Clinical trial results:
A Phase 2, Multicenter, Randomized, Open-label Trial Assessing the Efficacy and Safety of Talimogene Laherparepvec Neoadjuvant Treatment Plus Surgery Versus Surgery Alone for Resectable, Stage IIIB to IVM1a Melanoma

Summary

EudraCT number	2014-001146-13
Trial protocol	ES GR
Global end of trial date	28 April 2022

Results information

Result version number	v1 (current)
This version publication date	03 March 2023
First version publication date	03 March 2023

Trial information

Trial identification

Sponsor protocol code	20110266

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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, medinfo@amgen.com
Scientific contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, medinfo@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	16 August 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 April 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a phase 2, multicenter, randomized, open-label study to estimate the efficacy of talimogene laherparepvec as a neoadjuvant treatment followed by surgery compared to surgery alone in participants with completely resectable stage IIIB, IIIC, or IVM1a melanoma.

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	03 February 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 18
Country: Number of subjects enrolled	Brazil: 10
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Poland: 8
Country: Number of subjects enrolled	Russian Federation: 15
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Switzerland: 14
Country: Number of subjects enrolled	United States: 71
Worldwide total number of subjects	150
EEA total number of subjects	22

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)	82
From 65 to 84 years	66
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 35 centers in Australia, Brazil, Europe, Russia, and the United States. Participants were enrolled between 03 February 2015 and 28 April 2022.

Pre-assignment

Screening details:

Participants were randomized 1:1 to receive either talimogene laherparepvec for 6 doses followed by surgical resection of melanoma tumor lesions or immediate surgical resection of melanoma tumor lesion(s). Randomization was stratified by disease stage and planned adjuvant therapy.

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	Surgery

Arm description:

Immediate surgical resection of melanoma lesion(s) any time during Weeks 1 to 6.

Arm type	Surgery alone

No investigational medicinal product assigned in this arm

Arm title	Talimogene Laherparepvec Plus Surgery

Arm description:

Talimogene laherparepvec up to 4.0 mL of 10^6 PFU/mL followed by up to 4.0 mL of 10^8 PFU/mL administered 21 (+5) days after the initial dose. Subsequent doses up to 4.0 mL of 10^8 PFU/mL every 14 (± 3) days until Week 12, all injectable tumors have disappeared, or intolerance of study treatment, whichever occurs first. Followed by surgical resection of melanoma lesions(s) anytime during Weeks 13 to 18.

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

Dosage and administration details:

Talimogene laherparepvec was be administered by intralesional injection into the injectable cutaneous, subcutaneous, and nodal tumors initially at a dose of 10^6 plaque forming units (PFU)/mL at Day 1 of Week 1 followed by a dose of 10^8 PFU/mL at Day 1 (±3 days) of Week 4, 6, 8, 10 and 12 or until all injectable tumors disappeared, intolerance of study treatment or in the opinion of the investigator, immediate surgical resection or any other treatment for melanoma was warranted, whichever occurred first.

Number of subjects in period 1	Surgery	Talimogene Laherparepvec Plus Surgery
Started	74	76
Completed	40	48
Not completed	34	28
Consent withdrawn by subject	3	8
Death	26	16
Decision by Sponsor	1	1
Lost to follow-up	4	3

Baseline characteristics

Reporting groups	
Reporting group title	Surgery
Reporting group description:	
Immediate surgical resection of melanoma lesion(s) any time during Weeks 1 to 6.	
Reporting group title	Talimogene Laherparepvec Plus Surgery
Reporting group description:	
Talimogene laherparepvec up to 4.0 mL of 10^6 PFU/mL followed by up to 4.0 mL of 10^8 PFU/mL administered 21 (+5) days after the initial dose. Subsequent doses up to 4.0 mL of 10^8 PFU/mL every 14 (± 3) days until Week 12, all injectable tumors have disappeared, or intolerance of study treatment, whichever occurs first. Followed by surgical resection of melanoma lesions(s) anytime during Weeks 13 to 18.	

Reporting group values	Surgery	Talimogene Laherparepvec Plus Surgery	Total
Number of subjects	74	76	150
Age categorical Units: Subjects			
Adults (18-64 years)	42	40	82
From 65-84 years	31	35	66
85 years and over	1	1	2
Age Continuous Units: years			
arithmetic mean	59.1	62.6	
standard deviation	± 16.1	± 12.6	-
Sex: Female, Male Units: participants			
Female	27	27	54
Male	47	49	96
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	0	1	1
White	73	73	146
More than one race	0	0	0
Unknown or Not Reported	0	1	1
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	5	5	10
Not Hispanic or Latino	69	70	139
Unknown or Not Reported	0	1	1
Stratification Factor: Disease Stage			
The clinical participants were staged according to the American Joint Committee of Cancer (AJCC) 7th edition Melanoma Staging System, which combines tumor staging, nodal staging and metastasis to derive an overall stage. The order of prognostication is as follows: stage IIIB (better prognosis) > stage IIIC > stage IV M1a (worse prognosis). Randomization was stratified by disease stage and planned adjuvant therapy (adjuvant systemic therapy with or without radiotherapy vs radiotherapy without			

adjuvant systemic therapy vs none).			
Units: Subjects			
Stage IIIB Nodal	14	15	29
Stage IIIB In-Transit	17	16	33
Stage IIIC Nodal	14	13	27
Stage IIIC In-Transit With Nodal	17	17	34
Stage IV M1a	12	15	27
Stratification Factor: Planned Adjuvant Therapy			
Randomization was stratified by disease stage (IIIB nodal vs IIIB in-transit vs IIIC nodal vs IIIC in-transit with nodal vs IVM1a) and planned adjuvant therapy (adjuvant systemic therapy with (W/) or without (W/O) radiotherapy vs radiotherapy without (W/O) adjuvant systemic therapy vs none).			
Units: Subjects			
Adjuvant Systemic Therapy W/ or W/O Radiotherapy	9	9	18
Radiotherapy W/O Adjuvant Systemic Therapy	3	3	6
None	62	64	126

End points

End points reporting groups

Reporting group title	Surgery
Reporting group description:	
Immediate surgical resection of melanoma lesion(s) any time during Weeks 1 to 6.	
Reporting group title	Talimogene Laherparepvec Plus Surgery
Reporting group description:	
Talimogene laherparepvec up to 4.0 mL of 10^6 PFU/mL followed by up to 4.0 mL of 10^8 PFU/mL administered 21 (+5) days after the initial dose. Subsequent doses up to 4.0 mL of 10^8 PFU/mL every 14 (± 3) days until Week 12, all injectable tumors have disappeared, or intolerance of study treatment, whichever occurs first. Followed by surgical resection of melanoma lesions(s) anytime during Weeks 13 to 18.	

Primary: Recurrence-Free Survival (RFS)

End point title	Recurrence-Free Survival (RFS)
End point description:	
Recurrence free survival (RFS) is defined as the time from randomization to the date of event, and is presented as a Kaplan Meier estimate of time to events. The event for RFS is defined as the first of local, regional, or distant recurrence of melanoma or death due to any cause. Participants without a histopathology tumor-free margin (R0) surgical outcome or those who withdrew prior to surgery were considered an event at randomization. Participants without an event were censored at their last evaluable tumor assessment.	
End point type	Primary
End point timeframe:	
5 years after the last subject was randomized (last subject last visit occurred on 28 April 2022)	

End point values	Surgery	Talimogene Laherparepvec Plus Surgery		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	76		
Units: months				
median (confidence interval 80%)	0.0 (-99999 to 99999)	0.0 (0.0 to 6.5)		

Statistical analyses

Statistical analysis title	Log Rank Test
Comparison groups	Surgery v Talimogene Laherparepvec Plus Surgery
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.092 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.76

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.6
upper limit	0.97

Notes:

[1] - Unstratified log-rank test

Secondary: Kaplan-Meier (K-M) Estimate of RFS Rate at 1 year, 2 years, 3 years, and 5 years

End point title	Kaplan-Meier (K-M) Estimate of RFS Rate at 1 year, 2 years, 3 years, and 5 years

End point description:

Kaplan-Meier estimates of the percentage of participants with RFS at 1 year, 2 years, 3 years, and 5 years from randomization. The event for RFS is defined as the first of local, regional, or distant recurrence of melanoma or death due to any cause. Participants without an R0 surgical outcome or those who withdrew prior to surgery are considered an event at randomization. Participants without an event were censored at their last evaluable tumor assessment. Rate is presented as the percentage of participants with RFS at given time point.

End point type	Secondary

End point timeframe:

5 years after the last subject was randomized (last subject last visit occurred on 28 April 2022)

End point values	Surgery	Talimogene Laherparepvec Plus Surgery		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	76		
Units: percentage of participants				
number (confidence interval 80%)				
RFS at 1 Year	21.95 (15.88 to 28.65)	33.73 (26.82 to 40.76)		
RFS at 2 Years	16.88 (11.44 to 23.23)	29.51 (22.91 to 36.40)		
RFS at 3 Years	16.88 (11.44 to 23.23)	28.11 (21.62 to 36.94)		
RFS at 5 Years	15.19 (10.01 to 21.38)	22.32 (16.39 to 28.84)		

Statistical analyses

No statistical analyses for this end point

Secondary: Histopathology Tumor-Free Margin (R0) Surgical Resection Rate

End point title	Histopathology Tumor-Free Margin (R0) Surgical Resection Rate

End point description:

Histopathology tumor-free margin (R0) surgical resection is defined by pathologist as absence of ink on the tumor for all disease. Rate is presented as the percentage of participants with histopathology tumor-free margin (R0) surgical resection.

End point type	Secondary

End point timeframe:

18 weeks after last participant randomized (data cutoff date of 30 April 2019)

End point values	Surgery	Talimogene Laherparepvec Plus Surgery		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	76		
Units: percentage of participants				
number (confidence interval 80%)	37.8 (30.3 to 45.9)	42.1 (34.4 to 50.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pathological Complete Response (pCR) Rate

End point title	Pathological Complete Response (pCR) Rate

End point description:

Pathological Complete Response (pCR) is defined as no evidence of viable tumor cells on complete pathological evaluation of the surgical specimen per institutional standards of care. Rate is presented as the percentage of participants with pCR.

End point type	Secondary

End point timeframe:

18 weeks after last participant randomized (data cutoff date of 30 April 2019)

End point values	Surgery	Talimogene Laherparepvec Plus Surgery		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	76		
Units: percentage of participants				
number (confidence interval 80%)	2.7 (0.7 to 7.0)	17.1 (11.6 to 24.0)		

Statistical analyses

Statistical analysis title	Chi-squared
Comparison groups	Surgery v Talimogene Laherparepvec Plus Surgery

Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.003 [2]
Method	Chi-squared
Parameter estimate	Treatment Difference
Point estimate	14.4
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	7.4
upper limit	21.6

Notes:

[2] - The two-sided p-value is based on the Pearson's Chi-square test.

Secondary: Local Recurrence-Free Survival (LRFS)

End point title	Local Recurrence-Free Survival (LRFS)

End point description:

Local recurrence-free survival (LRFS) is defined as the time from randomization to the earlier date of the first of local disease recurrence or death due to any cause. Participants without an R0 surgical outcome or those who withdrew prior to surgery are considered an event at randomization. Local recurrence is defined as histologically or cytologically confirmed reappearance of melanoma in the area of up to 2 cm from the scar from the surgical excision or at the edge of the skin graft if that was used for closure.

End point type	Secondary

End point timeframe:

5 years after the last subject was randomized (last subject last visit occurred on 28 April 2022)

End point values	Surgery	Talimogene Laherparepvec Plus Surgery		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	76		
Units: months				
median (confidence interval 80%)	0.0 (-99999 to 99999)	0.0 (0.0 to 7.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Regional Recurrence-Free Survival (RRFS)

End point title	Regional Recurrence-Free Survival (RRFS)

End point description:

Regional recurrence-free survival (RRFS) is defined as the time from randomization to the date of the first of regional disease recurrence or death due to any cause. Participants without an R0 surgical outcome or those who withdrew prior to surgery are considered an event at randomization. Regional recurrence excludes local recurrence and is defined as histologically, cytologically, or radiographically confirmed reappearance of melanoma in the regional lymph node basin.

End point type	Secondary

End point timeframe:

5 years after the last subject was randomized (last subject last visit occurred on 28 April 2022)

End point values	Surgery	Talimogene Laherparepvec Plus Surgery		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	76		
Units: months				
median (confidence interval 80%)	0.0 (-99999 to 99999)	0.0 (0.0 to 12.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Distant Metastases-Free Survival (DMFS)

End point title	Distant Metastases-Free Survival (DMFS)

End point description:

Distant metastases-free survival (DMFS) is defined as the time from randomization to the date of the first of distant metastases or death due to any cause. Participants without an R0 surgical outcome or those who withdrew prior to surgery are considered an event at randomization. Distant metastases exclude local and regional recurrence and will include distant cutaneous/subcutaneous metastases, distant nodal metastases, or visceral, central nervous system, brain, or bone metastases.

End point type	Secondary

End point timeframe:

5 years after the last subject was randomized (last subject last visit occurred on 28 April 2022)

End point values	Surgery	Talimogene Laherparepvec Plus Surgery		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	76		
Units: months				
median (confidence interval 80%)	0.0 (-99999 to 99999)	0.0 (0.0 to 6.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival (OS) is defined as the time from randomization to the date of death due to any cause.

End point type	Secondary

End point timeframe:

5 years after the last subject was randomized (last subject last visit occurred on 28 April 2022)

End point values	Surgery	Talimogene Laherparepvec Plus Surgery		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	76		
Units: months				
median (confidence interval 80%)	0.0 (-99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier (K-M) Estimate of OS at 1 year, 2 years, 3 years, and 5 years

End point title	Kaplan-Meier (K-M) Estimate of OS at 1 year, 2 years, 3 years, and 5 years

End point description:

Kaplan-Meier estimates of the percentage of participants with OS at 1 year, 2 years, 3 years, and 5 years from randomization. OS is defined as death due to any cause.

End point type	Secondary

End point timeframe:

5 years after the last subject was randomized (last subject last visit occurred on 28 April 2022)

End point values	Surgery	Talimogene Laherparepvec Plus Surgery		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	76		
Units: percentage of participants				
number (confidence interval 80%)				
OS at 1 Year	85.92 (79.63 to 90.38)	95.89 (91.58 to 98.02)		
OS at 2 Years	77.44 (70.29 to 83.08)	88.94 (83.16 to 92.82)		
OS at 3 Years	71.59 (64.03 to 77.84)	83.27 (76.70 to 88.13)		
OS at 5 Years	62.29 (54.75 to 69.62)	77.32 (70.12 to 83.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Tumor Response per Investigator Response Rate (Talimogene Laherparepvec Arm Only)

End point title	Best Overall Tumor Response per Investigator Response Rate (Talimogene Laherparepvec Arm Only)[3]

End point description:

Response was assessed based on the response of the index lesions and nonindex lesions as described in protocol-defined World Health Organization (WHO) criteria (for complete response [CR], partial response [PR], stable disease [SD], progressive disease [PD]), and presence or absence of new lesions. Best response for a participant is the best overall response observed across all time points. Response rate is reported as the percentage of participants with the best overall response (per investigator) of CR or PR. CR: complete disappearance of all index lesions, including any new measurable tumor lesions which might have appeared. PR: ≥ 50% reduction in the sum of the products of the 2 largest perpendicular diameters of all index lesions and new measurable lesions, if applicable, at the time of assessment as compared to the sum of the products of the perpendicular diameters of all index lesions at baseline.

End point type	Secondary

End point timeframe:

18 months after last participant randomized (data cutoff date of 30 April 2019).

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Talimogene Laherparepvec Arm Only

End point values	Talimogene Laherparepvec Plus Surgery			
Subject group type	Reporting group			
Number of subjects analysed	76			
Units: percentage of participants				
number (confidence interval 80%)	13.2 (8.3 to 19.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Lesion Objective Response Rate: Injected Lesions (Talimogene Laherparepvec Arm Only)

End point title	Lesion Objective Response Rate: Injected Lesions (Talimogene Laherparepvec Arm Only)[4]

End point description:

The investigator-assessed tumor response rate for injected lesions, reported as the percentage of evaluable lesions in response. A lesion is in response if the decrease in tumor area is ≥ 50%.

End point type	Secondary

End point timeframe:

18 months after last participant randomized (data cutoff date of 30 April 2019).

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Talimogene Laherparepvec Arm Only

End point values	Talimogene Laherparepvec Plus Surgery			
Subject group type	Reporting group			
Number of subjects analysed	76			
Units: percentage of lesions				
number (confidence interval 80%)	26.3 (19.7 to 33.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Lesion Objective Response Rate: Uninjected Lesions (Talimogene Laherparepvec Arm Only)

End point title	Lesion Objective Response Rate: Uninjected Lesions (Talimogene Laherparepvec Arm Only)[5]

End point description:

The investigator-assessed tumor response rate for uninjected lesions, reported as the percentage of evaluable lesions in response. A lesion is in response if the decrease in tumor area is ≥ 50%.

End point type	Secondary

End point timeframe:

18 months after last participant randomized (data cutoff date of 30 April 2019).

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Talimogene Laherparepvec Arm Only

End point values	Talimogene Laherparepvec Plus Surgery			
Subject group type	Reporting group			
Number of subjects analysed	76			
Units: percentage of lesions				
number (confidence interval 80%)	3.9 (1.5 to 8.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-Emergent Adverse Events (TEAEs), Serious Adverse Events (SAEs), Fatal Adverse Events (AEs), and TEAEs Leading to Discontinuations or Interruptions

End point title	Number of Participants With Treatment-Emergent Adverse Events (TEAEs), Serious Adverse Events (SAEs), Fatal Adverse Events (AEs), and TEAEs Leading to Discontinuations or Interruptions

End point description:

Adverse event (AE): any untoward medical occurrence that does not necessarily have a causal relationship with study treatment. SAE: AE meeting at least 1 of the following serious criteria: fatal; life threatening; requires in-patient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; congenital anomaly/birth defect; other medically important serious event. Event severity grades: 1 (mild), 2 (moderate), 3 (severe), 4 (life-threatening), 5 (death). Treatment begins when the first dose of protocol-required therapies is administered to a subject (Talimogene Laherparepvec Arm) or the participant undergoes surgery (Surgery Arm). Events are reported from first day of study drug or the surgery through 30 days after the last administration of talimogene laherparepvec or 30 days after the surgical resection of melanoma tumor lesion(s), whichever is later.

End point type	Secondary

End point timeframe:

Adverse Events are reported from first day of study drug or the surgery through 30 days after the last administration of talimogene laherparepvec or 30 days after the surgical resection of melanoma tumor lesion(s), whichever is later.

End point values	Surgery	Talimogene Laherparepvec Plus Surgery		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	73		
Units: participants				
All TEAEs	32	70		
Grade ≥2	19	38		
Grade ≥3	4	11		
Grade ≥4	0	1		
Serious TEAEs	2	13		
Leading to DC of TL	99999	3		
Leading to Interruption of TL	99999	0		
Leading to <4 ml TL Administered	99999	3		
Leading to <4 ml TL Administered: Serious	99999	2		
Leading to <4 ml TL Administered: Nonserious	99999	1		
Fatal Adverse Events	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Talimogene Laherparepvec-Related TEAEs, SAEs, Fatal AEs, and TEAEs Leading to Discontinuations or Interruptions

End point title	Number of Participants With Talimogene Laherparepvec-Related TEAEs, SAEs, Fatal AEs, and TEAEs Leading to Discontinuations or Interruptions[6]

End point description:

Adverse event (AE): any untoward medical occurrence that does not necessarily have a causal relationship with study treatment. SAE: AE meeting at least 1 of the

following serious criteria: fatal; life threatening; requires in-patient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; congenital anomaly/birth defect; other medically important serious event. Event severity grades: 1 (mild), 2 (moderate), 3 (severe), 4 (life-threatening), 5 (death). Treatment begins when the first dose of protocol-required therapies is administered to a subject (Talimogene Laherparepvec Arm) or the participant undergoes surgery (Surgery Arm). Events are reported from first day of study drug or the surgery through 30 days after the last administration of talimogene laherparepvec or 30 days after the surgical resection of melanoma tumor lesion(s), whichever is later.

End point type	Secondary

End point timeframe:

Adverse Events are reported from first day of study drug or the surgery through 30 days after the last administration of talimogene laherparepvec or 30 days after the surgical resection of melanoma tumor lesion(s), whichever is later.

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Talimogene Laherparepvec Arm Only

End point values	Talimogene Laherparepvec Plus Surgery			
Subject group type	Reporting group			
Number of subjects analysed	73			
Units: participants				
All TEAEs	64			
Grade ≥2	20			
Grade ≥3	3			
Grade ≥4	0			
Serious TEAEs	2			
Leading to DC of TL	1			
Leading to Interruption of TL	0			
Leading to <4 ml TL Administered	1			
Leading to <4 ml TL Administered: Serious	1			
Leading to <4 ml TL Administered: Nonserious	0			
Fatal Adverse Events	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are reported from first day of study drug or the surgery through 30 days after the last administration of talimogene laherparepvec or 30 days after the surgical resection of melanoma tumor lesion(s), whichever is later.

Adverse event reporting additional description:

All-cause mortality is reported for all participants randomized in the study. Serious adverse events and other adverse events are reported for all randomized subjects who received talimogene laherparepvec or surgical resection of melanoma tumor lesion(s).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	TALIMOGENE LAHERPAREPVEC PLUS SURGERY

Reporting group description:

Talimogene Laherparepvec Plus Surgery

Reporting group title	SURGERY

Reporting group description:

Surgery Only

Serious adverse events	TALIMOGENE LAHERPAREPVEC PLUS SURGERY	SURGERY	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 73 (17.81%)	2 / 69 (2.90%)	
number of deaths (all causes)	16	25	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Glioblastoma			
subjects affected / exposed	1 / 73 (1.37%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral embolism			
subjects affected / exposed	0 / 73 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Neck dissection			

subjects affected / exposed	1 / 73 (1.37%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	1 / 73 (1.37%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Anembryonic gestation			
subjects affected / exposed	1 / 73 (1.37%)	0 / 69 (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			
Pain			
subjects affected / exposed	1 / 73 (1.37%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	1 / 73 (1.37%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 73 (1.37%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Small intestinal obstruction			
subjects affected / exposed	1 / 73 (1.37%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	1 / 73 (1.37%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	1 / 73 (1.37%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	1 / 73 (1.37%)	0 / 69 (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			
Postoperative wound infection			
subjects affected / exposed	1 / 73 (1.37%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 73 (1.37%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 73 (2.74%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	1 / 73 (1.37%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound abscess			
subjects affected / exposed	0 / 73 (0.00%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device occlusion			
subjects affected / exposed	1 / 73 (1.37%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	TALIMOGENE LAHERPAREPVEC PLUS SURGERY	SURGERY	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	62 / 73 (84.93%)	14 / 69 (20.29%)	
Nervous system disorders			
Headache			
subjects affected / exposed	17 / 73 (23.29%)	0 / 69 (0.00%)	
occurrences (all)	36	0	
Dizziness			
subjects affected / exposed	7 / 73 (9.59%)	0 / 69 (0.00%)	
occurrences (all)	7	0	
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	4 / 73 (5.48%)	0 / 69 (0.00%)	
occurrences (all)	7	0	
Injection site pain			
subjects affected / exposed	6 / 73 (8.22%)	0 / 69 (0.00%)	
occurrences (all)	12	0	
Injection site erythema			

subjects affected / exposed	4 / 73 (5.48%)	0 / 69 (0.00%)	
occurrences (all)	4	0	
Influenza like illness			
subjects affected / exposed	26 / 73 (35.62%)	0 / 69 (0.00%)	
occurrences (all)	57	0	
Fatigue			
subjects affected / exposed	20 / 73 (27.40%)	1 / 69 (1.45%)	
occurrences (all)	29	1	
Chills			
subjects affected / exposed	18 / 73 (24.66%)	0 / 69 (0.00%)	
occurrences (all)	34	0	
Pain			
subjects affected / exposed	5 / 73 (6.85%)	6 / 69 (8.70%)	
occurrences (all)	7	6	
Pyrexia			
subjects affected / exposed	24 / 73 (32.88%)	2 / 69 (2.90%)	
occurrences (all)	60	2	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	8 / 73 (10.96%)	0 / 69 (0.00%)	
occurrences (all)	8	0	
Nausea			
subjects affected / exposed	7 / 73 (9.59%)	1 / 69 (1.45%)	
occurrences (all)	8	1	
Vomiting			
subjects affected / exposed	7 / 73 (9.59%)	0 / 69 (0.00%)	
occurrences (all)	9	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 73 (5.48%)	0 / 69 (0.00%)	
occurrences (all)	5	0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	4 / 73 (5.48%)	1 / 69 (1.45%)	
occurrences (all)	4	1	
Musculoskeletal and connective tissue disorders			

Pain in extremity			
subjects affected / exposed	1 / 73 (1.37%)	4 / 69 (5.80%)	
occurrences (all)	1	4	
Myalgia			
subjects affected / exposed	8 / 73 (10.96%)	0 / 69 (0.00%)	
occurrences (all)	16	0	
Arthralgia			
subjects affected / exposed	10 / 73 (13.70%)	0 / 69 (0.00%)	
occurrences (all)	13	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 June 2014	The protocol was amended for the following reasons: • To update the Data Review Team section.
22 April 2016	The protocol was amended for the following reasons: • Regional recurrence-free survival was added as secondary objective and endpoint. • The DMFS endpoint was clarified. • The randomization stratification was updated to replace adjuvant interferon with adjuvant interferon alpha and ipilimumab. • The number of sites was changed from 40 to 50. • The 30-day safety follow-up was modified to specify that subjects would be followed for local, regional, and distant disease recurrence and adverse events potentially related to talimogene laherparepvec. • Inclusion criteria of measurable disease, serum lactate dehydrogenase, serum albumin were modified. • Exclusion criteria of autoimmune disease, clinically significant immunosuppression, tumor vaccine, and sexually active subjects and partners unwilling to use latex condoms were updated. • Long-term follow-up was updated to include reporting of adverse events potentially related to talimogene laherparepvec. • Physical examination and ECOG performance status were added at weeks 4 and 8. • Oral and genital swabs were removed from the safety follow-up visit as this information is already being collected in another protocol. • Surgical safety evaluation and subsequent anticancer therapy for melanoma were added to safety follow-up procedures. • Statistical considerations were updated to add RRFS analysis, to clarify DRT review of interim analyses, and to specify that ad hoc analyses may be conducted if required for submission to regulatory authorities. • The definition of progressive disease was clarified to include the unequivocal appearance of new measurable lesion since the last response assessment.
23 March 2018	The protocol was amended for the following reasons: • Add a third interim analysis to the protocol 1 year after the end of randomization in order to help inform Amgen regarding future potential clinical trials and data collection in this setting. • Update the time points for assessment of secondary objectives to start at first year. • Update the exclusion criteria for sexually active subjects and their partners with allergy by providing option for alternative condom type. • Provide guidance to sites on how to report data for fully resected lymph nodes after surgery with specific qualitative and quantitative features. • Make minor corrections and clarifications throughout the document, including administrative, typographical, and formatting errors.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported