 1,on Day 1 in cycles 2-6 (every 21 days) and on Day 1 during maintenance treatment with afatinib (every 4 weeks).

Serious adverse events	mCisFUA		
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 55 (49.09%)		
number of deaths (all causes)	49		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour bleeding			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Oedema	Additional description: Face, limbs and trunk		
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fatigue			

subjects affected / exposed	2 / 55 (3.64%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Fever				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Allergic reaction				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Creatinine increased				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Chest pain-cardiac				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Sinus bradycardia				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebrovascular accident				
subjects affected / exposed	3 / 55 (5.45%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Paresis				

subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Thrombopenia			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Periorbital oedema			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences causally related to treatment / all	4 / 5		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Anorexia			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Dysphagia			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal perforation			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mucositis oral			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Oesophageal haemorrhage			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Stevens-Johnson syndrome			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			

Renal disorder				
subjects affected / exposed	2 / 55 (3.64%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Catheter related infection				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enterocolitis infectious				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Joint infection				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Kidney infection				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mycosis				
subjects affected / exposed	1 / 55 (1.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	2 / 55 (3.64%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				

Dehydration			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Hypomagnesaemia			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	mCisFUA		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 55 (90.91%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Thromboembolic event			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	4		
General disorders and administration site conditions			
Oedema	Additional description: Oedema limbs		
subjects affected / exposed	7 / 55 (12.73%)		
occurrences (all)	9		
Fatigue			

subjects affected / exposed	8 / 55 (14.55%)		
occurrences (all)	13		
Infusion site extravasation			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Fever			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	6		
Immune system disorders			
Allergic reaction			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	5		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Dyspnoea			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	10		
Hiccups			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	2		
Nasal congestion			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Pleural effusion			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Lung nodule	Additional description: Post inflammatory lower right lung lesions		
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Pleuritic pain			

subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Catarrh			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Dry nose			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Alanine aminotransferase increased			
subjects affected / exposed	9 / 55 (16.36%)		
occurrences (all)	41		
Alkaline phosphatase increased			
subjects affected / exposed	10 / 55 (18.18%)		
occurrences (all)	22		
Aspartate aminotransferase increased			
subjects affected / exposed	11 / 55 (20.00%)		
occurrences (all)	37		
Blood bilirubin increased			
subjects affected / exposed	8 / 55 (14.55%)		
occurrences (all)	12		
CPK increased			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Cholesterol high			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	7		
Creatinine increased			
subjects affected / exposed	16 / 55 (29.09%)		
occurrences (all)	53		
Gamma-glutamyltransferase increased			

subjects affected / exposed	7 / 55 (12.73%)		
occurrences (all)	23		
TSH increased			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Lymphocyte count decreased			
subjects affected / exposed	6 / 55 (10.91%)		
occurrences (all)	28		
Neutrophil count decreased			
subjects affected / exposed	29 / 55 (52.73%)		
occurrences (all)	144		
Platelet count decreased			
subjects affected / exposed	12 / 55 (21.82%)		
occurrences (all)	31		
Amylase increased	Additional description: serum		
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Weight loss			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	5		
White blood cell count decreased			
subjects affected / exposed	31 / 55 (56.36%)		
occurrences (all)	169		
Glucose urine increased			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Sinus tachycardia			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			

subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Dysgeusia			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	19		
Peripheral sensory neuropathy			
subjects affected / exposed	7 / 55 (12.73%)		
occurrences (all)	10		
Somnolence			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Neuropathic pain			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Postoperative pain	Additional description: pain at the field of surgery		
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	27 / 55 (49.09%)		
occurrences (all)	95		
Ear and labyrinth disorders			
Hearing impaired			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Tinnitus			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Eyelid oedema			

subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	11		
Constipation			
subjects affected / exposed	6 / 55 (10.91%)		
occurrences (all)	6		
Diarrhoea			
subjects affected / exposed	19 / 55 (34.55%)		
occurrences (all)	62		
Dry mouth			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	3		
Dysphagia			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Flatulence			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Bloody stool			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	7		
Bad breath			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Gastrointestinal pain	Additional description: Colic Bowel		
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Mucositis oral			
subjects affected / exposed	11 / 55 (20.00%)		
occurrences (all)	16		
Nausea			
subjects affected / exposed	15 / 55 (27.27%)		
occurrences (all)	46		

Vomiting			
subjects affected / exposed	18 / 55 (32.73%)		
occurrences (all)	59		
Rectal mucositis			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Stomach pain			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Dry skin	Additional description: 1 occurence of skin cracking at feet		
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	6		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Rash	Additional description: Rash Acneiform		
subjects affected / exposed	11 / 55 (20.00%)		
occurrences (all)	17		
Rash maculo-papular			
subjects affected / exposed	9 / 55 (16.36%)		
occurrences (all)	13		
Petechial rash			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	12		
Proteinuria			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Renal disorder			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	4		
Renal failure			

subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	2		
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Hypothyroidism			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Jaw pain	Additional description: lower jaw		
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Back pain	Additional description: lumbar pain in one occurrence		
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	2		
Contraction skeletal muscle	Additional description: muscle contraction lower limbs		
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Bone pain			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Neck pain			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Infections and infestations			
Cold sores			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Nosocomial infection			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Joint injection			

subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	2		
Mucosal infection			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Paronychia			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Upper respiratory tract infection			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	7		
Urinary tract infection			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	9		
Dehydration			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Hypercalcaemia			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Hyperglycaemia			
subjects affected / exposed	22 / 55 (40.00%)		
occurrences (all)	70		
Hyperkalaemia			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	12		
Hypermagnesaemia			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	8		
Hypernatraemia			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		

Hypertriglyceridaemia			
subjects affected / exposed	6 / 55 (10.91%)		
occurrences (all)	7		
Hyperuricaemia			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	6		
Hypocalcaemia			
subjects affected / exposed	17 / 55 (30.91%)		
occurrences (all)	40		
Hypoglycaemia			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	13		
Hypokalaemia			
subjects affected / exposed	17 / 55 (30.91%)		
occurrences (all)	47		
Hypomagnesaemia			
subjects affected / exposed	8 / 55 (14.55%)		
occurrences (all)	27		
Hyponatraemia			
subjects affected / exposed	15 / 55 (27.27%)		
occurrences (all)	33		
Hypophosphataemia			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	5		
Hypoalbuminaemia			
subjects affected / exposed	16 / 55 (29.09%)		
occurrences (all)	34		

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