Clinical trial results:
An Extension Protocol to Evaluate the Efficacy and Safety of Extended Use Treatment with OncoVEX^GM-CSF for Eligible Melanoma Patients Participating in Study 005/05

Summary

EudraCT number	2010-021070-11
Trial protocol	GB
Global end of trial date	08 August 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	005/05-E

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01368276
WHO universal trial number (UTN)	-
Other trial identifiers	Amgen study ID: 20110279

Notes:

Sponsors

Sponsor organisation name	Amgen, Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States, 91320
Public contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com
Scientific contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.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	08 August 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 August 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to learn about the safety and the risks of using talimogene laherparepvec in patients who already received treatment with talimogene laherparepvec in study 005/05 (2008-006140-20), and to see if extended treatment with talimogene laherparepvec can destroy melanoma tumors.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines.
Written informed consent, properly witnessed and executed, was obtained from each subject before study entry.
The protocol, informed consent, and other appropriate study documentation were approved by the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) of each study center before the study began.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 October 2010
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	South Africa: 2
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	United States: 27
Worldwide total number of subjects	31
EEA total number of subjects	2

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	13
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

This extension was available to patients who participated in study 005/05 (2008-006140-20), received the maximum allowable number of treatments or developed new lesion(s) within ≤ 12 months from the end of treatment visit after previous resolution of all disease while on study 005/05, and warranted further treatment per the investigator.

Pre-assignment

Screening details:

Participants received the same treatment as randomized under the 005/05 study.

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	GM-CSF

Arm description:

Granulocyte macrophage colony-stimulating factor (GM-CSF) was administered at a dose of 125 µg/m²/day subcutaneously for 14 consecutive days followed by 14 days of rest, in 28-day treatment cycles for up to 12 months or until a complete response, occurrence of an unacceptable toxicity, death or another criterion for withdrawal from treatment was met. Participants who demonstrated a partial response after being on treatment for 12 months could continue to be treated until disease progression or another treatment discontinuation criterion was met.

Arm type	Active comparator
Investigational medicinal product name	Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

125 µg/m² subcutaneous injection

Arm title	Talimogene Laherparepvec

Arm description:

Talimogene laherparepvec was administered at a concentration of 10^8 plaque forming units (PFU)/mL injected into 1 or more skin or subcutaneous tumors on Days 1 and 15 of each 28-day cycle for up to 12 months or until a complete response, occurrence of an unacceptable toxicity, death or another criterion for withdrawal from treatment was met. Participants who demonstrated a partial response after being on treatment for 12 months could continue to be treated until disease progression or another treatment discontinuation criterion was met.

Arm type	Experimental
Investigational medicinal product name	Talimogene Laherparepvec
Investigational medicinal product code	
Other name	OncoVEX^GM-CSF, IMLYGIC™
Pharmaceutical forms	Solution for injection
Routes of administration	Intratumoral use

Dosage and administration details:

Up to 4 mL of 10^8 pfu/mL/per intratumoral injection

Number of subjects in period 1	GM-CSF	Talimogene Laherparepvec
Started	3	28
Completed	2	18
Not completed	1	10
Death	1	10

Baseline characteristics

Reporting groups	
Reporting group title	GM-CSF

Reporting group description:

Granulocyte macrophage colony-stimulating factor (GM-CSF) was administered at a dose of 125 µg/m²/day subcutaneously for 14 consecutive days followed by 14 days of rest, in 28-day treatment cycles for up to 12 months or until a complete response, occurrence of an unacceptable toxicity, death or another criterion for withdrawal from treatment was met. Participants who demonstrated a partial response after being on treatment for 12 months could continue to be treated until disease progression or another treatment discontinuation criterion was met.

Reporting group title	Talimogene Laherparepvec

Reporting group description:

Talimogene laherparepvec was administered at a concentration of 10^8 plaque forming units (PFU)/mL injected into 1 or more skin or subcutaneous tumors on Days 1 and 15 of each 28-day cycle for up to 12 months or until a complete response, occurrence of an unacceptable toxicity, death or another criterion for withdrawal from treatment was met. Participants who demonstrated a partial response after being on treatment for 12 months could continue to be treated until disease progression or another treatment discontinuation criterion was met.

Reporting group values	GM-CSF	Talimogene Laherparepvec	Total
Number of subjects	3	28	31
Age categorical Units: Subjects			
Adults (18-64 years)	1	15	16
From 65-84 years	2	11	13
85 years and over	0	2	2
Age Continuous Units: years			
arithmetic mean	54.7	64.2	
standard deviation	± 25	± 13.2	-
Gender, Male/Female Units: participants			
Female	2	14	16
Male	1	14	15
Race/Ethnicity, Customized Units: Subjects			
White	3	28	31
Eastern Cooperative Oncology Group (ECOG) Performance Status			
Scale used to assess how a patient's disease is progressing, how the disease affects the daily living abilities of the patient: 0 = Fully active, able to carry on all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity, ambulatory, able to carry out work of a light nature; 2 = Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about > 50% of waking hours; 3 = Capable of only limited self care, confined to a bed or chair > 50% of waking hours; 4 = Completely disabled, confined to bed or chair; 5 = Dead.			
Units: Subjects			
Grade 0	3	20	23
Grade 1	0	8	8
Disease Stage			
Stage IIIB: Ulcerated lesion and 1 lymph node or 2-3 nodes with micrometastasis, or any-depth lesion with no ulceration, and 1 lymph node or 2-3 nodes with macrometastasis; Stage IIIC: Ulcerated lesion and 1 lymph node with macrometastasis; 2-3 nodes with macrometastasis or ≥ 4 metastatic lymph nodes, matted lymph nodes, or in-transit met(s)/satellite(s); Stage IV: M1a: Spread to skin,			

subcutaneous tissue, or lymph nodes; normal lactate dehydrogenase (LDH) level; M1b: Spread to lungs; normal LDH; M1c: Spread to all other visceral organs, normal LDH or any distant disease with elevated LDH.			
Units: Subjects			
Stage IIIB	0	1	1
Stage IIIC	0	6	6
Stage IV M1a	1	9	10
Stage IV M1b	1	8	9
Stage IV M1c	1	4	5

End points

End points reporting groups

Reporting group title	GM-CSF

Reporting group description:

Granulocyte macrophage colony-stimulating factor (GM-CSF) was administered at a dose of 125 µg/m²/day subcutaneously for 14 consecutive days followed by 14 days of rest, in 28-day treatment cycles for up to 12 months or until a complete response, occurrence of an unacceptable toxicity, death or another criterion for withdrawal from treatment was met. Participants who demonstrated a partial response after being on treatment for 12 months could continue to be treated until disease progression or another treatment discontinuation criterion was met.

Reporting group title	Talimogene Laherparepvec

Reporting group description:

Talimogene laherparepvec was administered at a concentration of 10^8 plaque forming units (PFU)/mL injected into 1 or more skin or subcutaneous tumors on Days 1 and 15 of each 28-day cycle for up to 12 months or until a complete response, occurrence of an unacceptable toxicity, death or another criterion for withdrawal from treatment was met. Participants who demonstrated a partial response after being on treatment for 12 months could continue to be treated until disease progression or another treatment discontinuation criterion was met.

Primary: Number of Participants with Treatment-emergent Adverse Events (AEs)

End point title	Number of Participants with Treatment-emergent Adverse Events (AEs)[1]

End point description:

AEs were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 based on the following guideline:
Grade 1: Mild AE; Grade 2: Moderate AE; Grade 3: Severe AE; Grade 4: Life-threatening or disabling AE; Grade 5: Death related to AE.
Treatment-related AE refers to AEs that have possible or probable relation to study treatment as determined by the investigator.
A serious AE is one that meets one or more of the following criteria/outcomes:
• Results in death.
• Is life-threatening.
• Requires inpatient hospitalization or prolongation of existing hospitalization.
• Results in persistent or significant disability/incapacity.
• Is a congenital anomaly/birth defect.
• Is an important medical event.

End point type	Primary

End point timeframe:

From first administration of study drug in the extension period until 30 days after last dose. Median duration of treatment was 50 weeks in the GM-CSF group and 36 weeks in the talimogene laherparepvec group.

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: Statistical analyses were not performed.

End point values	GM-CSF	Talimogene Laherparepvec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	28		
Units: participants				
number (not applicable)				
All adverse events	3	26		
Worst grade of 3	0	5		
Worst grade of 4	0	1		

Worst grade of 5	0	2		
Serious adverse events	0	9		
Treatment-related adverse events	3	20		
Treatment-related serious adverse events	0	1		
Leading to discontinuation of study treatment	0	4		
Leading to study treatment delay	0	4		
Fatal adverse events on-study	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate

End point title	Objective Response Rate

End point description:

Objective response rate was defined as the percentage of participants with a best overall response of complete response (CR) or partial response (PR) assessed by the investigator. Best overall response for a patient is the best overall response observed across all time points and is cumulative (ie, includes responses during the parent study 005/05 and during Study 005/05-E).
Disease assessments were performed at the beginning of each treatment cycle and assessed in accordance with modified World Health Organization criteria.
CR: Disappearance of all clinical evidence of tumor (both measurable and non-measurable but evaluable disease); PR: ≥ 50% reduction in the sum of the products of the perpendicular diameters of all measurable tumors at the time of assessment as compared to baseline.
For 100% response, the asymptotic 95% CI was not estimated since the mathematical formula is not considered appropriate in such extreme cases; this is represented by "100" in the table below.

End point type	Secondary

End point timeframe:

From randomization in study 005/05 until the data-cut-off date for the extension period of 08 August 2014; median treatment duration for 005/05 and 005/05-E studies combined was 88 weeks for talimogene laherparepvec and 100 weeks for GM-CSF.

End point values	GM-CSF	Talimogene Laherparepvec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	28		
Units: percentage of participants				
number (confidence interval 95%)	100 (100 to 100)	57.1 (38.8 to 75.5)		

Statistical analyses

Statistical analysis title	Objective Response Rate Analysis
Comparison groups	GM-CSF v Talimogene Laherparepvec

Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.2645
Method	Fisher exact

Notes:

[2] - Descriptive

Secondary: Durable Response Rate

End point title	Durable Response Rate

End point description:

Durable response rate is defined as the percentage of participants with a complete response (CR) or partial response (PR) assessed by the investigator, initiating at any time while receiving talimogene laherparepvec or GM-CSF therapy on the 005/05 or the 005/05-E study and maintained continuously for at least 6 months from response initiation. This reflects all new sites of disease as well as disease sites identified at baseline.
Disease assessments were performed at the beginning of each treatment cycle in accordance with modified World Health Organization criteria.
CR: Disappearance of all clinical evidence of tumor (both measurable and non-measurable but evaluable disease); PR: ≥ 50% reduction in the sum of the products of the perpendicular diameters of all measurable tumors at the time of assessment as compared to baseline.

End point type	Secondary

End point timeframe:

From randomization in study 005/05 until the data-cut-off date for the extension period of 08 August 2014; median treatment duration for 005/05 and 005/05-E studies combined was 88 weeks for talimogene laherparepvec and 100 weeks for GM-CSF.

End point values	GM-CSF	Talimogene Laherparepvec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	28		
Units: percentage of participants				
number (confidence interval 95%)	33.3 (0 to 86.7)	32.1 (14.8 to 49.4)		

Statistical analyses

Statistical analysis title	Durable Response Rate Analysis
Comparison groups	GM-CSF v Talimogene Laherparepvec
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 1
Method	Fisher exact
Parameter estimate	Treatment Difference
Point estimate	-1.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-57.3
upper limit	54.9

Notes:

[3] - Descriptive

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first administration of study drug in the extension period until 30 days after last dose. Median duration of treatment was 50 weeks in the GM-CSF group and 36 weeks in the talimogene laherparepvec group.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Talimogene Laherparepvec

Reporting group description:

Talimogene laherparepvec was administered at a concentration of 10^8 PFU/mL injected into 1 or more skin or subcutaneous tumors on Days 1 and 15 of each 28-day cycle for up to 12 months or until a complete response, occurrence of an unacceptable toxicity, death or another criterion for withdrawal from treatment was met. Participants who demonstrated a partial response after being on treatment for 12 months could continue to be treated until disease progression or another treatment discontinuation criterion was met.

Reporting group title	GM-CSF

Reporting group description:

GM-CSF was administered at a dose of 125 µg/m²/day subcutaneously for 14 consecutive days followed by 14 days of rest, in 28-day treatment cycles for up to 12 months or until a complete response, occurrence of an unacceptable toxicity, death or another criterion for withdrawal from treatment was met. Participants who demonstrated a partial response after being on treatment for 12 months could continue to be treated until disease progression or another treatment discontinuation criterion was met.

Serious adverse events	Talimogene Laherparepvec	GM-CSF	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 28 (32.14%)	0 / 3 (0.00%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemangioma of liver			
subjects affected / exposed	1 / 28 (3.57%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 28 (3.57%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic malignant melanoma			

subjects affected / exposed	1 / 28 (3.57%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	1 / 28 (3.57%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypovolaemic shock			
subjects affected / exposed	1 / 28 (3.57%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasculitis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 28 (3.57%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Restrictive cardiomyopathy			
subjects affected / exposed	1 / 28 (3.57%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	1 / 28 (3.57%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			

subjects affected / exposed	1 / 28 (3.57%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 28 (3.57%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 28 (3.57%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 28 (3.57%)	0 / 3 (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			
Upper respiratory tract infection			
subjects affected / exposed	1 / 28 (3.57%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 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	Talimogene Laherparepvec	GM-CSF	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 28 (75.00%)	3 / 3 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lipoma			
subjects affected / exposed	1 / 28 (3.57%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
Tumour pain			
subjects affected / exposed	2 / 28 (7.14%)	0 / 3 (0.00%)	
occurrences (all)	4	0	

Vascular disorders Flushing subjects affected / exposed occurrences (all)	 0 / 28 (0.00%) 0	 1 / 3 (33.33%) 2	
Nervous system disorders Headache subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all)	 2 / 28 (7.14%) 4 3 / 28 (10.71%) 3	 0 / 3 (0.00%) 0 0 / 3 (0.00%) 0	
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Chills subjects affected / exposed occurrences (all) Injection site mass subjects affected / exposed occurrences (all) Injection site pain subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all) Influenza like illness subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	 3 / 28 (10.71%) 4 5 / 28 (17.86%) 13 0 / 28 (0.00%) 0 2 / 28 (7.14%) 2 3 / 28 (10.71%) 3 1 / 28 (3.57%) 1 5 / 28 (17.86%) 13	 2 / 3 (66.67%) 9 1 / 3 (33.33%) 7 1 / 3 (33.33%) 1 0 / 3 (0.00%) 0 1 / 3 (33.33%) 1 1 / 3 (33.33%) 1 1 / 3 (33.33%) 7	
Ear and labyrinth disorders Ear pain			

subjects affected / exposed	2 / 28 (7.14%)	0 / 3 (0.00%)	
occurrences (all)	5	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 28 (14.29%)	1 / 3 (33.33%)	
occurrences (all)	5	2	
Abdominal discomfort			
subjects affected / exposed	2 / 28 (7.14%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Abdominal pain			
subjects affected / exposed	3 / 28 (10.71%)	0 / 3 (0.00%)	
occurrences (all)	4	0	
Nausea			
subjects affected / exposed	2 / 28 (7.14%)	1 / 3 (33.33%)	
occurrences (all)	2	1	
Vomiting			
subjects affected / exposed	3 / 28 (10.71%)	1 / 3 (33.33%)	
occurrences (all)	3	1	
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	0 / 28 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Dyspnoea			
subjects affected / exposed	1 / 28 (3.57%)	1 / 3 (33.33%)	
occurrences (all)	1	4	
Cough			
subjects affected / exposed	1 / 28 (3.57%)	2 / 3 (66.67%)	
occurrences (all)	1	2	
Hypopnoea			
subjects affected / exposed	0 / 28 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	2 / 28 (7.14%)	1 / 3 (33.33%)	
occurrences (all)	5	3	
Skin and subcutaneous tissue disorders			

Ecchymosis			
subjects affected / exposed	1 / 28 (3.57%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
Blood blister			
subjects affected / exposed	0 / 28 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Urticaria			
subjects affected / exposed	0 / 28 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	4	
Pruritus			
subjects affected / exposed	2 / 28 (7.14%)	1 / 3 (33.33%)	
occurrences (all)	2	4	
Skin irritation			
subjects affected / exposed	3 / 28 (10.71%)	0 / 3 (0.00%)	
occurrences (all)	3	0	
Hyperhidrosis			
subjects affected / exposed	1 / 28 (3.57%)	1 / 3 (33.33%)	
occurrences (all)	1	5	
Night sweats			
subjects affected / exposed	0 / 28 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Vitiligo			
subjects affected / exposed	3 / 28 (10.71%)	0 / 3 (0.00%)	
occurrences (all)	3	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 28 (14.29%)	0 / 3 (0.00%)	
occurrences (all)	4	0	
Myalgia			
subjects affected / exposed	2 / 28 (7.14%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Folliculitis			
subjects affected / exposed	0 / 28 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Pneumonia			

subjects affected / exposed	1 / 28 (3.57%)	1 / 3 (33.33%)	
occurrences (all)	2	1	
Upper respiratory tract infection			
subjects affected / exposed	3 / 28 (10.71%)	1 / 3 (33.33%)	
occurrences (all)	3	1	
Oral herpes			
subjects affected / exposed	0 / 28 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 November 2011	- Allowed the inclusion of subjects randomized to GM-CSF in the parent study in this extension study. The subjects remained on GM-CSF and information on GM-CSF administration was included in the protocol. - Inclusion criteria 1b revised to read "New lesion(s) appearing after 12 months from randomization after previous resolution of all disease while on study 005/05" - Verbiage added stating the subject will receive study drug randomized under the 005/05 study, crossover is not permitted. - Verbiage added stating that if a subject demonstrates central nervous system (CNS) progressive disease, they may be allowed to remain on study provided CNS lesions can be treated with radiotherapy or surgery.
29 October 2012	- Continued treatment of ongoing subjects who met the protocol-specified tumor response criteria of partial response after being on study treatment for 12 months and are still benefiting from study treatment - Revised the eligibility criteria to restrict enrollment to subjects with new injectable lesions that appeared within ≤ 12 months from the End of Treatment visit on the Study 005/05. - Revised the eligibility criteria to add a requirement that subjects must not have received anti-tumor therapies for melanoma after end of treatment on Study 05/05 and prior to enrollment on Study 005/05-E with the exception of radiation for palliation or surgical resection of melanoma tumor. - Revised the response criteria to align with the response criteria in the protocol amendment 4 of the Study 005/05. - Deleted the Data Monitoring Committee (DMC) section from the protocol because the procedures in the DMC Charter of the Study 005/05 do not include review of safety data from the extension study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported