Clinical trial results:
A Phase 2, Multicenter, Open-label, Single-arm Trial to Evaluate the Correlation Between Objective Response Rate and Baseline Intratumoral CD8+ Cell Density in Subjects With Unresected Stage IIIB to IVM1c Melanoma Treated With Talimogene Laherparepvec

Summary

EudraCT number	2013-005552-15
Trial protocol	IT ES DE BE AT HU PL GR NL
Global end of trial date	25 December 2020

Results information

Result version number	v1 (current)
This version publication date	14 October 2021
First version publication date	14 October 2021

Trial information

Trial identification

Sponsor protocol code	20120325

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02366195
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States,
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	25 December 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to explore the correlation between baseline intratumoral CD8+ cell density and objective response rate (ORR) in participants with unresected stage IIIB to IVM1c melanoma treated with talimogene laherparepvec.

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 April 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	France: 17
Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	Greece: 10
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	Russian Federation: 15
Country: Number of subjects enrolled	Spain: 16
Country: Number of subjects enrolled	United Kingdom: 11
Worldwide total number of subjects	112
EEA total number of subjects	86

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)	48
From 65 to 84 years	54
85 years and over	10

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 36 centers across 12 countries in Europe from 07 April 2015 to 25 December 2020.

Pre-assignment

Screening details:

Participants were screened within 28 days of receiving treatment.

Period 1

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

Arms

Arm title	Talimogene Laherparepvec

Arm description:

Talimogene laherparepvec was administered by intralesional injection into injectable cutaneous, subcutaneous, and nodal lesions at an initial dose of 10 plaque-forming units (PFU) per mL on day 1 followed by a dose of 10^8 PFU/mL 21 days after the initial dose and every 14 days thereafter. Participants were treated with talimogene laherparepvec until they achieved a complete response, all injectable tumors had disappeared, clinically significant (resulting in clinical deterioration or requiring change of therapy) disease progression beyond 6 months of treatment, per modified World Health Organization (WHO) response criteria, or intolerance of study treatment, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Talimogene Laherparepvec
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intralesional use

Dosage and administration details:

Talimogene laherparepvec administered by intralesional injection into injectable cutaneous, subcutaneous, and nodal lesions.

Number of subjects in period 1	Talimogene Laherparepvec
Started	112
Received Study Drug	111
Completed	58
Not completed	54
Adverse event, serious fatal	41
Consent withdrawn by subject	9
Lost to follow-up	1
Protocol-specified criteria	3

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	112	112	
Age categorical			
Data is only available for 111 participants who received at least 1 dose of treatment.			
Units: Subjects			
< 50 years	19	19	
≥ 50 years	92	92	
No data available	1	1	
Age Continuous			
Data is only available for 111 participants who received at least 1 dose of treatment.			
Units: years			
arithmetic mean	65.7		
standard deviation	± 15.1	-	
Sex: Female, Male			
Data is only available for 111 participants who received at least 1 dose of treatment.			
Units: participants			
Female	62	62	
Male	49	49	
No data available	1	1	
Ethnicity (NIH/OMB)			
Data is only available for 111 participants who received at least 1 dose of treatment.			
Units: Subjects			
Hispanic or Latino	1	1	
Not Hispanic or Latino	110	110	
Unknown or Not Reported	0	0	
No data available	1	1	
Race/Ethnicity, Customized			
Data is only available for 111 participants who received at least 1 dose of treatment.			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Black or African American	0	0	
Multiple	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
White	111	111	
Other	0	0	
No data available	1	1	
Eastern Cooperative Oncology Group (ECOG) Performance Status			
A scale to assess a patient's disease status. 0 = Fully active, able to carry out all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity, ambulatory and able to carry out work of a light nature; 2 = Ambulatory and capable of all self-care, unable to carry out any work activities. Up and about > 50% of waking hours; 3 = Capable of only limited self-care, confined to			

bed or chair > 50% of waking hours; 4 = Completely disabled, confined to bed or chair; 5 = Dead. Data is only available for 111 participants who received at least 1 dose of treatment.			
Units: Subjects			
0 (Fully active, no restrictions)	87	87	
1 (Restricted but ambulatory)	24	24	
No data available	1	1	
Log2(Intratumoral Cluster of Differentiation 8-positive (CD8+) Cell Density)			
Data available for 93 participants with non-missing data.			
Units: Log2 CD8+ cells/mm²			
arithmetic mean	8.109		
standard deviation	± 1.940	-	

End points

End points reporting groups

Reporting group title	Talimogene Laherparepvec

Reporting group description:

Talimogene laherparepvec was administered by intralesional injection into injectable cutaneous, subcutaneous, and nodal lesions at an initial dose of 10 plaque-forming units (PFU) per mL on day 1 followed by a dose of 10^8 PFU/mL 21 days after the initial dose and every 14 days thereafter. Participants were treated with talimogene laherparepvec until they achieved a complete response, all injectable tumors had disappeared, clinically significant (resulting in clinical deterioration or requiring change of therapy) disease progression beyond 6 months of treatment, per modified World Health Organization (WHO) response criteria, or intolerance of study treatment, whichever occurred first.

Primary: Odds Ratio of Baseline Intratumoral CD8+ Cell Density and Objective Response Rate

End point title	Odds Ratio of Baseline Intratumoral CD8+ Cell Density and Objective Response Rate[1]

End point description:

A univariate logistic regression model was performed to evaluate baseline log2(CD8+ cell density) as a predictor of objective response.

Response was assessed according to the modified version of the World Health Organization (WHO) response criteria. Objective response rate (ORR) was defined as the percentage of participants with a complete response (CR) or partial response (PR) according to the modified WHO criteria.

The unadjusted odds ratio of log2(baseline intratumoral CD8+ cell density) for objective response rate is reported. P value = 0.435 (method = Regression, Logistic)

End point type	Primary

End point timeframe:

Intratumoral CD8+ cell density: Baseline. Response: every 12 weeks until disease progression beyond 6 months of treatment or the start of new anticancer therapy; median time on follow-up: 108 weeks (2.7 to 245.6 weeks)

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: Due to the single arm nature of this study, no comparative analysis was performed.

End point values	Talimogene Laherparepvec			
Subject group type	Reporting group			
Number of subjects analysed	93[2]			
Units: ratio				
number (confidence interval 95%)	1.10 (0.87 to 1.38)			

Notes:

[2] - Participants who received at least 1 dose of study treatment & baseline CD8+ cell density data

Statistical analyses

No statistical analyses for this end point

Secondary: Odds Ratio of Baseline Intratumoral CD8+ Cell Density and Durable Response Rate

End point title	Odds Ratio of Baseline Intratumoral CD8+ Cell Density and

	Durable Response Rate

End point description:

A univariate logistic regression model was performed to evaluate baseline log2(CD8+ cell density) as a predictor of durable response.

Response was assessed according to the modified version of the World Health Organization (WHO) response criteria. Durable response rate (DRR) was defined as the percentage of participants with an objective response lasting continuously for 6 months and starting any time within 12 months of initiating therapy.

The unadjusted odds ratio of log2(baseline intratumoral CD8+ cell density) for durable response rate is reported. P value = 0.222 (Method = Regression, Logistic).

End point type	Secondary

End point timeframe:

Intratumoral CD8+ cell density: Baseline. Response: every 12 weeks until disease progression beyond 6 months of treatment or the start of new anticancer therapy; median time on follow-up: 108 weeks (2.7 to 245.6 weeks)

End point values	Talimogene Laherparepvec			
Subject group type	Reporting group			
Number of subjects analysed	93[3]			
Units: ratio				
number (confidence interval 95%)	1.18 (0.91 to 1.53)			

Notes:

[3] - Participants who received at least 1 dose of study treatment & baseline CD8+ cell density data.

Statistical analyses

No statistical analyses for this end point

Secondary: Hazard Ratio of Baseline Intratumoral CD8+ Cell Density and Duration of Response

End point title	Hazard Ratio of Baseline Intratumoral CD8+ Cell Density and Duration of Response

End point description:

A Cox proportional hazards regression model was performed to evaluate baseline log2(CD8+ cell density) as a predictor of duration of response.

Response was assessed according to the modified version of the World Health Organization (WHO) response criteria. Duration of response (DOR) is defined as the longest individual period from entering an objective response (CR/PR) to the first documented evidence of the participant no longer meeting the criteria for being in the response (i.e. an overall response of either stable disease [SD] as compared with baseline or progressive disease [PD]).

The unadjusted hazard ratio of log2(baseline intratumoral CD8+ cell density) for duration of response is reported. P value = 0.597 (Method: Cox proportional hazards).

Participants who received at least 1 dose of study treatment and had an objective response and with baseline CD8+ cell density data.

End point type	Secondary

End point timeframe:

Intratumoral CD8+ cell density: Baseline. Response: every 12 weeks until disease progression beyond 6 months of treatment or the start of new anticancer therapy; median time on follow-up: 108 weeks (2.7 to 245.6 weeks)

End point values	Talimogene Laherparepvec			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: ratio				
number (confidence interval 95%)	0.91 (0.63 to 1.30)			

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation Between Baseline Intratumoral CD8+ Cell Density and Changes in Tumor Burden

End point title	Correlation Between Baseline Intratumoral CD8+ Cell Density and Changes in Tumor Burden

End point description:

Pearson’s correlation coefficient (r) was estimated to assess the relationship between baseline log2(CD8+ cell density) and the maximum decrease in measurable tumor burden.

Tumor burden is the sum of the products of the 2 largest perpendicular diameters (SPD) for all index lesions selected at baseline.

The Pearson’s correlation coefficient (r) of log2(baseline intratumoral CD8+ cell density) and the maximum decrease in tumor burden is reported. P value = 0.90 (Method: Fisher's Z transformation).

Includes all participants who received at least 1 dose of study treatment with available tumor burden data and non-missing baseline CD8+ cell density data.

End point type	Secondary

End point timeframe:

Intratumoral CD8+ cell density: Baseline; Tumor burden: First dose of study drug until end of follow-up; median time on follow-up:108 weeks (2.7 to 245.6 weeks)

End point values	Talimogene Laherparepvec			
Subject group type	Reporting group			
Number of subjects analysed	85			
Units: Pearson’s correlation coefficient				
number (confidence interval 95%)	0.01 (-0.20 to 0.23)			

Statistical analyses

No statistical analyses for this end point

Secondary: Odds Ratio of Change from Baseline Intratumoral CD8+ Cell Density and Objective Response Rate

End point title	Odds Ratio of Change from Baseline Intratumoral CD8+ Cell Density and Objective Response Rate

End point description:

A univariate logistic regression model was performed to evaluate change from baseline to week 6 in log2(CD8+ cell density) in uninjected tumors as a predictor of objective response.

Response was assessed according to the modified version of the World Health Organization (WHO) response criteria. Objective response rate (ORR) was defined as the percentage of participants with a complete response or partial response according to the modified WHO criteria. The unadjusted odds ratio of log2(change from baseline intratumoral CD8+ cell density) for objective response rate is reported. P value = 0.881 (Method: Regression, Logistic)

Included all participants who received at least 1 dose of study treatment with non-missing baseline & week 6 CD8+ cell density data for uninjected lesions.

End point type	Secondary

End point timeframe:

Intratumoral CD8+ cell density: Baseline & Week 6. Response: every 12 weeks until disease progression beyond 6 months of treatment or the start of new anticancer therapy; median time on follow up: 108 weeks (2.7 to 245.6 weeks)

End point values	Talimogene Laherparepvec			
Subject group type	Reporting group			
Number of subjects analysed	63			
Units: ratio				
number (confidence interval 95%)	0.98 (0.76 to 1.27)			

Statistical analyses

No statistical analyses for this end point

Secondary: Odds Ratio of Change from Baseline in Intratumoral CD8+ Cell Density and Durable Response Rate

End point title	Odds Ratio of Change from Baseline in Intratumoral CD8+ Cell Density and Durable Response Rate

End point description:

A univariate logistic regression model was performed to evaluate change from baseline to week 6 in log2(CD8+ cell density) in uninjected lesions as a predictor of durable response.

Response was assessed according to the modified version of the World Health Organization (WHO) response criteria. Durable response rate (DRR) was defined as the percentage of participants with an objective response lasting continuously for 6 months and starting any time within 12 months of initiating therapy.

The unadjusted odds ratio of log2(change from baseline in intratumoral CD8+ cell density) for durable response rate is reported. P value = 0.612 (Method: Regression, Logistic)

Includes all participants who received at least 1 dose of study treatment with non-missing baseline and week 6 CD8+ cell density data in uninjected lesions.

End point type	Secondary

End point timeframe:

Intratumoral CD8+ cell density: Baseline & Week 6. Response: every 12 weeks until disease progression beyond 6 months of treatment or the start of new anticancer therapy; median time on follow-up: 108 weeks (2.7 to 245.6 weeks)

End point values	Talimogene Laherparepvec			
Subject group type	Reporting group			
Number of subjects analysed	63			
Units: ratio				
number (confidence interval 95%)	0.93 (0.68 to 1.25)			

Statistical analyses

No statistical analyses for this end point

Secondary: Hazard Ratio of Change from Baseline in Intratumoral CD8+ Cell Density and Duration of Response

End point title	Hazard Ratio of Change from Baseline in Intratumoral CD8+ Cell Density and Duration of Response

End point description:

A Cox proportional hazards regression model was performed to evaluate change from baseline in log2(CD8+ cell density) as a predictor of duration of response.

Response was assessed according to the modified version of the World Health Organization (WHO) response criteria. Duration of response (DOR) is defined as the longest individual period from entering an objective response (CR/PR) to the first documented evidence of the participant no longer meeting the criteria for being in the response (i.e. an overall response of either stable disease [SD] as compared with baseline or progressive disease [PD]).

The unadjusted hazard ratio of log2(change from baseline intratumoral CD8+ cell density) for duration of response is reported. P value = 0.579 (Method: Cox proportional hazards).

Included all participants who received at least 1 dose of study treatment, who had an objective response, and with non-missing baseline & week 6 CD8+ cell density data for uninjected lesions.

End point type	Secondary

End point timeframe:

Intratumoral CD8+ cell density: Baseline & Week 6. Response: every 12 weeks until disease progression beyond 6 months of treatment or the start of new anticancer therapy; median time on follow-up: 108 weeks (2.7 to 245.6 weeks)

End point values	Talimogene Laherparepvec			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: ratio				
number (confidence interval 95%)	1.12 (0.74 to 1.69)			

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation Between Change from Baseline in Intratumoral CD8+ Cell Density and Changes in Tumor Burden

End point title	Correlation Between Change from Baseline in Intratumoral CD8+ Cell Density and Changes in Tumor Burden

End point description:

Pearson's correlation coefficient (r) was estimated to assess the relationship between change from baseline in log2(CD8+ cell density) in uninjected lesions and the maximum decrease in measurable tumor burden.

Tumor burden is the sum of the products of the 2 largest perpendicular diameters (SPD) for all index lesions selected at baseline. The Pearson's correlation coefficient (r) of log2(change from baseline intratumoral CD8+ cell density) and the maximum decrease in tumor burden is reported. P value = 0.14 (Method: Fisher's Z transformation).

Includes all participants who received at least 1 dose of study treatment with available tumor burden data and non-missing baseline and week 6 CD8+ cell density data for uninjected lesions.

End point type	Secondary

End point timeframe:

Intratumoral CD8+ cell density: Baseline & Week 6. Response: every 12 weeks until disease progression beyond 6 months of treatment or the start of new anticancer therapy; median time on follow-up: 108 weeks (2.7 to 245.6 weeks)

End point values	Talimogene Laherparepvec			
Subject group type	Reporting group			
Number of subjects analysed	60			
Units: Pearson's correlation coefficient				
number (confidence interval 95%)	-0.19 (-0.43 to 0.06)			

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 is defined as the percentage of participants with either a CR or PR based on Modified WHO Response Criteria.

CR: Complete disappearance of all index lesions, all non-index lesions, and any new tumors which might

have appeared. Any residual cutaneous or subcutaneous index lesions must be documented by representative biopsy to not contain viable tumor.

PR: Disappearance of all index lesions with persistence of one or more non-index tumor(s), or, 50% or greater reduction in the 2 largest perpendicular diameters (SPD) of all index lesions as compared to baseline, and disappearance or persistence of non-index lesions.

End point type	Secondary

End point timeframe:

Response was assessed every 12 weeks until PD beyond 6 months of treatment or the start of new anticancer therapy; median time on follow-up: 108 weeks (2.7 to 245.6 weeks)

End point values	Talimogene Laherparepvec			
Subject group type	Reporting group			
Number of subjects analysed	111[4]			
Units: percentage of participants				
number (confidence interval 95%)	28.8 (20.6 to 38.2)			

Notes:

[4] - All participants who received at least one dose of study treatment

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response

End point description:

Duration of response (DOR) was defined as the longest individual period from entering an objective response (CR/PR) to the first documented evidence of the participant no longer meeting the criteria for objective response (i.e. an overall response of either stable disease [SD] as compared with baseline or progressive disease [PD]).

SD: Neither sufficient tumor shrinkage of index lesion to qualify for response (PR or CR) nor sufficient tumor increase of index lesion to qualify for PD, with no increase in size of non index lesions.

PD: A > 25% increase in the sum of the SPD of all index tumors since baseline, or the unequivocal appearance of a new tumor since the last response assessment time point, or unequivocal progression of one or more non-index lesions.

Participants last reported to be either a CR or PR were censored at that time point.

99999 = Not calculated: Median duration of response was not reached as most participants were still in response.

End point type	Secondary

End point timeframe:

Response was assessed every 12 weeks until PD beyond 6 months of treatment or the start of new anticancer therapy; median time on follow-up: 108 weeks (2.7 to 245.6 weeks)

End point values	Talimogene Laherparepvec			
Subject group type	Reporting group			
Number of subjects analysed	32[5]			
Units: months				
median (confidence interval 95%)	99999 (14.1 to 99999)			

Notes:

[5] - Participants who received at least 1 dose of study treatment and had an objective response

Statistical analyses

No statistical analyses for this end point

Secondary: Durable Response Rate

End point title	Durable Response Rate

End point description:

Durable response rate (DRR) was defined as the percentage of participants with an objective response (CR or PR) based on modified WHO response criteria lasting continuously for 6 months and starting any time within 12 months of initiating therapy.

End point type	Secondary

End point timeframe:

Response was assessed every 12 weeks until PD beyond 6 months of treatment or the start of new anticancer therapy; median time on follow-up: 108 weeks (2.7 to 245.6 weeks)

End point values	Talimogene Laherparepvec			
Subject group type	Reporting group			
Number of subjects analysed	111[6]			
Units: percentage of participants				
number (confidence interval 95%)	21.6 (14.4 to 30.4)			

Notes:

[6] - All participants who received at least 1 dose of study treatment

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Treatment Failure

End point title	Time to Treatment Failure

End point description:

Time to treatment failure (TTF) was calculated from first dosing until one or more of the following: (1) clinically relevant disease progression (PDr); (2) death from any cause; (3) non clinically relevant disease progression (PDn) associated with a requirement for alternative therapy as the reason for ending treatment or start of new anti-cancer therapy.

Participants with no event were censored at their last evaluable tumor assessment

End point type	Secondary

End point timeframe:

From first dose of study drug until end of follow-up; median time on follow-up: 108 weeks (2.7 to 245.6 weeks)

End point values	Talimogene Laherparepvec			
Subject group type	Reporting group			
Number of subjects analysed	111[7]			
Units: months				
median (confidence interval 95%)	8.1 (5.4 to 11.0)			

Notes:

[7] - All participants who received at least 1 dose of study treatment

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival (OS) was defined as the time from the date of first dose to the date of death from any cause. OS time was censored at the last date the participant was known to be alive when the confirmation of death is absent or unknown.

99999 = Not calculated: Median overall survival was not reached due to the low number of deaths.

End point type	Secondary

End point timeframe:

From first dose of study drug until end of follow-up; median time on follow-up: 108 weeks (2.7 to 245.6 weeks)

End point values	Talimogene Laherparepvec			
Subject group type	Reporting group			
Number of subjects analysed	111[8]			
Units: months				
median (confidence interval 95%)	99999 (34.9 to 99999)			

Notes:

[8] - All participants who received at least 1 dose of study treatment

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Tumor Burden

End point title	Change from Baseline in Tumor Burden

End point description:

Tumor burden is the sum of the products of the 2 largest perpendicular diameters (SPD) for all index lesions selected at baseline. Change from baseline in tumor burden was assessed in participants with an objective response.

99999 = Not calculated: Only 1 participant with non-missing data at that time point, so standard deviation could not be calculated.

End point type	Secondary

End point timeframe:

Baseline and Day 1 of cycle 6, 12 , 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, 96, 102, 108, 114, and 120. The first cycle was 21 days and all subsequent cycles were 14 days

End point values	Talimogene Laherparepvec			
Subject group type	Reporting group			
Number of subjects analysed	32[9]			
Units: cm^2				
arithmetic mean (standard deviation)				
Baseline (N = 32)	16.420 (± 41.269)			
Change from baseline at Cycle 6 day 1 (N = 32)	-5.883 (± 12.158)			
Change from baseline at Cycle 12 day 1 (N = 30)	-10.085 (± 22.862)			
Change from baseline at Cycle 18 day 1 (N = 23)	-13.074 (± 27.798)			
Change from baseline at Cycle 24 day 1 (N = 15)	-21.407 (± 42.221)			
Change from baseline at Cycle 30 day 1 (N = 12)	-30.404 (± 55.593)			
Change from baseline at Cycle 36 day 1 (N = 10)	-31.803 (± 69.358)			
Change from baseline at Cycle 42 day 1 (N = 9)	-10.208 (± 14.188)			
Change from baseline at Cycle 48 day 1 (N = 8)	-11.396 (± 14.885)			
Change from baseline at Cycle 54 day 1 (N = 8)	-11.693 (± 15.720)			
Change from baseline at Cycle 60 day 1 (N = 6)	-13.122 (± 17.791)			
Change from baseline at Cycle 66 day 1 (N = 6)	-16.797 (± 14.659)			
Change from baseline at Cycle 72 day 1 (N = 6)	-16.797 (± 14.659)			
Change from baseline at Cycle 78 day 1 (N = 6)	-16.858 (± 14.730)			
Change from baseline at Cycle 84 day 1 (N = 6)	-17.022 (± 14.992)			
Change from baseline at Cycle 90 day 1 (N = 5)	-13.916 (± 14.381)			
Change from baseline at Cycle 96 day 1 (N = 4)	-16.505 (± 15.244)			
Change from baseline at Cycle 102 day 1 (N = 3)	-17.793 (± 18.413)			
Change from baseline at Cycle 108 day 1 (N = 3)	-17.733 (± 18.426)			
Change from baseline at Cycle 114 day 1 (N = 1)	-1.694 (± 99999)			
Change from baseline at Cycle 120 day 1 (N = 1)	-39.930 (± 99999)			

Notes:

[9] - Participants who received at least 1 dose of study treatment with an objective response

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events

End point title	Number of Participants with Adverse Events

End point description:

The severity of each adverse event (AE) was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 grading scale, where
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 adverse events (TRAE) were those assessed by the investigator as possibly related to talimogene laherparepvec.

End point type	Secondary

End point timeframe:

From first dose through 30 days after last dose of talimogene laherparepvec; median duration of treatment was 25.143 weeks (range 0.14 to 241.43 weeks)

End point values	Talimogene Laherparepvec			
Subject group type	Reporting group			
Number of subjects analysed	111			
Units: participants				
Any adverse event	108			
Adverse events ≥ grade 3	38			
Adverse events ≥ grade 4	11			
Serious adverse events	33			
AE leading to discontinuation of study drug	4			
Fatal adverse events	4			
Treatment-related adverse events	93			
Treatment-related adverse events ≥ grade 3	11			
Treatment-related adverse events ≥ grade 4	2			
Treatment-related serious adverse events	9			
TRAE leading to discontinuation of study drug	3			
Treatment-related fatal adverse events	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Deaths: first dose through to end of follow-up; median time on follow up was 108.0 weeks (2.7 to 245.6 weeks). Adverse events: first dose through 30 days after last dose; median duration of treatment was 25.143 weeks (0.14 to 241.43 weeks)

Adverse event reporting additional description:

All-cause mortality, serious adverse events and other adverse events are reported for all participants who received at least one dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Talimogene Laherparepvec

Reporting group description:

Talimogene laherparepvec was administered by intralesional injection into injectable cutaneous, subcutaneous, and nodal lesions at an initial dose of 10 plaque-forming units (PFU) per mL on day 1 followed by a dose of 10^8 PFU/mL 21 days after the initial dose and every 14 days thereafter. Participants were treated with talimogene laherparepvec until they achieved a complete response, all injectable tumors had disappeared, clinically significant (resulting in clinical deterioration or requiring change of therapy) disease progression beyond 6 months of treatment, per modified World Health Organization (WHO) response criteria, or intolerance of study treatment, whichever occurred first.

Serious adverse events	Talimogene Laherparepvec		
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 111 (29.73%)		
number of deaths (all causes)	41		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to central nervous system			
subjects affected / exposed	2 / 111 (1.80%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Metastases to lymph nodes			

subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastatic malignant melanoma			
subjects affected / exposed	3 / 111 (2.70%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Metastases to pleura			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour haemorrhage			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nodular melanoma			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neurofibrosarcoma			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Meningioma			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Cardiac pacemaker replacement			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			

General physical health deterioration			
subjects affected / exposed	2 / 111 (1.80%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Pyrexia			
subjects affected / exposed	2 / 111 (1.80%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Oedema peripheral			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Paranoia			

subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Medical observation			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Humerus fracture			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardio-respiratory arrest			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo positional			

subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Faecaloma			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ileus			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 111 (1.80%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			

subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
COVID-19 pneumonia			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Talimogene Laherparepvec		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	97 / 111 (87.39%)		
Nervous system disorders			
Headache			
subjects affected / exposed	21 / 111 (18.92%)		
occurrences (all)	74		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	18 / 111 (16.22%)		
occurrences (all)	29		
Chills			
subjects affected / exposed	30 / 111 (27.03%)		
occurrences (all)	69		
Fatigue			
subjects affected / exposed	24 / 111 (21.62%)		
occurrences (all)	42		
Pain			
subjects affected / exposed	7 / 111 (6.31%)		
occurrences (all)	7		
Injection site pain			
subjects affected / exposed	19 / 111 (17.12%)		
occurrences (all)	31		
Influenza like illness			

subjects affected / exposed	29 / 111 (26.13%)		
occurrences (all)	115		
Pyrexia			
subjects affected / exposed	52 / 111 (46.85%)		
occurrences (all)	232		
Oedema peripheral			
subjects affected / exposed	7 / 111 (6.31%)		
occurrences (all)	7		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 111 (7.21%)		
occurrences (all)	12		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	26 / 111 (23.42%)		
occurrences (all)	36		
Diarrhoea			
subjects affected / exposed	14 / 111 (12.61%)		
occurrences (all)	19		
Abdominal pain			
subjects affected / exposed	7 / 111 (6.31%)		
occurrences (all)	7		
Vomiting			
subjects affected / exposed	11 / 111 (9.91%)		
occurrences (all)	16		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 111 (7.21%)		
occurrences (all)	11		
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	6 / 111 (5.41%)		
occurrences (all)	9		
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	20 / 111 (18.02%)		
occurrences (all)	26		
Back pain			
subjects affected / exposed	9 / 111 (8.11%)		
occurrences (all)	11		
Pain in extremity			
subjects affected / exposed	16 / 111 (14.41%)		
occurrences (all)	23		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	11 / 111 (9.91%)		
occurrences (all)	17		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	8 / 111 (7.21%)		
occurrences (all)	8		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 August 2015	The following updates were made: * Removed Inclusion Criterion 105 to allow participants to join the study after having received first-line therapy. * Removed exclusion of participants receiving any non oncology vaccine therapies used for the prevention of infectious disease within 28 days prior to enrollment and during treatment period. * Clarified that if no viable cells were found following surgery, the response definition will be complete response (CR). * Added testing for herpes simplex virus type 2 (HSV-2) within 3 days prior to dose at day 1 of week 1 [Cycle 1], week 6 [Cycle 3], and week 12 [Cycle 6]. * Increased the window to 5 days for tumor biopsy for biomarker analysis for the Week 1 biopsy, 7 days for the Week 6 biopsy, and to 7 days after documentation of disease progression at PD. * Added assessment of Eastern Cooperative Oncology Group (ECOG) performance status every 3 months during treatment period. * Revised photography assessments in the schedule of assessments to remove requirement at screening, update cycles, and removed the word "measurable." * In Schedule of Assessments, clarified that the week 1 biopsy should not be collected prior to the participant being enrolled. * Removed word "uninjected" from the correlation between changes in intratumoral CD8+ cell density during treatment and objective response rate in the study endpoints. * Revised the number of planned sites to be 50, and removed reference to including sites in the United States. * Added male contraceptive language to the inclusion criteria. * Specified how lesions that separate or merging are to be assessed. * Added an interim analysis. * Added reporting of treatment related adverse events during the long-term follow-up. * Added addition of anti-cancer therapy for melanoma during long term period follow-up.
31 August 2015	31-Aug-2015 amendment continued: * In Table 5: Definition of Index Lesion Tumor Response Including New Lesions, removed the following text from the definition of partial response, "Any residual cutaneous or subcutaneous index or new lesions that must be tumor free for the participant to meet the criteria for partial response (PR) must be documented as such by representative biopsy". * Updated text throughout document to specify cycle number corresponding to study week. * Implemented minor administrative and formatting changes. * Added references in Section 2.2 and in the reference list. * Added ECOG and physical examination during treatment period and follow-up period. * Added exclusion criteria as specified in the Country-specific protocol supplement for Germany to exclude participants who are unwilling to minimize exposure with his/her blood or other body fluids to individuals who are at higher risks for HSV-1 induced complications and participants for whom there is any concern of potential harmful effect due to the interaction between talimogene laherparepvec and the residual of prior investigational drug. * Defined the final analysis after 24 months from LSE rather than keeping it open ended. * Clarified that unless patients dies or withdraws full consent after they have completed the LTFU portion of the study they will then be transferred to the registry protocol where they will continue to be followed up, until death or full consent withdraw.

21 September 2015	The following changes were made: * Added exclusion criterion to avoid potential viral transmission during sexual contact.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported