Clinical trial results:
Phase 2 Study of Ipilimumab in Children and Adolescents (12<18 years) with Previously Treated or Untreated, Unresectable Stage III or Stage IV Malignant Melanoma

Summary

EudraCT number	2012-002249-39
Trial protocol	GB BE FR DE ES IT Outside EU/EEA DK
Global end of trial date	22 June 2016

Results information

Result version number	v1 (current)
This version publication date	21 January 2017
First version publication date	21 January 2017

Trial information

Trial identification

Sponsor protocol code	CA184-178

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01696045
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium,
Public contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, clinical.trials@bms.com
Scientific contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, clinical.trials@bms.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000117-PIP02-10, EMEA-000117-PIP01-07
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 June 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 June 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

- To estimate the survival rate at 1 year in adolescent patients (12 to < 18 years) with previously treated or untreated, unresectable Stage III or Stage IV malignant melanoma.
- To assess safety and tolerability, specifically the frequency of severe (grade 3 - 5) immune-mediated adverse reactions of ipilimumab in adolescent patients (12 to < 18 years).

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	31 December 2012
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: 1
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	14
EEA total number of subjects	7

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)	14
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

14 subjects were enrolled in the study. 12 subjects received study treatment. 2 subjects were enrolled and not treated because they no longer met study criteria.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ipilimumab 3mg/kg

Arm description:

Ipilimumab 3mg/kg

Arm type	Experimental
Investigational medicinal product name	ipilimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ipilimumab was administered intravenously (IV) over 90 minutes on Day 1 of each 21-day cycle for 4 cycles.

Arm title	Ipilimumab 10mg/kg

Arm description:

Ipilimumab 10mg/kg

Arm type	Experimental
Investigational medicinal product name	ipilimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ipilimumab was administered intravenously (IV) over 90 minutes on Day 1 of each 21-day cycle for 4 cycles.

Number of subjects in period 1[1]	Ipilimumab 3mg/kg	Ipilimumab 10mg/kg
Started	4	8
Completed	1	1
Not completed	3	7
Disease progression	2	2

Study drug toxicity	1	5

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: Of the 14 subjects enrolled in the trial, only 12 received treatment.

Baseline characteristics

Reporting groups	
Reporting group title	Ipilimumab 3mg/kg
Reporting group description: Ipilimumab 3mg/kg	
Reporting group title	Ipilimumab 10mg/kg
Reporting group description: Ipilimumab 10mg/kg	

Reporting group values	Ipilimumab 3mg/kg	Ipilimumab 10mg/kg	Total
Number of subjects	4	8	12
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)	4	8	12
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	13.3	14.9	
standard deviation	± 1.89	± 0.64	-
Gender categorical Units: Subjects			
Female	2	3	5
Male	2	5	7

End points

End points reporting groups

Reporting group title	Ipilimumab 3mg/kg
Reporting group description: Ipilimumab 3mg/kg	
Reporting group title	Ipilimumab 10mg/kg
Reporting group description: Ipilimumab 10mg/kg	

Primary: Overall Survival (OS) Rate at 1 year

End point title	Overall Survival (OS) Rate at 1 year[1]

End point description:

Overall Survival (OS) was defined as the time from the start of ipilimumab treatment date to death due to any cause. If a subject had not died, the subject was censored at the time of last contact (last known alive date). OS rates at 1 year were calculated from both Kaplan-Meier estimates and the proportion of subjects alive at 1 year following start of treatment. All treated subjects were included in these analyses.

End point type	Primary

End point timeframe:

1 year following start of treatment

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 summary statistics were planned for this endpoint.

End point values	Ipilimumab 3mg/kg	Ipilimumab 10mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	8		
Units: percentage of subjects				
number (confidence interval 95%)				
OS Rate - Kaplan-Meier estimates	75 (12.8 to 96.1)	62.5 (22.9 to 86.1)		
OS Rate - Proportion of surviving treated subjects	75 (19.4 to 99.4)	62.5 (24.5 to 91.5)		

Statistical analyses

No statistical analyses for this end point

Primary: Proportion of Subjects with Severe Immune-Mediated Adverse Reactions (imARs)

End point title	Proportion of Subjects with Severe Immune-Mediated Adverse Reactions (imARs)[2]

End point description:

The proportion of severe Immune-mediated Adverse Reactions (imARs) was calculated by dividing the number of subjects with grade 3 or worse imARs by the total number of treated subjects. imARs were AEs determined by the investigator to have an immune-mediated etiology, including inflammatory events associated with ipilimumab treatment. All treated subjects were included in the analysis.

End point type	Primary

End point timeframe:

From first dose to 90 days after last dose.

Notes:

[2] - 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 summary statistics were planned for this endpoint.

End point values	Ipilimumab 3mg/kg	Ipilimumab 10mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	8		
Units: percentage of subjects				
number (confidence interval 95%)	25 (0.6 to 80.6)	62.5 (24.5 to 91.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate

End point title	Disease Control Rate

End point description:

Disease control rate was defined as the percentage of all treated subjects with a best overall response of Complete Response (CR), Partial Response (PR), or Stable disease (SD), based on the investigator's assessment per mWHO Criteria.

CR= Complete disappearance of all non-index lesions. PR= Decrease, relative to baseline, of 50% or greater in the sum of the products of the two largest perpendicular diameters of all index lesions. SD= Does not meet criteria for complete or partial response, in the absence of progressive disease. PD= At least 25% increase in the sum of the products of all index lesions (taking as reference the smallest sum recorded at or following baseline) and/or the appearance of any new lesion(s).

End point type	Secondary

End point timeframe:

Day 1 of first patient, first treatment to Day 365 of last patient, first treatment (Approximately 24 months)

End point values	Ipilimumab 3mg/kg	Ipilimumab 10mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	8		
Units: percentage of subjects				
number (confidence interval 95%)	25 (0.6 to 80.6)	37.5 (8.5 to 75.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Median Number of Months of Progression-Free Survival

End point title	Median Number of Months of Progression-Free Survival

End point description:

Progression-Free Survival was defined as the time from the start of ipilimumab treatment to disease progression or death, whichever occurs first. A subject who died without reported progression were considered to have progressed on their date of death. For subjects who remained alive and had not progressed, PFS was censored on the date of the last tumor assessment. All treated subjects were included in this analysis.

End point type	Secondary

End point timeframe:

From first treatment until disease progression or death

End point values	Ipilimumab 3mg/kg	Ipilimumab 10mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	8		
Units: months				
median (confidence interval 95%)	2.6 (2.3 to 8.5)	2.9 (0.7 to 99999)		

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) was defined as the total number of treated subjects with the best overall response of Complete Response (CR) or Partial Response (PR) divided by the total number of treated subjects. All treated subjects were included in this analysis.

CR= Complete disappearance of all non-index lesions. PR= Decrease, relative to baseline, of 50% or greater in the sum of the products of the two largest perpendicular diameters of all index lesions. SD= Does not meet criteria for complete or partial response, in the absence of progressive disease. PD= At least 25% increase in the sum of the products of all index lesions (taking as reference the smallest sum recorded at or following baseline) and/or the appearance of any new lesion(s).

End point type	Secondary

End point timeframe:

Day 1 of first subject, first treatment to Day 365 of last subject, first treatment (Approximately 24 months)

End point values	Ipilimumab 3mg/kg	Ipilimumab 10mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	8		
Units: percentage of subjects				
number (confidence interval 95%)	0 (0 to 60.2)	25 (3.2 to 65.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Median Overall Survival Time

End point title	Median Overall Survival Time

End point description:

Overall Survival time was defined as the time from the start of ipilimumab treatment date to death. If a subject had not died, the subject was censored at the time of last contact (last known alive date). All treated subjects were included in this analysis.

End point type	Secondary

End point timeframe:

Date of First Patient, First Treatment until study completion date (Approximately 38 months)

End point values	Ipilimumab 3mg/kg	Ipilimumab 10mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	8		
Units: months				
median (confidence interval 95%)	18.2 (8.9 to 18.2)	99999 (5.2 to 99999)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
On Study (i.e. events from 1st dose date through last dose date + 90 days)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	Ipilimumab 3 mg/kg
Reporting group description:	
Ipilimumab 3 mg/kg	
Reporting group title	Ipilimumab 10 mg/kg
Reporting group description:	
Ipilimumab 10 mg/kg	

Serious adverse events	Ipilimumab 3 mg/kg	Ipilimumab 10 mg/kg	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 4 (25.00%)	6 / 8 (75.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastatic malignant melanoma			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			

subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	1 / 4 (25.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 4 (0.00%)	2 / 8 (25.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			

subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
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	Ipilimumab 3 mg/kg	Ipilimumab 10 mg/kg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	8 / 8 (100.00%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Hypotension			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Axillary pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Chest pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Chills			

subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	0 / 4 (0.00%)	4 / 8 (50.00%)	
occurrences (all)	0	4	
Pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	1 / 4 (25.00%)	3 / 8 (37.50%)	
occurrences (all)	1	12	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Hypersensitivity			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 4 (25.00%)	3 / 8 (37.50%)	
occurrences (all)	1	3	
Dyspnoea			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Epistaxis			
subjects affected / exposed	0 / 4 (0.00%)	2 / 8 (25.00%)	
occurrences (all)	0	2	
Hypoxia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Laryngeal pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Nasal congestion			

subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Pleural effusion			
subjects affected / exposed	0 / 4 (0.00%)	2 / 8 (25.00%)	
occurrences (all)	0	2	
Pneumothorax			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Psychiatric disorders			
Mood altered			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 4 (0.00%)	2 / 8 (25.00%)	
occurrences (all)	0	7	
Amylase increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	2	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 4 (0.00%)	2 / 8 (25.00%)	
occurrences (all)	0	8	
Blood albumin decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	2	
Blood bilirubin increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Blood calcium decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	4	
Blood glucose increased			

subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Blood magnesium decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	2	
Blood phosphorus decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Blood potassium decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	6	
Blood sodium decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Coagulation factor increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Lipase increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	3	
Platelet count decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Weight decreased			
subjects affected / exposed	0 / 4 (0.00%)	4 / 8 (50.00%)	
occurrences (all)	0	6	
White blood cell count increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	3	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Infusion related reaction			

subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Ventricular extrasystoles			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Ventricular tachycardia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Dysgeusia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	2 / 4 (50.00%)	5 / 8 (62.50%)	
occurrences (all)	3	7	
Tremor			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	4	
Eye disorders			
Eyelid pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Photophobia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Vision blurred			

subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 4 (25.00%)	2 / 8 (25.00%)	
occurrences (all)	1	3	
Ascites			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	2	
Constipation			
subjects affected / exposed	0 / 4 (0.00%)	3 / 8 (37.50%)	
occurrences (all)	0	4	
Diarrhoea			
subjects affected / exposed	0 / 4 (0.00%)	4 / 8 (50.00%)	
occurrences (all)	0	12	
Haematochezia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	1 / 4 (25.00%)	6 / 8 (75.00%)	
occurrences (all)	3	10	
Pancreatitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	1 / 4 (25.00%)	7 / 8 (87.50%)	
occurrences (all)	3	21	
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	
occurrences (all)	3	0	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Dry skin			

subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Hyperhidrosis			
subjects affected / exposed	0 / 4 (0.00%)	2 / 8 (25.00%)	
occurrences (all)	0	2	
Pain of skin			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	1 / 4 (25.00%)	2 / 8 (25.00%)	
occurrences (all)	1	2	
Rash			
subjects affected / exposed	1 / 4 (25.00%)	3 / 8 (37.50%)	
occurrences (all)	2	4	
Skin disorder			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Muscle fatigue			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Muscle spasms			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 8 (25.00%)	
occurrences (all)	0	2	
Pain in jaw			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Infections and infestations			

Candida nappy rash			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Conjunctivitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Rotavirus infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Tonsillitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 4 (0.00%)	4 / 8 (50.00%)	
occurrences (all)	0	8	
Dehydration			
subjects affected / exposed	0 / 4 (0.00%)	2 / 8 (25.00%)	
occurrences (all)	0	8	
Hyperglycaemia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 8 (25.00%)	
occurrences (all)	0	3	
Hyperkalaemia			

subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Hypernatraemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Hyperuricaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Hypoalbuminaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	2	
Hypocalcaemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Hypokalaemia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 8 (25.00%)	
occurrences (all)	0	14	
Hyponatraemia			
subjects affected / exposed	0 / 4 (0.00%)	3 / 8 (37.50%)	
occurrences (all)	0	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 May 2014	The purpose of this amendment is to change the study medication dose from 10 mg/kg to 3 mg/kg based on the approved adult ipilimumab dose for this indication, to remove the maintenance phase since maintenance has not been proven to add additional benefit based on previous ipilimumab studies and the approved schedule of ipilimumab does not include maintenance, to allow for one reinduction/retreatment for eligible subjects, to update the definition and guidance for Women of Child Bearing Potential (WOCB), to update the ipilimumab program specific language for defining immune-mediated adverse events, to update the maximum number of index, non index and new lesions to be followed, to clarify the PK pre-dose window time frame, to allow for re-enrollment of eligible subjects, and to add additional TSH testing at Week 24. This amendment applies to all subjects, although the dose of 3 mg/kg only applies to subjects who are enrolled after this amendment is implemented.

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.

Because the rarity of the patient population was greater than anticipated and the availability of competing therapies (eg, anti-PD-L1), most sites were unable to enroll a participant over the 3.5 year period, and the DMC recommended study closure.

Notes: