Clinical trial results:
A Randomized, Open-Label, Multicenter Phase II Study of Ipilimumab Retreatment Versus Chemotherapy for Subjects With Advanced Melanoma Who Progressed After Initially Achieving Disease Control With Ipilimumab Therapy

Summary

EudraCT number	2012-003291-38
Trial protocol	DE GB BE AT IT
Global end of trial date	30 July 2014

Results information

Result version number	v1 (current)
This version publication date	30 April 2016
First version publication date	30 April 2016

Trial information

Trial identification

Sponsor protocol code	CA184-243

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01709162
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol Myers Squibb
Sponsor organisation address	Chaussee de la Hulpe 185, Brussels, Belgium, 1170
Public contact	Bristol Myers Squibb Study Director, Bristol Myers Squibb, clinical.trials@bms.com
Scientific contact	Bristol Myers Squibb Study Director, Bristol Myers Squibb, clinical.trials@bms.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	30 July 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 July 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of the study is to compare overall survival in subjects with advanced melanoma receiving ipilimumab monotherapy (3 mg/kg) as re-treatment versus chemotherapy of investigator’s choice in subjects who are randomized at the time of ipilimumab re-treatment eligibility.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 March 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	Austria: 3
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Italy: 10
Country: Number of subjects enrolled	United States: 10
Worldwide total number of subjects	31
EEA total number of subjects	21

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)	16

From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 17 centres in 4 countries.

Pre-assignment

Screening details:

A total of 31 subjects were enrolled in the study, out of which 23 were randomised and 22 received treatment. The subjects discontinued the study as they no longer meet the study criteria (4), withdrew consent (3), administrative reasons (1) and other reasons (1).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ipilimumab

Arm description:

Subjects received ipilimumab, 3 mg/kg, intravenously every 3 weeks (at Week 1, Week 4, Week 7, and Week 10) for a total of 4 doses or until disease progression, unacceptable toxicity, or withdrawal of consent.

Arm type	Experimental
Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	BMS-734016
Other name	Yervoy
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects were administered with ipilimumab 3mg/kg intravenously via 90-minute infusion every three weeks.

Arm title	Chemotherapy

Arm description:

Subjects received the investigator's choice of chemotherapy, dosed per package instructions. Chemotherapy was defined as cytotoxic or cytostatic agents or vemurafenib, but did not include immunotherapy or experimental agents.

Arm type	Active comparator
Investigational medicinal product name	Fotemustine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects were administered with fotemustine 75 mg/m^2 infusion.

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

Dosage and administration details:

Subjects were administered with dacarbazine 1000 mg/m^2 infusion.

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

Dosage and administration details:

Subjects were administered with bevacizumab 10 mg/kg infusion.

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

Dosage and administration details:

Subjects were administered with carboplatin 6 mg/kg infusion.

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

Dosage and administration details:

Subjects were administered with paclitaxel 150/175 mg/m^2 infusion.

Number of subjects in period 1[1]	Ipilimumab	Chemotherapy
Started	18	5
Receive treatment	18	4
Completed	12	0
Not completed	6	5
Consent withdrawn by subject	-	1
Disease progression	3	3
Study drug toxicity	2	-
Other reasons	1	-
Administrative reason by sponsor	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of subjects reported in the baseline period are different from the worldwide number enrolled in the trial, as 8 subjects were not randomised in the study due to various reasons.

Baseline characteristics

Reporting groups	
Reporting group title	Ipilimumab
Reporting group description:	
Subjects received ipilimumab, 3 mg/kg, intravenously every 3 weeks (at Week 1, Week 4, Week 7, and Week 10) for a total of 4 doses or until disease progression, unacceptable toxicity, or withdrawal of consent.	
Reporting group title	Chemotherapy
Reporting group description:	
Subjects received the investigator's choice of chemotherapy, dosed per package instructions. Chemotherapy was defined as cytotoxic or cytostatic agents or vemurafenib, but did not include immunotherapy or experimental agents.	

Reporting group values	Ipilimumab	Chemotherapy	Total
Number of subjects	18	5	23
Age categorical Units: Subjects			
< 65 years	9	2	11
>= 65 years	9	3	12
Age continuous Units: years			
arithmetic mean	62.3	64.2	
standard deviation	± 11.38	± 4.32	-
Gender categorical Units: Subjects			
Female	6	1	7
Male	12	4	16
Race/Ethnicity Units: Subjects			
White	18	5	23
Eastern Cooperative Oncology Group (ECOG) Performance Status			
ECOG is a 6-item scale used to assess disease progression, daily functioning, appropriate treatment, and prognosis. Performance status is scored on a scale ranging from 0-5, with (best score) 0=fully active and able to carry on all predisease performance without restriction and (worst score) 5=death.			
Units: Subjects			
0 scale	13	5	18
1 scale	5	0	5
Disease Stage at Study Entry			
By the American Joint Committee on Cancer staging: Stage 1=no spread to lymph nodes/organs, <1 mm thick and not ulcerated (1A) or <1 mm thick and ulcerated or 1–2 mm thick and not ulcerated (1B). Stage 2=no spread to lymph nodes (LN) or other organs, 1–2 mm thick and ulcerated or 2–4 mm thick and not ulcerated (2A) or 2–4 mm thick and ulcerated or >4 mm thick and not ulcerated (2B), or >4 mm thick and ulcerated (2C). Stage 3 (A,B,C)=any thickness, ulcerated or not, and spread to nearby LN or nearby tissue but not LN. Stage 4=spread to LN, other organs, or areas far from original tumor site.			
Units: Subjects			
Stage III	1	1	2
Stage IV	17	4	21
Response to Prior Ipilimumab Treatment			
Tumor responses were based on investigator assessment according to modified world health organization (mWHO) criteria. Criteria for target lesions: Complete response (CR) = disappearance of all target lesions. Partial response (PR) = Decrease of 50% or greater in sum of the products of diameters			

(SPD) relative to baseline. Progressive disease (PD) = At least 25% increase in SPD relative to nadir. Stable disease= Does not meet criteria for CR or PR, in the absence of PD. Objective response=number of subjects with best response of CR or PR.			
Units: Subjects			
Complete response/Partial response	6	0	6
Stable disease	12	5	17

End points

End points reporting groups

Reporting group title	Ipilimumab

Reporting group description:

Subjects received ipilimumab, 3 mg/kg, intravenously every 3 weeks (at Week 1, Week 4, Week 7, and Week 10) for a total of 4 doses or until disease progression, unacceptable toxicity, or withdrawal of consent.

Reporting group title	Chemotherapy

Reporting group description:

Subjects received the investigator's choice of chemotherapy, dosed per package instructions. Chemotherapy was defined as cytotoxic or cytostatic agents or vemurafenib, but did not include immunotherapy or experimental agents.

Primary: Overall Survival

End point title	Overall Survival[1]

End point description:

Overall survival was defined for each subject as the time between randomization and death. If a subject has not died, he or she will be censored at the time of last contact (last known alive date). The analysis was performed in all subjects who were randomised in the study.

End point type	Primary

End point timeframe:

From randomisation to death or last known alive date, assessed up to 15.6 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive summary statistics was planned for this outcome measure.

End point values	Ipilimumab	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	5		
Units: Months				
median (full range (min-max))	6.3 (3.2 to 15.6)	3.1 (0 to 8.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Disease Control

End point title	Number of Subjects With Disease Control

End point description:

Number of subjects with Disease Control is defined per arm as the total number of randomised subjects with best overall response as complete response, partial response, or stable disease. The study was terminated early because the study would not meet its scientific objective in the predefined time-frame. Because the study ended before best overall response could be determined, no subjects were analyzed. The analysis
was performed in all subjects who were randomised in the study.

End point type	Secondary

End point timeframe:

Every 3 months for approximately 3.5 years after start of randomisation and then every 6 months until confirmed and documented progressive disease

End point values	Ipilimumab	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: Subjects				

Notes:

[2] - The study was terminated before Disease Control Rate could be determined, no subject was analysed.
[3] - The study was terminated before Disease Control Rate could be determined, no subject was analysed.

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response Rate

End point title	Best Overall Response Rate

End point description:

Best Overall Response Rate (BORR) is defined per arm as the total number of randomised subjects with a best overall response of complete response or partial response, divided by the total number of randomised subjects in the arm. The study was terminated early because the study would not meet its scientific objective in the predefined time-frame. Because the study ended before best overall response for all subjects was defined, no subject data was analyzed. The analysis was performed in all subjects who were randomised in the study.

End point type	Secondary

End point timeframe:

Every 3 months for approximately 3.5 years after start of randomisation and then every 6 months until confirmed and documented progressive disease

End point values	Ipilimumab	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: Subjects				

Notes:

[4] - The study was terminated before best overall response could be determined, no subject was analysed.
[5] - The study was terminated before best overall response could be determined, no subject was analysed.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Death as Outcome, Serious Adverse Events (SAEs), Adverse Events (AEs) Leading to Discontinuation, and Immune-related AEs (irAEs)

End point title	Number of Subjects With Death as Outcome, Serious Adverse

	Events (SAEs), Adverse Events (AEs) Leading to Discontinuation, and Immune-related AEs (irAEs)

End point description:

AE=any new unfavorable symptom, sign, or disease or worsening of a preexisting condition that may not have a causal relationship with treatment. SAE=a medical event that at any dose results in death, persistent or significant disability/incapacity, or drug dependency/abuse; is life-threatening, an important medical event, or a congenital anomaly/birth defect; or requires or prolonged hospitalization. The analysis was performed in all subjects who received at least one dose of study drug.

End point type	Other pre-specified

End point timeframe:

From Day 1 of treatment to 90 days after last dose (or to death date for death information)

End point values	Ipilimumab	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	4		
Units: Subjects				
Deaths	5	1		
Deaths within 90 days of last dose	1	0		
AEs leading to discontinuation	2	0		
SAEs	7	0		
Immune related AEs	10	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Day 1 of treatment to 90 days after last dose (or to death date for death information)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Ipilimumab

Reporting group description:

Subjects received ipilimumab, 3 mg/kg, intravenously by 90-minute infusion every 3 weeks (at Week 1, Week 4, Week 7, and Week 10) for a total of 4 doses or until disease progression, unacceptable toxicity, or withdrawal of consent.

Reporting group title	Chemotherapy

Reporting group description:

Subjects received the investigator's choice of chemotherapy, dosed per package instructions. Chemotherapy was defined as cytotoxic or cytostatic agents or vemurafenib, but did not include immunotherapy or experimental agents.

Serious adverse events	Ipilimumab	Chemotherapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 18 (38.89%)	0 / 4 (0.00%)	
number of deaths (all causes)	5	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Intracranial tumour haemorrhage			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (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			
Syncope			

subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	2 / 18 (11.11%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	

Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental disorder			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (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			
Myopathy			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ipilimumab	Chemotherapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 18 (83.33%)	4 / 4 (100.00%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Influenza like illness			

subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Asthenia			
subjects affected / exposed	3 / 18 (16.67%)	1 / 4 (25.00%)	
occurrences (all)	7	1	
Oedema peripheral			
subjects affected / exposed	2 / 18 (11.11%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Chest pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	4 / 18 (22.22%)	2 / 4 (50.00%)	
occurrences (all)	4	3	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Throat irritation			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Epistaxis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Dyspnoea			
subjects affected / exposed	2 / 18 (11.11%)	1 / 4 (25.00%)	
occurrences (all)	2	1	
Hypoxia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Pneumonitis			

subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	2 / 18 (11.11%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Blood corticotrophin decreased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Transaminases increased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Weight decreased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Radiation skin injury			
subjects affected / exposed	0 / 18 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Nervous system disorders			
Somnolence			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Syncope			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences (all)	1	0	

Dizziness			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Neuropathy peripheral			
subjects affected / exposed	0 / 18 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Carpal tunnel syndrome			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 18 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	4	0	
Heparin-induced thrombocytopenia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Thrombocytopenia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Lacrimation increased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Oral dysaesthesia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Pancreatitis acute			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	6 / 18 (33.33%)	0 / 4 (0.00%)	
occurrences (all)	7	0	
Diverticulum			

subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Tongue disorder			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Oesophagitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Dyspepsia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	3 / 18 (16.67%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
Haematochezia			
subjects affected / exposed	2 / 18 (11.11%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
Skin lesion			
subjects affected / exposed	0 / 18 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	2 / 18 (11.11%)	1 / 4 (25.00%)	
occurrences (all)	3	2	
Decubitus ulcer			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Alopecia			
subjects affected / exposed	0 / 18 (0.00%)	2 / 4 (50.00%)	
occurrences (all)	0	2	
Rash maculo-papular			
subjects affected / exposed	0 / 18 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	

Erythema			
subjects affected / exposed	2 / 18 (11.11%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Ingrown hair			
subjects affected / exposed	0 / 18 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	3 / 18 (16.67%)	1 / 4 (25.00%)	
occurrences (all)	5	1	
Endocrine disorders			
Hypopituitarism			
subjects affected / exposed	2 / 18 (11.11%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Hypophysitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Flank pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	1 / 18 (5.56%)	1 / 4 (25.00%)	
occurrences (all)	1	1	
Muscle fatigue			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Arthralgia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Infections and infestations			
Influenza			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences (all)	1	0	

Pneumonia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Bronchitis			
subjects affected / exposed	2 / 18 (11.11%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Otitis media			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 18 (11.11%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Hypokalaemia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Hyponatraemia			
subjects affected / exposed	2 / 18 (11.11%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Hyperlipidaemia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Hypoglycaemia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 4 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 July 2013	• The primary endpoint of overall survival was changed from a time-point driven endpoint to an event driven endpoint as a result of a communication with a regulatory authority • The estimated accrual period was modified from 12 months to 21 months

Notes:

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.

As planned, accrual of subjects was to be completed within 21 months. However, the projections showed that 4 to 5 years were needed. The study was terminated early because the scientific objective could not be met in the predefined time-frame.

Notes: