Clinical trial results:
Adjuvant peginterferon alfa-2b for 2 years vs Observation in patients with an ulcerated primary cutaneous melanoma with T(2-4)bN0M0: a randomized phase III trial of the EORTC Melanoma Group.

Summary

EudraCT number	2009-010273-20
Trial protocol	BE GB DE FR AT IT DK ES NL PT PL
Global end of trial date	11 July 2019

Results information

Result version number	v1 (current)
This version publication date	25 March 2020
First version publication date	25 March 2020

Trial information

Trial identification

Sponsor protocol code	18081

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01502696
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	EORTC
Sponsor organisation address	Avenue Emmanuel Mounier 83/11, Brussels, Belgium, 1200
Public contact	Project Mgt & Regulatory Unit, EORTC, 32 27741654, eortc@eortc.be
Scientific contact	Project Mgt & Regulatory Unit, EORTC, 32 27741654, eortc@eortc.be

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	11 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 July 2019
Global end of trial reached?	Yes
Global end of trial date	11 July 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine whether post-operative adjuvant therapy with peginterferon alfa-2b improves relapse-free survival (RFS) as compared to observation.

Protection of trial subjects:

Safety data were reviewed within the EORTC Headquarters on a regular basis as part of the Medical Review process. Safety information was included in trial status reports which served as a basis of discussion during EORTC Group meetings.

Background therapy:

Before randomization, patients underwent a resection of ulcerated primary cutaneous melanoma. 1 to 2 cm normal tissue excision margins according to Breslow thickness were recommended.

Evidence for comparator:

Observation was used as comparator. No effective adjuvant treatments were available at the time of the study.

Actual start date of recruitment	08 January 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	Netherlands: 4
Country: Number of subjects enrolled	Poland: 14
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	United Kingdom: 21
Country: Number of subjects enrolled	Austria: 7
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	France: 35
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Switzerland: 2
Worldwide total number of subjects	112
EEA total number of subjects	110

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)	93
From 65 to 84 years	19
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study intended to randomize 1200 patients. It was expected that 1200 patients would be randomized in 4.125 years from the accrual of the first patient.

In total, 112 patients had been randomized by January 2017. Due to the low accrual, the recruitment was terminated at that time.

Pre-assignment

Screening details:

Main eligibility criteria:

Age: 18-70 years
Complete resection of ulcerated primary cutaneous melanoma stage T(2-4)bN0M0
SLN biopsy mandatory
No evidence of lymph node involvement or satellite / in-transit metastases
ECOG performance status of 0 or 1
Adequate hepatic, renal and bone marrow function
No active autoimmune disease

Period 1

Period 1 title	Adjuvant treatment and observation (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Observation

Arm description:

Observation for two years

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	PEG-IFN

Arm description:

Peginterferon alfa-2b (3.0 µg/kg), weekly for 2 years or until relapse of the disease, unacceptable toxicity, patient's refusal, patient's best interest to stop according to treating physician.

Arm type	Experimental
Investigational medicinal product name	Pegylated interferon alfa-2b
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Dose reductions as needed were used in order to assure ECOG performance score of 0 to 1.

Dose reduction steps: 3.0 – 2.0 –1.0 µg/kg.

Patients deemed competent to self administer the subcutaneous injections of peginterferon alfa-2b were allowed to do so.

Number of subjects in period 1	Observation	PEG-IFN
Started	56	56
Completed	33	16
Not completed	23	40
Relapse	12	2
Consent withdrawn by subject	6	8
Adverse event, non-fatal	-	23
Due to delay of the treatment start	-	1
Failure to administer the treatment	-	1
Pregnancy	-	1
Other malignancy	1	-
Patient moved	1	-
Stopped eariler but received all planned doses	-	1
Lost to follow-up	3	1
Suspected relapse	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Observation
Reporting group description: Observation for two years	
Reporting group title	PEG-IFN
Reporting group description: Peginterferon alfa-2b (3.0 µg/kg), weekly for 2 years or until relapse of the disease, unacceptable toxicity, patient's refusal, patient's best interest to stop according to treating physician.	

Reporting group values	Observation	PEG-IFN	Total
Number of subjects	56	56	112
Age categorical Units: Subjects			
Adults (18-64 years)	44	49	93
From 65-84 years	12	7	19
Age continuous Units: years			
median	55	53	
full range (min-max)	27 to 70	28 to 69	-
Gender categorical Units: Subjects			
Female	17	29	46
Male	39	27	66
Primary site, Breslow thickness			
Stratification factor used for randomization.			
Units: Subjects			
Head, neck or trunk, 2mm or less	9	8	17
Extremity, 2mm or less	8	6	14
Head, neck or trunk, 2+ to 4mm	14	16	30
Extremity, 2+ to 4mm	10	11	21
Head, neck or trunk, >4mm	7	7	14
Extremity, >4mm	8	8	16

End points

End points reporting groups

Reporting group title	Observation
Reporting group description:	
Observation for two years	
Reporting group title	PEG-IFN
Reporting group description:	
Peginterferon alfa-2b (3.0 µg/kg), weekly for 2 years or until relapse of the disease, unacceptable toxicity, patient's refusal, patient's best interest to stop according to treating physician.	

Primary: Relapse-free survival

End point title	Relapse-free survival
End point description:	
Relapse-free survival was defined as the time between the date of randomization and the date of first relapse (local, regional, distant metastasis) or death (whatever the cause), whichever occurs first. For subjects who remained alive and whose disease has not recurred, RFS was censored on the date of last visit.	
End point type	Primary
End point timeframe:	
Originally planned after reaching 330 RFS events. The accrual was stopped prematurepy due to the low accrual rate. The analysis was performed when all patients had finished the protocol treatment.	

End point values	Observation	PEG-IFN		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	56		
Units: % at three years				
number (confidence interval 95%)	73 (58 to 83)	80 (66 to 89)		

Statistical analyses

Statistical analysis title	Relapse-free survival
Statistical analysis description:	
HR values smaller than 1 indicate longer RFS in the experimental arm.	
Comparison groups	Observation v PEG-IFN
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.66

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	1.37

Secondary: Distant metastasis-free survival

End point title	Distant metastasis-free survival

End point description:

End point type	Secondary

End point timeframe:

Analysis performed at the same time as the RFS analysis.

End point values	Observation	PEG-IFN		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	56		
Units: % at three years				
number (confidence interval 95%)	76 (62 to 86)	91 (79 to 96)		

Statistical analyses

Statistical analysis title	Distant metastasis-free survival

Statistical analysis description:

HR values smaller than 1 indicate longer DMFS in the experimental arm

Comparison groups	Observation v PEG-IFN
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	0.97

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The number of patients who had specific adverse events in the period between the randomization and the time of treatment/observation discontinuation was reported. The maximum time was 2 years and one week.

Adverse event reporting additional description:

CRF for AEs contains pre-specified items + additional boxes for all "other" AEs. AEs are evaluated using CTC grading, SAEs using MedDra.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	Observation

Reporting group description:

All patients who underwent observation, irrespective of the randomized treatment. This group includes 55 patients randomized to the observation arm and 1 patient randomized to the PEG-IFN arm who has not received PEG-IFN.

Reporting group title	PEG-IFN

Reporting group description:

This group includes all patients who received at least one dose of PEG-IFN, that is 54 patients. All have been randomized to the PEG-IFN arm.

Serious adverse events	Observation	PEG-IFN	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 56 (10.71%)	4 / 54 (7.41%)	
number of deaths (all causes)	4	1	
number of deaths resulting from adverse events	0	0	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASPARTATE AMINOTRANSFERASE INCREASED			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

GAMMA-GLUTAMYLTRANSFERASE INCREASED			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
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)			
BASAL CELL CARCINOMA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 56 (1.79%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COLON ADENOMA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMANGIOMA OF LIVER			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 56 (1.79%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALIGNANT MELANOMA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	2 / 56 (3.57%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SQUAMOUS CELL CARCINOMA OF SKIN			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 56 (1.79%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

ABDOMINAL PAIN			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
PULMONARY EMBOLISM			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 56 (1.79%)	0 / 54 (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			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Observation	PEG-IFN	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 56 (76.79%)	53 / 54 (98.15%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - OTHER, SPECIFY			
alternative dictionary used: CTC 4			
subjects affected / exposed	10 / 56 (17.86%)	3 / 54 (5.56%)	
occurrences (all)	16	4	

Vascular disorders			
HEMATOMA			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
HOT FLASHES			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	3 / 54 (5.56%)	
occurrences (all)	0	3	
HYPERTENSION			
alternative dictionary used: CTC 4			
subjects affected / exposed	7 / 56 (12.50%)	10 / 54 (18.52%)	
occurrences (all)	19	26	
HYPOTENSION			
alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	3 / 54 (5.56%)	
occurrences (all)	1	5	
THROMBOEMBOLIC EVENT			
alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
VASCULAR DISORDERS - OTHER, SPECIFY			
alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	1 / 54 (1.85%)	
occurrences (all)	1	1	
VASCULITIS			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
CHILLS			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	13 / 54 (24.07%)	
occurrences (all)	0	16	
FATIGUE			
alternative dictionary used: CTC 4			

subjects affected / exposed	7 / 56 (12.50%)	37 / 54 (68.52%)	
occurrences (all)	8	61	
FEVER			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	22 / 54 (40.74%)	
occurrences (all)	0	29	
FLU LIKE SYMPTOMS			
alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	23 / 54 (42.59%)	
occurrences (all)	1	38	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - OTHER, SPECIFY			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
INFUSION RELATED REACTION			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
INJECTION SITE REACTION			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	12 / 54 (22.22%)	
occurrences (all)	0	12	
IRRITABILITY			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	3 / 54 (5.56%)	
occurrences (all)	0	3	
MALAISE			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
NON-CARDIAC CHEST PAIN			
alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
PAIN			

alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Immune system disorders			
ALLERGIC REACTION			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	2 / 54 (3.70%)	
occurrences (all)	0	2	
Reproductive system and breast disorders			
BREAST PAIN			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	2 / 54 (3.70%)	
occurrences (all)	0	2	
DYSMENORRHEA			
alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
GENITAL EDEMA			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
GYNECOMASTIA			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
IRREGULAR MENSTRUATION			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
MENORRHAGIA			
alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	1 / 54 (1.85%)	
occurrences (all)	1	1	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - OTHER, SPECIFY			
alternative dictionary used: CTC 4			

subjects affected / exposed	1 / 56 (1.79%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
VAGINAL HEMORRHAGE alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	2	
VAGINAL INFLAMMATION alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
BRONCHOSPASM alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
COUGH alternative dictionary used: CTC 4			
subjects affected / exposed	2 / 56 (3.57%)	2 / 54 (3.70%)	
occurrences (all)	3	2	
DYSPNEA alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	3 / 54 (5.56%)	
occurrences (all)	1	3	
LARYNGEAL INFLAMMATION alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
PNEUMONITIS alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
POSTNASAL DRIP alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Psychiatric disorders			

AGITATION			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
ANXIETY			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	6 / 54 (11.11%)	
occurrences (all)	0	6	
DEPRESSION			
alternative dictionary used: CTC 4			
subjects affected / exposed	2 / 56 (3.57%)	8 / 54 (14.81%)	
occurrences (all)	2	8	
INSOMNIA			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	10 / 54 (18.52%)	
occurrences (all)	0	10	
PSYCHIATRIC DISORDERS - OTHER, SPECIFY			
alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	2 / 54 (3.70%)	
occurrences (all)	1	3	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	17 / 54 (31.48%)	
occurrences (all)	2	38	
ALKALINE PHOSPHATASE INCREASED			
alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
ASPARTATE AMINOTRANSFERASE INCREASED			
alternative dictionary used: CTC 4			
subjects affected / exposed	2 / 56 (3.57%)	15 / 54 (27.78%)	
occurrences (all)	2	27	
BLOOD BILIRUBIN INCREASED			
alternative dictionary used: CTC 4			

subjects affected / exposed	1 / 56 (1.79%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
CHOLESTEROL HIGH alternative dictionary used: CTC 4			
subjects affected / exposed	3 / 56 (5.36%)	4 / 54 (7.41%)	
occurrences (all)	5	6	
CREATININE INCREASED alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	2 / 54 (3.70%)	
occurrences (all)	0	3	
GGT INCREASED alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	16 / 54 (29.63%)	
occurrences (all)	3	44	
HEMOGLOBIN INCREASED alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	2	
INVESTIGATIONS - OTHER, SPECIFY alternative dictionary used: CTC 4			
subjects affected / exposed	6 / 56 (10.71%)	12 / 54 (22.22%)	
occurrences (all)	10	32	
LYMPHOCYTE COUNT DECREASED alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	7 / 54 (12.96%)	
occurrences (all)	1	25	
NEUTROPHIL COUNT DECREASED alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	27 / 54 (50.00%)	
occurrences (all)	1	81	
PLATELET COUNT DECREASED alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	15 / 54 (27.78%)	
occurrences (all)	1	27	
WEIGHT GAIN alternative dictionary used: CTC 4			

subjects affected / exposed	6 / 56 (10.71%)	4 / 54 (7.41%)	
occurrences (all)	9	5	
WEIGHT LOSS			
alternative dictionary used: CTC 4			
subjects affected / exposed	8 / 56 (14.29%)	19 / 54 (35.19%)	
occurrences (all)	9	39	
WHITE BLOOD CELL DECREASED			
alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	26 / 54 (48.15%)	
occurrences (all)	1	75	
Injury, poisoning and procedural complications			
FRACTURE			
alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - OTHER, SPECIFY			
alternative dictionary used: CTC 4			
subjects affected / exposed	2 / 56 (3.57%)	2 / 54 (3.70%)	
occurrences (all)	2	2	
Cardiac disorders			
PALPITATIONS			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Nervous system disorders			
COGNITIVE DISTURBANCE			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
CONCENTRATION IMPAIRMENT			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
DIZZINESS			
alternative dictionary used: CTC 4			

subjects affected / exposed	0 / 56 (0.00%)	8 / 54 (14.81%)	
occurrences (all)	0	9	
DYSGEUSIA			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	2 / 54 (3.70%)	
occurrences (all)	0	3	
HEADACHE			
alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	23 / 54 (42.59%)	
occurrences (all)	1	32	
MOVEMENTS INVOLUNTARY			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
NERVOUS SYSTEM DISORDERS - OTHER, SPECIFY			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	2 / 54 (3.70%)	
occurrences (all)	0	2	
PARESTHESIA			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	4 / 54 (7.41%)	
occurrences (all)	0	4	
PERIPHERAL SENSORY NEUROPATHY			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
PRESYNCOPE			
alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
SPASTICITY			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
TREMOR			
alternative dictionary used: CTC 4			

subjects affected / exposed	0 / 56 (0.00%)	3 / 54 (5.56%)	
occurrences (all)	0	3	
Blood and lymphatic system disorders			
ANEMIA			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	9 / 54 (16.67%)	
occurrences (all)	0	13	
BLOOD AND LYMPHATIC SYSTEM DISORDERS - OTHER, SPECIFY			
alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	2 / 54 (3.70%)	
occurrences (all)	1	2	
FEBRILE NEUTROPENIA			
alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
EAR AND LABYRINTH DISORDERS - OTHER, SPECIFY			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
TINNITUS			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	2 / 54 (3.70%)	
occurrences (all)	0	2	
VERTIGO			
alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	3 / 54 (5.56%)	
occurrences (all)	1	3	
Eye disorders			
BLURRED VISION			
alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	2 / 54 (3.70%)	
occurrences (all)	1	2	
CATARACT			
alternative dictionary used: CTC 4			

subjects affected / exposed	1 / 56 (1.79%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
DRY EYE alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
EYE DISORDERS - OTHER, SPECIFY alternative dictionary used: CTC 4			
subjects affected / exposed	2 / 56 (3.57%)	2 / 54 (3.70%)	
occurrences (all)	2	2	
FLOATERS alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
PHOTOPHOBIA alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	2 / 54 (3.70%)	
occurrences (all)	0	2	
RETINOPATHY alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	1 / 54 (1.85%)	
occurrences (all)	1	1	
WATERING EYES alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
ABDOMINAL PAIN alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	2 / 54 (3.70%)	
occurrences (all)	1	3	
CONSTIPATION alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	3 / 54 (5.56%)	
occurrences (all)	1	3	
DIARRHEA alternative dictionary used: CTC 4			

subjects affected / exposed	2 / 56 (3.57%)	14 / 54 (25.93%)	
occurrences (all)	2	16	
DRY MOUTH			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	2 / 54 (3.70%)	
occurrences (all)	0	2	
DYSPEPSIA			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	2 / 54 (3.70%)	
occurrences (all)	0	2	
ESOPHAGEAL PAIN			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
GASTRIC ULCER			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
GASTRITIS			
alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
GASTROESOPHAGEAL REFLUX DISEASE			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
GASTROINTESTINAL DISORDERS - OTHER, SPECIFY			
alternative dictionary used: CTC 4			
subjects affected / exposed	2 / 56 (3.57%)	3 / 54 (5.56%)	
occurrences (all)	2	3	
MUCOSITIS ORAL			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
NAUSEA			

alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	19 / 54 (35.19%)	
occurrences (all)	1	27	
ORAL PAIN			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
RECTAL HEMORRHAGE			
alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
STOMACH PAIN			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	2 / 54 (3.70%)	
occurrences (all)	0	2	
VOMITING			
alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	8 / 54 (14.81%)	
occurrences (all)	1	11	
Hepatobiliary disorders			
HEPATOBILIARY DISORDERS - OTHER, SPECIFY			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	3 / 54 (5.56%)	
occurrences (all)	0	3	
Skin and subcutaneous tissue disorders			
ALOPECIA			
alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	12 / 54 (22.22%)	
occurrences (all)	1	13	
DRY SKIN			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	3 / 54 (5.56%)	
occurrences (all)	0	4	
ERYTHEMA MULTIFORME			
alternative dictionary used: CTC 4			

subjects affected / exposed	1 / 56 (1.79%)	2 / 54 (3.70%)	
occurrences (all)	1	2	
ERYTHRODERMA alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
HYPERHIDROSIS alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	2 / 54 (3.70%)	
occurrences (all)	1	2	
PRURITUS alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	7 / 54 (12.96%)	
occurrences (all)	1	8	
RASH ACNEIFORM alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	2 / 54 (3.70%)	
occurrences (all)	1	2	
RASH MACULO-PAPULAR alternative dictionary used: CTC 4			
subjects affected / exposed	2 / 56 (3.57%)	6 / 54 (11.11%)	
occurrences (all)	2	9	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - OTHER, SPECIFY alternative dictionary used: CTC 4			
subjects affected / exposed	8 / 56 (14.29%)	9 / 54 (16.67%)	
occurrences (all)	9	13	
SKIN HYPOPIGMENTATION alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
URTICARIA alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			

HEMATURIA			
alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
RENAL AND URINARY DISORDERS - OTHER, SPECIFY			
alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	1 / 54 (1.85%)	
occurrences (all)	1	1	
RENAL CALCULI			
alternative dictionary used: CTC 4			
subjects affected / exposed	2 / 56 (3.57%)	0 / 54 (0.00%)	
occurrences (all)	2	0	
URINARY FREQUENCY			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
URINARY TRACT PAIN			
alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
HYPERTHYROIDISM			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	5 / 54 (9.26%)	
occurrences (all)	0	5	
HYPOTHYROIDISM			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	2 / 54 (3.70%)	
occurrences (all)	0	4	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
alternative dictionary used: CTC 4			
subjects affected / exposed	3 / 56 (5.36%)	7 / 54 (12.96%)	
occurrences (all)	3	10	
BACK PAIN			
alternative dictionary used: CTC 4			

subjects affected / exposed	3 / 56 (5.36%)	3 / 54 (5.56%)		
occurrences (all)	3	5		
BONE PAIN				
alternative dictionary used: CTC 4				
subjects affected / exposed	0 / 56 (0.00%)	3 / 54 (5.56%)		
occurrences (all)	0	3		
CHEST WALL PAIN				
alternative dictionary used: CTC 4				
subjects affected / exposed	1 / 56 (1.79%)	0 / 54 (0.00%)		
occurrences (all)	1	0		
FLANK PAIN				
alternative dictionary used: CTC 4				
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)		
occurrences (all)	0	1		
GENERALIZED MUSCLE WEAKNESS				
alternative dictionary used: CTC 4				
subjects affected / exposed	0 / 56 (0.00%)	2 / 54 (3.70%)		
occurrences (all)	0	2		
MUSCLE WEAKNESS LOWER LIMB				
alternative dictionary used: CTC 4				
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)		
occurrences (all)	0	1		
MUSCLE WEAKNESS TRUNK				
alternative dictionary used: CTC 4				
subjects affected / exposed	1 / 56 (1.79%)	0 / 54 (0.00%)		
occurrences (all)	1	0		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDER - OTHER, SPECIFY				
alternative dictionary used: CTC 4				
subjects affected / exposed	1 / 56 (1.79%)	0 / 54 (0.00%)		
occurrences (all)	1	0		
MYALGIA				
alternative dictionary used: CTC 4				
subjects affected / exposed	1 / 56 (1.79%)	16 / 54 (29.63%)		
occurrences (all)	1	26		
OSTEOPOROSIS				

alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
PAIN IN EXTREMITY			
alternative dictionary used: CTC 4			
subjects affected / exposed	2 / 56 (3.57%)	1 / 54 (1.85%)	
occurrences (all)	2	1	
Infections and infestations			
BRONCHIAL INFECTION			
alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
INFECTIONS AND INFESTATIONS - OTHER, SPECIFY			
alternative dictionary used: CTC 4			
subjects affected / exposed	5 / 56 (8.93%)	0 / 54 (0.00%)	
occurrences (all)	5	0	
LIP INFECTION			
alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	2 / 54 (3.70%)	
occurrences (all)	1	3	
LUNG INFECTION			
alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
PAPULOPUSTULAR RASH			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	2 / 54 (3.70%)	
occurrences (all)	0	2	
RASH PUSTULAR			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
RHINITIS INFECTIVE			
alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	

SINUSITIS alternative dictionary used: CTC 4 subjects affected / exposed occurrences (all)	 1 / 56 (1.79%) 1	 0 / 54 (0.00%) 0	
SKIN INFECTION alternative dictionary used: CTC 4 subjects affected / exposed occurrences (all)	 3 / 56 (5.36%) 4	 1 / 54 (1.85%) 1	
UPPER RESPIRATORY INFECTION alternative dictionary used: CTC 4 subjects affected / exposed occurrences (all)	 2 / 56 (3.57%) 4	 1 / 54 (1.85%) 1	
URINARY TRACT INFECTION alternative dictionary used: CTC 4 subjects affected / exposed occurrences (all)	 0 / 56 (0.00%) 0	 3 / 54 (5.56%) 4	
VULVAL INFECTION alternative dictionary used: CTC 4 subjects affected / exposed occurrences (all)	 1 / 56 (1.79%) 2	 0 / 54 (0.00%) 0	
WOUND INFECTION alternative dictionary used: CTC 4 subjects affected / exposed occurrences (all)	 2 / 56 (3.57%) 2	 0 / 54 (0.00%) 0	
Metabolism and nutrition disorders ANOREXIA alternative dictionary used: CTC 4 subjects affected / exposed occurrences (all)	 0 / 56 (0.00%) 0	 14 / 54 (25.93%) 19	
DEHYDRATION alternative dictionary used: CTC 4 subjects affected / exposed occurrences (all)	 0 / 56 (0.00%) 0	 1 / 54 (1.85%) 1	
HYPERTRIGLYCERIDEMIA alternative dictionary used: CTC 4 subjects affected / exposed occurrences (all)	 5 / 56 (8.93%) 5	 14 / 54 (25.93%) 26	

HYPOKALEMIA alternative dictionary used: CTC 4			
subjects affected / exposed	1 / 56 (1.79%)	1 / 54 (1.85%)	
occurrences (all)	1	1	
HYPOMAGNESEMIA alternative dictionary used: CTC 4			
subjects affected / exposed	0 / 56 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
METABOLISM AND NUTRITION DISORDERS - OTHER, SPECIFY alternative dictionary used: CTC 4			
subjects affected / exposed	3 / 56 (5.36%)	1 / 54 (1.85%)	
occurrences (all)	3	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The study was closed prematurely due to a low recruitment rate and the required sample size was not reached for any of the endpoints. The performed analysis has a descriptive character.

Notes: