Clinical trial results:
A Phase 1b/2, Multicenter, Open-label Trial to Evaluate the Safety and Efficacy of Talimogene Laherparepvec and Ipilimumab Compared to Ipilimumab Alone in Subjects With Unresected, Stage IIIB-IV Melanoma

Summary

EudraCT number	2012-000307-32
Trial protocol	DE
Global end of trial date	09 March 2021

Results information

Result version number	v1 (current)
This version publication date	01 March 2022
First version publication date	01 March 2022

Trial information

Trial identification

Sponsor protocol code	20110264

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01740297
WHO universal trial number (UTN)	-

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	09 March 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the Phase 1b part was to determine the safety and tolerability of talimogene laherparepvec in combination with ipilimumab as assessed by incidence of dose-limiting toxicities (DLT) in subjects with previously untreated, unresected, stages IIIB to IV melanoma.
The main objective of the Phase 2 part was to evaluate the efficacy as assessed by confirmed objective response rate (ORR) of treatment with talimogene laherparepvec in combination with ipilimumab versus ipilimumab alone in subjects with unresected, stages IIIB to IV melanoma.

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines.
The study protocol and all amendments, the informed consent form, and any accompanying materials provided to the subjects were reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) at each study center.
The investigator or his/her designee informed the subject of all aspects pertaining to the subject's participation in the study before any screening procedures were performed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 February 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	60 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 202
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 10
Worldwide total number of subjects	217
EEA total number of subjects	15

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)	111
From 65 to 84 years	99
85 years and over	7

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 33 centers in the United States of America, France, and Germany. Participants were enrolled in Phase 1b from 07 February 2013 to 08 July 2013 and in Phase 2 from 13 August 2013 to 25 February 2016.

Pre-assignment

Screening details:

In Phase 1b all participants received talimogene laherparepvec in combination with ipilimumab. In Phase 2 participants were randomized 1:1 to receive talimogene laherparepvec plus ipilimumab or ipilimumab. Participants were stratified by disease stage and either v-raf murine sarcoma viral oncogene homolog B1 (BRAF) mutation V600E or prior 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	Phase 1b: Talimogene Laherparepvec + Ipilimumab

Arm description:

Participants received talimogene laherparepvec at an initial dose of 10 plaque-forming units (PFU)/mL injected into 1 or more skin, nodal, or subcutaneous tumors with maximum total volume of 4 mL. Subsequent doses of talimogene laherparepvec at 10^8 PFU/mL (up to 4 mL total) began 3 weeks after the first dose and were administered every 2 weeks until complete response (CR), all injectable tumors had disappeared, confirmed disease progression per the modified immune-related response criteria (irRC), or intolerance of study treatment, whichever occurred first. Participants also received 3 mg/kg ipilimumab administered intravenously every 3 weeks for a total of 4 infusions starting at the time of the third dose of talimogene laherparepvec (week 6).

Arm type	Experimental
Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	
Other name	Yervoy®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ipilimumab administered intravenously every 3 weeks starting at week 6, for a total of 4 infusions.

Investigational medicinal product name	Talimogene Laherparepvec
Investigational medicinal product code	AMG 678
Other name	IMLYGIC®
Pharmaceutical forms	Solution for injection
Routes of administration	Intratumoral use

Dosage and administration details:

Talimogene laherparepvec administered by intratumoral injection on Day 1 of Week 1, Day 1 of Week 4, then every two weeks thereafter.

Arm title	Phase 2: Ipilimumab

Arm description:

Participants received ipilimumab 3 mg/kg intravenously every 3 weeks for a total of 4 infusions starting at week 1.

Arm type	Active comparator

Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	
Other name	Yervoy®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ipilimumab administered intravenously every 3 weeks starting at week 1, for a total of 4 infusions.

Arm title	Phase 2: Talimogene Laherparepvec + Ipilimumab

Arm description:

Participants received talimogene laherparepvec at an initial dose of 10 PFU/mL injected into 1 or more skin, nodal, or subcutaneous tumors with a maximum total volume of 4 mL. Subsequent doses of talimogene laherparepvec at 10^8 PFU/mL (up to 4 mL total) began 3 weeks after the first dose and were administered every 2 weeks until CR, all injectable tumors had disappeared, confirmed disease progression per the modified irRC, or intolerance of study treatment, whichever occurred first. Participants also received 3 mg/kg ipilimumab intravenously every 3 weeks for a total of 4 infusions starting at the time of the third dose of talimogene laherparepvec (week 6).

Arm type	Experimental
Investigational medicinal product name	Talimogene Laherparepvec
Investigational medicinal product code	AMG 678
Other name	IMLYGIC®
Pharmaceutical forms	Solution for injection
Routes of administration	Intratumoral use

Dosage and administration details:

Talimogene laherparepvec administered by intratumoral injection on Day 1 of Week 1, Day 1 of Week 4, then every two weeks thereafter.

Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	
Other name	Yervoy®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ipilimumab administered intravenously every 3 weeks starting at week 6, for a total of 4 infusions.

Number of subjects in period 1	Phase 1b: Talimogene Laherparepvec + Ipilimumab	Phase 2: Ipilimumab	Phase 2: Talimogene Laherparepvec + Ipilimumab
Started	19	100	98
Received Talimogene Laherparepvec	19	0 [1]	95
Received Ipilimumab	18	95	92
Completed	6	36	37
Not completed	13	64	61
Consent withdrawn by subject	4	16	17
Death	8	46	40
Lost to follow-up	1	2	4

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Participants in this group did not receive talimogene laherparepvec.

Baseline characteristics

Reporting groups

Reporting group title	Phase 1b: Talimogene Laherparepvec + Ipilimumab

Reporting group description:

Participants received talimogene laherparepvec at an initial dose of 10 plaque-forming units (PFU)/mL injected into 1 or more skin, nodal, or subcutaneous tumors with maximum total volume of 4 mL. Subsequent doses of talimogene laherparepvec at 10^8 PFU/mL (up to 4 mL total) began 3 weeks after the first dose and were administered every 2 weeks until complete response (CR), all injectable tumors had disappeared, confirmed disease progression per the modified immune-related response criteria (irRC), or intolerance of study treatment, whichever occurred first. Participants also received 3 mg/kg ipilimumab administered intravenously every 3 weeks for a total of 4 infusions starting at the time of the third dose of talimogene laherparepvec (week 6).

Reporting group title	Phase 2: Ipilimumab

Reporting group description:

Participants received ipilimumab 3 mg/kg intravenously every 3 weeks for a total of 4 infusions starting at week 1.

Reporting group title	Phase 2: Talimogene Laherparepvec + Ipilimumab

Reporting group description:

Participants received talimogene laherparepvec at an initial dose of 10 PFU/mL injected into 1 or more skin, nodal, or subcutaneous tumors with a maximum total volume of 4 mL. Subsequent doses of talimogene laherparepvec at 10^8 PFU/mL (up to 4 mL total) began 3 weeks after the first dose and were administered every 2 weeks until CR, all injectable tumors had disappeared, confirmed disease progression per the modified irRC, or intolerance of study treatment, whichever occurred first. Participants also received 3 mg/kg ipilimumab intravenously every 3 weeks for a total of 4 infusions starting at the time of the third dose of talimogene laherparepvec (week 6).

Reporting group values	Phase 1b: Talimogene Laherparepvec + Ipilimumab	Phase 2: Ipilimumab	Phase 2: Talimogene Laherparepvec + Ipilimumab
Number of subjects	19	100	98
Age Categorical Units: participants			
< 65 years	11	54	46
≥ 65 years	8	46	52
Age Continuous Units: years			
arithmetic mean	61.1	64.2	63.6
standard deviation	± 12.1	± 13.3	± 14.0
Sex: Female, Male Units: participants			
Female	11	45	36
Male	8	55	62
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	1	0
Asian	0	1	0
Black (or African American)	0	3	0
Multiple	0	1	1
Native Hawaiian or Other Pacific Islander	0	0	0
White	18	92	97
Other	1	2	0

Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	4	0
Not Hispanic or Latino	18	96	98
Unknown or Not Reported	0	0	0
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			
0 (Fully active)	14	73	69
1 (Restrictive but ambulatory)	5	27	29
Tumor, Node, Metastasis (TNM) 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 - IVM1a	8	57	50
Stage IVM1b/c	11	43	48
BRAF V600 Mutation Status			
Mutation status of v-raf murine sarcoma viral oncogene homolog B1 (BRAF) gene was based on a gene mutation that results in an amino acid substitution from valine (V) to glutamic acid (E) at codon 600 (V600E) and/or a substitution from valine to lysine (K) (V600K).			
Units: Subjects			
Mutation	12	34	35
Wild-type	7	60	62
Missing/Unknown	0	6	1

Reporting group values	Total		
Number of subjects	217		
Age Categorical Units: participants			
< 65 years	111		
≥ 65 years	106		
Age Continuous Units: years arithmetic mean standard deviation	- -		
Sex: Female, Male Units: participants			
Female	92		
Male	125		

Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	1		
Asian	1		
Black (or African American)	3		
Multiple	2		
Native Hawaiian or Other Pacific Islander	0		
White	207		
Other	3		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	5		
Not Hispanic or Latino	212		
Unknown or Not Reported	0		
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			
0 (Fully active)	156		
1 (Restrictive but ambulatory)	61		
Tumor, Node, Metastasis (TNM) 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 - IVM1a	115		
Stage IVM1b/c	102		
BRAF V600 Mutation Status			
Mutation status of v-raf murine sarcoma viral oncogene homolog B1 (BRAF) gene was based on a gene mutation that results in an amino acid substitution from valine (V) to glutamic acid (E) at codon 600 (V600E) and/or a substitution from valine to lysine (K) (V600K).			
Units: Subjects			
Mutation	81		
Wild-type	129		
Missing/Unknown	7		

End points

End points reporting groups

Reporting group title	Phase 1b: Talimogene Laherparepvec + Ipilimumab

Reporting group description:

Participants received talimogene laherparepvec at an initial dose of 10 plaque-forming units (PFU)/mL injected into 1 or more skin, nodal, or subcutaneous tumors with maximum total volume of 4 mL. Subsequent doses of talimogene laherparepvec at 10^8 PFU/mL (up to 4 mL total) began 3 weeks after the first dose and were administered every 2 weeks until complete response (CR), all injectable tumors had disappeared, confirmed disease progression per the modified immune-related response criteria (irRC), or intolerance of study treatment, whichever occurred first. Participants also received 3 mg/kg ipilimumab administered intravenously every 3 weeks for a total of 4 infusions starting at the time of the third dose of talimogene laherparepvec (week 6).

Reporting group title	Phase 2: Ipilimumab

Reporting group description:

Participants received ipilimumab 3 mg/kg intravenously every 3 weeks for a total of 4 infusions starting at week 1.

Reporting group title	Phase 2: Talimogene Laherparepvec + Ipilimumab

Reporting group description:

Participants received talimogene laherparepvec at an initial dose of 10 PFU/mL injected into 1 or more skin, nodal, or subcutaneous tumors with a maximum total volume of 4 mL. Subsequent doses of talimogene laherparepvec at 10^8 PFU/mL (up to 4 mL total) began 3 weeks after the first dose and were administered every 2 weeks until CR, all injectable tumors had disappeared, confirmed disease progression per the modified irRC, or intolerance of study treatment, whichever occurred first. Participants also received 3 mg/kg ipilimumab intravenously every 3 weeks for a total of 4 infusions starting at the time of the third dose of talimogene laherparepvec (week 6).

Primary: Phase 1b: Number of Participants with Dose-limiting Toxicities

End point title	Phase 1b: Number of Participants with Dose-limiting

End point description:

A DLT was defined as any toxicity related to study drug which met any of the following criteria based on Common Terminology Criteria for Adverse Events version 3.0:
• treatment-related non-laboratory adverse events (AE) ≥ grade 4;
• ≥ grade 4 immune-mediated dermatitis;
• ≥ grade 4 immune-mediated endocrinopathy (except autoimmune thyroiditis);
• ≥ grade 3 immune-mediated enterocolitis;
• ≥ grade 3 immune-mediated hepatitis (except grade 3 that resolved to grade 1 or baseline within 28 days of onset);
• ≥ grade 3 immune-mediated neuropathy;
• ≥ grade 3 other immune-mediated AEs including hemolytic anemia, angiopathy, myocarditis, pericarditis, temporal arteritis, or vasculitis, autoimmune thyroiditis (except grade 3 that resolved to grade 1 or baseline within 28 days of onset), blepharitis, conjunctivitis, episcleritis, iritis, scleritis, or uveitis, pancreatitis, meningitis, arthritis or polymyalgia rheumatic, nephritis, pneumonitis, psoriasis or leukocytoclastic vasculitis.

End point type	Primary

End point timeframe:

The DLT evaluation period was 6 weeks from the initial administration of ipilimumab (week 6 to 12).

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: Phase 1b was a single-arm study with no statistical comparisons conducted.

[2] - 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: Results are reported separately for Phase 1b and Phase 2

End point values	Phase 1b: Talimogene Laherparepvec + Ipilimumab			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Primary: Phase 2: Objective Response Rate

End point title	Phase 2: Objective Response Rate[3]

End point description:

Objective response rate is defined as the percentage of participants with a best overall response of complete response (CR) or partial response (PR) according to the modified immune-related response criteria (irRC) assessed by the investigator. Tumors were examined clinically and by computed tomography (CT) or magnetic resonance imaging (MRI).
CR: Complete disappearance of all lesions and no new lesions; Any pathological lymph nodes reduced in short axis to <10 mm.
PR: Decrease in tumor burden ≥ 50% relative to baseline.
Response must have been confirmed by a repeat, consecutive assessment ≥ 4 weeks from the date first documented. Participants who did not have any follow-up tumor assessments were regarded as non-responders.

End point type	Primary

End point timeframe:

Tumor response was assessed every 12 weeks until disease progression; median follow-up time at the primary analysis was 57.7 weeks and 68.1 weeks in each treatment group respectively.

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: Results are reported separately for Phase 1b and Phase 2

End point values	Phase 2: Ipilimumab	Phase 2: Talimogene Laherparepvec + Ipilimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	98		
Units: percentage of participants				
number (confidence interval 95%)	18.0 (11.0 to 26.9)	38.8 (29.1 to 49.2)		

Statistical analyses

Statistical analysis title	Primary Analysis of ORR
Comparison groups	Phase 2: Ipilimumab v Phase 2: Talimogene Laherparepvec + Ipilimumab

Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Chi-squared corrected
Parameter estimate	Odds ratio (OR)
Point estimate	2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.5
upper limit	5.5

Secondary: Phase 1b: Objective Response Rate

End point title	Phase 1b: Objective Response Rate[4]

End point description:

Objective response rate is defined as the percentage of participants with a best overall response of complete response (CR) or partial response (PR) according to the modified immune-related response criteria (irRC) assessed by the investigator. Tumors were examined clinically and by computed tomography (CT) or magnetic resonance imaging (MRI).
CR: Complete disappearance of all lesions and no new lesions; Any pathological lymph nodes reduced in short axis to <10 mm.
PR: Decrease in tumor burden ≥ 50% relative to baseline.
Response must have been confirmed by a repeat, consecutive assessment ≥ 4 weeks from the date first documented. Participants who did not have any follow-up tumor assessments were regarded as non-responders.

End point type	Secondary

End point timeframe:

Tumor response was assesed every 12 weeks until disease progression; median follow-up time at the primary analysis was 148.4 weeks.

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: Results are reported separately for Phase 1b and Phase 2

End point values	Phase 1b: Talimogene Laherparepvec + Ipilimumab			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: percentage of participants				
number (confidence interval 95%)	52.6 (28.9 to 75.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Best Overall Response

End point title	Phase 2: Best Overall Response[5]

End point description:

Best overall response was categorized in descending order as a complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD) or unevaluable (UE) based on investigator assessment according to the modified irRC.
CR: Complete disappearance of all lesions and no new lesions; Any pathological lymph nodes reduced in short axis to <10 mm.
PR: Decrease in tumor burden ≥ 50% relative to baseline.
PD: Increase in tumor burden ≥ 25% relative to nadir.
SD: Not meeting criteria for CR or PR, in absence of PD and no earlier than 77 days after the date of enrollment/randomization.
CR, PR and PD must have been confirmed at 2 consecutive assessment ≥ 4 weeks apart.
Assessments occurring after the start of the first subsequent anticancer therapy or removal of a lesion were not included.

End point type	Secondary

End point timeframe:

Tumor response was assessed every 12 weeks until disease progression; median follow-up time at the primary analysis was 57.7 weeks and 68.1 weeks in each treatment group respectively.

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: Results are reported separately for Phase 1b and Phase 2

End point values	Phase 2: Ipilimumab	Phase 2: Talimogene Laherparepvec + Ipilimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	98		
Units: participants				
Complete Response (CR)	7	13		
Partial Response (PR)	11	25		
Stable Disease (SD)	24	19		
Progressive Disease (PD)	33	31		
Unevaluable (UE)	17	4		
Not Done (ND)	8	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Disease Control Rate

End point title	Phase 2: Disease Control Rate[6]

End point description:

Disease control rate (DCR) was defined as the percentage of participants with a best overall response of CR, PR or SD based on investigator assessment according to the modified irRC.
CR: Complete disappearance of all lesions and no new lesions; any pathological lymph nodes reduced in short axis to <10 mm.
PR: Decrease in tumor burden ≥ 50% relative to baseline.
SD: Not meeting criteria for CR or PR, in absence of PD and no earlier than 77 days after the date of enrollment/randomization.
CR and PR must have been confirmed at 2 consecutive assessments ≥ 4 weeks apart.

End point type	Secondary

End point timeframe:

Tumor response was assessed every 12 weeks until disease progression; median follow-up time at the primary analysis was 57.7 weeks and 68.1 weeks in each treatment group respectively.

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: Results are reported separately for Phase 1b and Phase 2

End point values	Phase 2: Ipilimumab	Phase 2: Talimogene Laherparepvec + Ipilimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	98		
Units: percentage of participants				
number (confidence interval 95%)	42.0 (32.2 to 52.3)	58.2 (47.8 to 68.1)		

Statistical analyses

Statistical analysis title	Primary Analysis of DCR
Comparison groups	Phase 2: Ipilimumab v Phase 2: Talimogene Laherparepvec + Ipilimumab
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.033 [7]
Method	Chi-squared corrected
Parameter estimate	Odds ratio (OR)
Point estimate	1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	3.4

Notes:

[7] - P-value is descriptive

Secondary: Phase 2: Durable Response Rate

End point title	Phase 2: Durable Response Rate[8]

End point description:

Durable response rate (DRR) was defined as the percentage of participants with a duration of response (best response of CR or PR) per modified irRC of at least 6 months. Duration of response is the time from the first confirmed CR or PR to confirmed disease progression per the modified irRC or death, whichever occurs earlier.

End point type	Secondary

End point timeframe:

Tumor response was assessed every 12 weeks until disease progression; median follow-up time at the primary analysis was 57.7 weeks and 68.1 weeks in each treatment group respectively.

Notes:

[8] - 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: Results are reported separately for Phase 1b and Phase 2

End point values	Phase 2: Ipilimumab	Phase 2: Talimogene Laherparepvec + Ipilimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	98		
Units: percentage of participants				
number (confidence interval 95%)	13.0 (7.1 to 21.2)	29.6 (20.8 to 39.7)		

Statistical analyses

Statistical analysis title	Primary Analysis of DRR
Comparison groups	Phase 2: Ipilimumab v Phase 2: Talimogene Laherparepvec + Ipilimumab
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.007 [9]
Method	Chi-squared corrected
Parameter estimate	Odds ratio (OR)
Point estimate	2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.4
upper limit	5.8

Notes:

[9] - P-value is descriptive.

Secondary: Phase 2: Time to Response

End point title	Phase 2: Time to Response[10]

End point description:

Time to confirmed response (TTR) was defined as the time from randomization to the date of the first confirmed CR or PR per modified irRC criteria. Participants who did not have a confirmed CR or PR were censored at their last evaluable tumor assessment date. "99999" indicates values that could not be estimated due to the low number of events.

End point type	Secondary

End point timeframe:

Tumor response was assessed every 12 weeks until disease progression; median follow-up time at the primary analysis was 57.7 weeks and 68.1 weeks in each treatment group respectively.

Notes:

[10] - 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: Results are reported separately for Phase 1b and Phase 2

End point values	Phase 2: Ipilimumab	Phase 2: Talimogene Laherparepvec + Ipilimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	98		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	5.8 (5.4 to 10.9)		

Statistical analyses

Statistical analysis title	Priamry Analysis of TTR
Comparison groups	Phase 2: Ipilimumab v Phase 2: Talimogene Laherparepvec + Ipilimumab
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.228 [11]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	2.49

Notes:

[11] - P-value is descriptive

Secondary: Phase 2: Duration of Response

End point title	Phase 2: Duration of Response[12]

End point description:

Duration of response was calculated only for participants with an objective response per modified irRC and was defined as the time from first confirmed objective response (CR or PR) to confirmed disease progression per the modified irRC or death, whichever was earlier. Responders who did not have an event of death or disease progression were censored at their last evaluable tumor assessment date. "99999" indicates values that could not be estimated due to the low number of events.

End point type	Secondary

End point timeframe:

Tumor response was assessed every 12 weeks until disease progression; median follow-up time at the primary analysis was 57.7 weeks and 68.1 weeks in each treatment group respectively.

Notes:

[12] - 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: Results are reported separately for Phase 1b and Phase 2

End point values	Phase 2: Ipilimumab	Phase 2: Talimogene Laherparepvec + Ipilimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[13]	38[14]		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Notes:

[13] - Participants with a confirmed CR or PR.

[14] - Participants with a confirmed CR or PR.

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Progression-free Survival

End point title	Phase 2: Progression-free Survival[15]

End point description:

Progression-free survival was measured from the date of randomization to the date of disease progression (as measured by modified irRC) or death on or before the data cutoff date, whichever occurred first. Participants who had no disease progression and did not die while on study were censored at the last disease assessment date.

End point type	Secondary

End point timeframe:

From randomization until the primary analysis data cut-off date of 23 August 2016; median follow-up time was 57.7 weeks and 68.1 weeks in each treatment group respectively.

Notes:

[15] - 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: Results are reported separately for Phase 1b and Phase 2

End point values	Phase 2: Ipilimumab	Phase 2: Talimogene Laherparepvec + Ipilimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	98		
Units: months				
median (confidence interval 95%)	6.4 (3.2 to 16.5)	8.2 (4.2 to 21.5)		

Statistical analyses

Statistical analysis title	Primary Analysis of PFS
Comparison groups	Phase 2: Ipilimumab v Phase 2: Talimogene Laherparepvec + Ipilimumab

Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.348
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.23

Secondary: Phase 2: Resection Rate

End point title	Phase 2: Resection Rate[16]

End point description:

Resection rate was defined as the percentage of participants who had surgical procedures for melanoma that resulted in a partial reduction or complete eradication of all previously unresectable cutaneous or visceral metastatic disease. Surgical procedures for melanoma with palliative intent (eg, for pain control) in the presence of disease progression were not considered resection.

End point type	Secondary

End point timeframe:

From randomization until the primary analysis data cut-off date of 23 August 2016; median follow-up time was 57.7 weeks and 68.1 weeks in each treatment group respectively.

Notes:

[16] - 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: Results are reported separately for Phase 1b and Phase 2

End point values	Phase 2: Ipilimumab	Phase 2: Talimogene Laherparepvec + Ipilimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	98		
Units: percentage of participants				
number (confidence interval 95%)	3.0 (0.6 to 8.5)	5.1 (1.7 to 11.5)		

Statistical analyses

Statistical analysis title	Primary Analysis of Resection Rate
Comparison groups	Phase 2: Ipilimumab v Phase 2: Talimogene Laherparepvec + Ipilimumab

Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.696
Method	Chi-squared corrected

Secondary: Phase 2: Overall Survival

End point title	Phase 2: Overall Survival[17]

End point description:

Overall survival was defined as the time from the date of randomization to the date of death from any cause. Participants without an event were censored at the last date they were known to be alive. Participants with a vital status obtained after the data cut-off were censored at the date cut-off date. "99999" indicates values that could not be estimated due to the low number of events.

End point type	Secondary

End point timeframe:

From randomization until the primary analysis data cut-off date of 23 August 2016; median follow-up time was 57.7 weeks and 68.1 weeks in each treatment group respectively.

Notes:

[17] - 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: Results are reported separately for Phase 1b and Phase 2

End point values	Phase 2: Ipilimumab	Phase 2: Talimogene Laherparepvec + Ipilimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	98		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Primary Analysis of OS
Comparison groups	Phase 2: Ipilimumab v Phase 2: Talimogene Laherparepvec + Ipilimumab
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.474
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	1.46

Secondary: Phase 2: Kaplan-Meier Estimate of Percentage of Participants Alive at Month 12 and 24

End point title	Phase 2: Kaplan-Meier Estimate of Percentage of Participants Alive at Month 12 and 24[18]

End point description:

The overall survival estimates at month 24 data were not mature as most participants had not been followed for 24 months at the time of data cutoff.

End point type	Secondary

End point timeframe:

Months 12 and 24; The median (Q1, Q3) follow-up time from randomization to the primary analysis data cutoff date was 80.6 (58.3, 106.3) weeks.

Notes:

[18] - 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: Results are reported separately for Phase 1b and Phase 2

End point values	Phase 2: Ipilimumab	Phase 2: Talimogene Laherparepvec + Ipilimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	98		
Units: percentage of participants				
number (confidence interval 95%)				
Month 12	81.4 (71.4 to 88.3)	86.9 (78.1 to 92.4)		
Month 24	67.7 (53.3 to 78.5)	76.6 (64.5 to 85.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Progression-free Survival - Final Analysis

End point title	Phase 2: Progression-free Survival - Final Analysis[19]

End point description:

Progression-free survival was measured from the date of randomization to the date of disease progression (as measured by modified irRC) or death, whichever occurred first. Participants who had no disease progression and did not die while on study were censored at the last disease assessment date.

End point type	Secondary

End point timeframe:

From randomization until the end of study (09 March 2021); median follow-up time was 155 weeks in the Ipilimumab group and 214 weeks in the Talimogene Laherparepvec + Ipilimumab group.

Notes:

[19] - 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: Results are reported separately for Phase 1b and Phase 2

End point values	Phase 2: Ipilimumab	Phase 2: Talimogene Laherparepvec + Ipilimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	98		
Units: months				
median (confidence interval 95%)	6.4 (3.8 to 17.1)	13.5 (5.2 to 25.0)		

Statistical analyses

Statistical analysis title	Final Analysis of PFS
Comparison groups	Phase 2: Ipilimumab v Phase 2: Talimogene Laherparepvec + Ipilimumab
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.14
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.09

Secondary: Phase 2: Overall Survival - Final Analysis

End point title	Phase 2: Overall Survival - Final Analysis[20]

End point description:

Overall survival was defined as the time from the date of randomization to the date of death from any cause. Participants without an event were censored at the last date they were known to be alive. "99999" indicates values that could not be estimated due to the low number of events.

End point type	Secondary

End point timeframe:

From randomization until the end of study (09 March 2021); median follow-up time was 155 weeks in the Ipilimumab group and 214 weeks in the Talimogene Laherparepvec + Ipilimumab group.

Notes:

[20] - 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: Results are reported separately for Phase 1b and Phase 2

End point values	Phase 2: Ipilimumab	Phase 2: Talimogene Laherparepvec + Ipilimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	98		
Units: months				
median (confidence interval 95%)	50.1 (32.0 to 99999)	84.9 (41.0 to 99999)		

Statistical analyses

Statistical analysis title	Final Analysis of OS
Comparison groups	Phase 2: Ipilimumab v Phase 2: Talimogene Laherparepvec + Ipilimumab
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.37
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.24

Secondary: Phase 2: Kaplan-Meier Estimate of Percentage of Participants Alive at Month 12 and 24 - Final Analysis

End point title	Phase 2: Kaplan-Meier Estimate of Percentage of Participants Alive at Month 12 and 24 - Final Analysis[21]

End point description:

End point type	Secondary

End point timeframe:

Months 12 and 24

Notes:

[21] - 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: Results are reported separately for Phase 1b and Phase 2

End point values	Phase 2: Ipilimumab	Phase 2: Talimogene Laherparepvec + Ipilimumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	98		
Units: percentage of participants				

number (confidence interval 95%)				
Month 12	79.9 (70.4 to 86.7)	83.3 (74.2 to 89.4)		
Month 24	69.3 (58.9 to 77.5)	72.7 (62.5 to 80.5)		

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:

Adverse events (AEs) were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, where grade 1 = mild AE, grade 2 = moderate AE, grade 3 = severe AE, grade 4 = life-threatening or disabling AE and grade 5 = death related to AE.
The investigator assessed whether each AE was possibly related to talimogene laherparepvec (T-VEC) and/or ipilimumab (Imab).

End point type	Secondary

End point timeframe:

From first dose of study drug until 30 days after last dose of talimogene laherparepvec or 60 days after last dose of ipilimumab, whichever was later; median duration of treatment was 14.7, 9.1, and 21.1 weeks in each treatment group respectively.

End point values	Phase 1b: Talimogene Laherparepvec + Ipilimumab	Phase 2: Ipilimumab	Phase 2: Talimogene Laherparepvec + Ipilimumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	19	95	95	
Units: participants				
All adverse events	19	90	92	
Adverse events ≥ grade 2	17	72	80	
Adverse events ≥ grade 3	7	41	44	
Adverse events ≥ grade 4	2	4	6	
Serious adverse events	6	34	34	
AEs leading to discontinuation of T-VEC	0	0	6	
AEs leading to discontinuation of ipilimumab	0	17	13	
Fatal adverse events	1	1	5	
T-VEC-related adverse events	17	0	82	
T-VEC-related adverse events AEs ≥ grade 2	12	0	44	
T-VEC-related adverse events AEs ≥ grade 3	3	0	15	
T-VEC-related adverse events ≥ grade 4	0	0	1	
T-VEC-related serious adverse events	1	0	10	
T-VEC-related AEs leading to T-VEC discontinuation	0	0	0	
Fatal T-VEC-related adverse events	0	0	0	
Ipilimumab-related adverse events	15	78	75	

Ipilimumab-related adverse events ≥ grade 2	8	50	48	
Ipilimumab-related adverse events ≥ grade 3	4	21	19	
Ipilimumab-related adverse events ≥ grade 4	1	2	1	
Ipilimumab-related serious adverse events	4	19	14	
Imab-related AEs leading to Imab discontinuation	0	12	11	
Fatal ipilimumab-related adverse events	0	0	1	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug until 30 days after last dose of talimogene laherparepvec or 60 days after last dose of ipilimumab, whichever was later; median duration of treatment was 14.7, 9.1, and 21.1 weeks in each treatment group respectively.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Phase 1b: Talimogene Laherparepvec + Ipilimumab

Reporting group description:

Participants received talimogene laherparepvec at an initial dose of 10 plaque-forming units (PFU)/mL injected into 1 or more skin, nodal, or subcutaneous tumors. Subsequent doses of talimogene laherparepvec at 10^8 PFU/mL began 3 weeks after the first dose and were administered every 2 weeks until complete response (CR), all injectable tumors had disappeared, confirmed disease progression per the modified immune-related response criteria (irRC), or intolerance of study treatment, whichever occurred first. Participants also received 3 mg/kg ipilimumab administered intravenously every 3 weeks for a total of 4 infusions starting at the time of the third dose of talimogene laherparepvec (week 6).

Reporting group title	Phase 2: Ipilimumab

Reporting group description:

Participants received ipilimumab 3 mg/kg intravenously every 3 weeks for a total of 4 infusions starting at week 1.

Reporting group title	Phase 2: Talimogene Laherparepvec + Ipilimumab

Reporting group description:

Participants received talimogene laherparepvec at an initial dose of 10 PFU/mL injected into 1 or more skin, nodal, or subcutaneous tumors. Subsequent doses of talimogene laherparepvec at 10^8 PFU/mL began 3 weeks after the first dose and were administered every 2 weeks until CR, all injectable tumors had disappeared, confirmed disease progression per the modified irRC, or intolerance of study treatment, whichever occurred first. Participants also received 3 mg/kg ipilimumab intravenously every 3 weeks for a total of 4 infusions starting at the time of the third dose of talimogene laherparepvec (week 6).

Serious adverse events	Phase 1b: Talimogene Laherparepvec + Ipilimumab	Phase 2: Ipilimumab	Phase 2: Talimogene Laherparepvec + Ipilimumab
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 19 (31.58%)	34 / 95 (35.79%)	34 / 95 (35.79%)
number of deaths (all causes)	9	51	43
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			
subjects affected / exposed	0 / 19 (0.00%)	2 / 95 (2.11%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Malignant neoplasm progression			

subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Malignant pleural effusion			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	2 / 95 (2.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			
subjects affected / exposed	1 / 19 (5.26%)	1 / 95 (1.05%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Tumour flare			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 19 (0.00%)	1 / 95 (1.05%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Fatigue			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 19 (0.00%)	1 / 95 (1.05%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza like illness			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	5 / 95 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	7 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injection site reaction			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 19 (0.00%)	1 / 95 (1.05%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	2 / 95 (2.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 19 (0.00%)	1 / 95 (1.05%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Dyspnoea			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	2 / 95 (2.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	2 / 95 (2.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 95 (1.05%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 19 (0.00%)	1 / 95 (1.05%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Amylase increased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 95 (0.00%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Blood creatinine increased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipase increased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 95 (0.00%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count decreased			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	0 / 19 (0.00%)	1 / 95 (1.05%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 19 (0.00%)	1 / 95 (1.05%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Atrial fibrillation			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial paralysis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 95 (0.00%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial mass			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			

Lymphopenia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 95 (1.05%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Exophthalmos			
subjects affected / exposed	0 / 19 (0.00%)	1 / 95 (1.05%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 19 (5.26%)	0 / 95 (0.00%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 19 (0.00%)	1 / 95 (1.05%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune colitis			
subjects affected / exposed	0 / 19 (0.00%)	3 / 95 (3.16%)	3 / 95 (3.16%)
occurrences causally related to treatment / all	0 / 0	5 / 5	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 19 (0.00%)	9 / 95 (9.47%)	6 / 95 (6.32%)
occurrences causally related to treatment / all	0 / 0	12 / 12	6 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 19 (0.00%)	1 / 95 (1.05%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Diarrhoea			
subjects affected / exposed	0 / 19 (0.00%)	2 / 95 (2.11%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	2 / 19 (10.53%)	0 / 95 (0.00%)	2 / 95 (2.11%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fissure			
subjects affected / exposed	0 / 19 (0.00%)	1 / 95 (1.05%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 19 (0.00%)	1 / 95 (1.05%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	0 / 19 (0.00%)	1 / 95 (1.05%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hypophysitis			

subjects affected / exposed	0 / 19 (0.00%)	1 / 95 (1.05%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphocytic hypophysitis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 95 (1.05%)	2 / 95 (2.11%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adrenocortical insufficiency acute			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 95 (1.05%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	1 / 19 (5.26%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 95 (1.05%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 19 (0.00%)	1 / 95 (1.05%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhabdomyolysis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myositis			

subjects affected / exposed	0 / 19 (0.00%)	1 / 95 (1.05%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus colitis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis aseptic			
subjects affected / exposed	0 / 19 (0.00%)	1 / 95 (1.05%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 95 (1.05%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			

Dehydration			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	2 / 95 (2.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 19 (0.00%)	2 / 95 (2.11%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 95 (1.05%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Phase 1b: Talimogene Laherparepvec + Ipilimumab	Phase 2: Ipilimumab	Phase 2: Talimogene Laherparepvec + Ipilimumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 19 (100.00%)	85 / 95 (89.47%)	91 / 95 (95.79%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	1 / 19 (5.26%)	4 / 95 (4.21%)	4 / 95 (4.21%)
occurrences (all)	1	5	4
Vascular disorders			
Embolism			

subjects affected / exposed	1 / 19 (5.26%)	0 / 95 (0.00%)	0 / 95 (0.00%)
occurrences (all)	1	0	0
Hot flush			
subjects affected / exposed	0 / 19 (0.00%)	1 / 95 (1.05%)	6 / 95 (6.32%)
occurrences (all)	0	1	6
Hypertension			
subjects affected / exposed	1 / 19 (5.26%)	3 / 95 (3.16%)	4 / 95 (4.21%)
occurrences (all)	1	3	9
General disorders and administration site conditions			
Application site pain			
subjects affected / exposed	1 / 19 (5.26%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences (all)	1	0	1
Asthenia			
subjects affected / exposed	0 / 19 (0.00%)	10 / 95 (10.53%)	7 / 95 (7.37%)
occurrences (all)	0	11	13
Chest pain			
subjects affected / exposed	1 / 19 (5.26%)	1 / 95 (1.05%)	1 / 95 (1.05%)
occurrences (all)	1	1	1
Chills			
subjects affected / exposed	11 / 19 (57.89%)	4 / 95 (4.21%)	50 / 95 (52.63%)
occurrences (all)	46	4	111
Fatigue			
subjects affected / exposed	11 / 19 (57.89%)	40 / 95 (42.11%)	56 / 95 (58.95%)
occurrences (all)	18	51	103
Influenza like illness			
subjects affected / exposed	3 / 19 (15.79%)	1 / 95 (1.05%)	27 / 95 (28.42%)
occurrences (all)	5	1	89
Injection site inflammation			
subjects affected / exposed	1 / 19 (5.26%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences (all)	1	0	1
Injection site pain			
subjects affected / exposed	1 / 19 (5.26%)	0 / 95 (0.00%)	27 / 95 (28.42%)
occurrences (all)	3	0	42
Injection site reaction			

subjects affected / exposed	2 / 19 (10.53%)	0 / 95 (0.00%)	15 / 95 (15.79%)
occurrences (all)	3	0	34
Injection site swelling			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	5 / 95 (5.26%)
occurrences (all)	0	0	6
Malaise			
subjects affected / exposed	1 / 19 (5.26%)	2 / 95 (2.11%)	7 / 95 (7.37%)
occurrences (all)	1	2	9
Oedema peripheral			
subjects affected / exposed	2 / 19 (10.53%)	5 / 95 (5.26%)	14 / 95 (14.74%)
occurrences (all)	2	6	19
Pain			
subjects affected / exposed	3 / 19 (15.79%)	4 / 95 (4.21%)	11 / 95 (11.58%)
occurrences (all)	7	7	20
Performance status decreased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 95 (0.00%)	0 / 95 (0.00%)
occurrences (all)	1	0	0
Peripheral swelling			
subjects affected / exposed	1 / 19 (5.26%)	1 / 95 (1.05%)	3 / 95 (3.16%)
occurrences (all)	1	1	5
Pyrexia			
subjects affected / exposed	11 / 19 (57.89%)	9 / 95 (9.47%)	36 / 95 (37.89%)
occurrences (all)	34	11	76
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 19 (5.26%)	11 / 95 (11.58%)	21 / 95 (22.11%)
occurrences (all)	1	13	24
Dyspnoea			
subjects affected / exposed	1 / 19 (5.26%)	10 / 95 (10.53%)	8 / 95 (8.42%)
occurrences (all)	1	11	13
Hiccups			
subjects affected / exposed	1 / 19 (5.26%)	1 / 95 (1.05%)	2 / 95 (2.11%)
occurrences (all)	1	1	2
Pleural effusion			

subjects affected / exposed	1 / 19 (5.26%)	1 / 95 (1.05%)	1 / 95 (1.05%)
occurrences (all)	2	1	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 19 (5.26%)	1 / 95 (1.05%)	7 / 95 (7.37%)
occurrences (all)	1	1	7
Depression			
subjects affected / exposed	0 / 19 (0.00%)	2 / 95 (2.11%)	5 / 95 (5.26%)
occurrences (all)	0	2	7
Insomnia			
subjects affected / exposed	0 / 19 (0.00%)	16 / 95 (16.84%)	10 / 95 (10.53%)
occurrences (all)	0	16	10
Nightmare			
subjects affected / exposed	1 / 19 (5.26%)	0 / 95 (0.00%)	0 / 95 (0.00%)
occurrences (all)	1	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 19 (15.79%)	6 / 95 (6.32%)	8 / 95 (8.42%)
occurrences (all)	4	7	14
Amylase increased			
subjects affected / exposed	1 / 19 (5.26%)	1 / 95 (1.05%)	1 / 95 (1.05%)
occurrences (all)	1	1	1
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 19 (0.00%)	5 / 95 (5.26%)	8 / 95 (8.42%)
occurrences (all)	0	6	17
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 19 (0.00%)	2 / 95 (2.11%)	5 / 95 (5.26%)
occurrences (all)	0	3	11
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 19 (0.00%)	3 / 95 (3.16%)	5 / 95 (5.26%)
occurrences (all)	0	3	8
Lipase increased			
subjects affected / exposed	1 / 19 (5.26%)	2 / 95 (2.11%)	0 / 95 (0.00%)
occurrences (all)	1	2	0
Weight decreased			

subjects affected / exposed	0 / 19 (0.00%)	6 / 95 (6.32%)	2 / 95 (2.11%)
occurrences (all)	0	6	2
Injury, poisoning and procedural complications			
Radius fracture			
subjects affected / exposed	1 / 19 (5.26%)	0 / 95 (0.00%)	0 / 95 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Brain oedema			
subjects affected / exposed	1 / 19 (5.26%)	1 / 95 (1.05%)	0 / 95 (0.00%)
occurrences (all)	1	1	0
Cluster headache			
subjects affected / exposed	1 / 19 (5.26%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences (all)	1	0	1
Dizziness			
subjects affected / exposed	1 / 19 (5.26%)	4 / 95 (4.21%)	10 / 95 (10.53%)
occurrences (all)	1	4	13
Headache			
subjects affected / exposed	8 / 19 (42.11%)	22 / 95 (23.16%)	34 / 95 (35.79%)
occurrences (all)	17	27	67
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 19 (5.26%)	2 / 95 (2.11%)	0 / 95 (0.00%)
occurrences (all)	1	3	0
Peripheral motor neuropathy			
subjects affected / exposed	1 / 19 (5.26%)	0 / 95 (0.00%)	0 / 95 (0.00%)
occurrences (all)	1	0	0
Speech disorder			
subjects affected / exposed	1 / 19 (5.26%)	0 / 95 (0.00%)	0 / 95 (0.00%)
occurrences (all)	1	0	0
Tension headache			
subjects affected / exposed	1 / 19 (5.26%)	0 / 95 (0.00%)	0 / 95 (0.00%)
occurrences (all)	5	0	0
Tremor			
subjects affected / exposed	1 / 19 (5.26%)	2 / 95 (2.11%)	0 / 95 (0.00%)
occurrences (all)	1	2	0
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	0 / 19 (0.00%)	5 / 95 (5.26%)	11 / 95 (11.58%)
occurrences (all)	0	6	18
Lymphopenia			
subjects affected / exposed	0 / 19 (0.00%)	3 / 95 (3.16%)	10 / 95 (10.53%)
occurrences (all)	0	7	20
Eye disorders			
Eye pain			
subjects affected / exposed	1 / 19 (5.26%)	0 / 95 (0.00%)	0 / 95 (0.00%)
occurrences (all)	1	0	0
Uveitis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 95 (0.00%)	0 / 95 (0.00%)
occurrences (all)	1	0	0
Vision blurred			
subjects affected / exposed	3 / 19 (15.79%)	8 / 95 (8.42%)	6 / 95 (6.32%)
occurrences (all)	3	8	7
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 19 (0.00%)	11 / 95 (11.58%)	15 / 95 (15.79%)
occurrences (all)	0	12	16
Constipation			
subjects affected / exposed	2 / 19 (10.53%)	8 / 95 (8.42%)	14 / 95 (14.74%)
occurrences (all)	2	8	21
Diarrhoea			
subjects affected / exposed	8 / 19 (42.11%)	33 / 95 (34.74%)	40 / 95 (42.11%)
occurrences (all)	13	49	81
Dyspepsia			
subjects affected / exposed	1 / 19 (5.26%)	2 / 95 (2.11%)	4 / 95 (4.21%)
occurrences (all)	1	3	4
Nausea			
subjects affected / exposed	9 / 19 (47.37%)	26 / 95 (27.37%)	36 / 95 (37.89%)
occurrences (all)	10	27	71
Vomiting			
subjects affected / exposed	5 / 19 (26.32%)	13 / 95 (13.68%)	19 / 95 (20.00%)
occurrences (all)	5	13	27
Colitis			

subjects affected / exposed	0 / 19 (0.00%)	6 / 95 (6.32%)	2 / 95 (2.11%)
occurrences (all)	0	10	2
Haematochezia			
subjects affected / exposed	0 / 19 (0.00%)	5 / 95 (5.26%)	0 / 95 (0.00%)
occurrences (all)	0	5	0
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 19 (0.00%)	2 / 95 (2.11%)	6 / 95 (6.32%)
occurrences (all)	0	2	7
Erythema			
subjects affected / exposed	2 / 19 (10.53%)	2 / 95 (2.11%)	6 / 95 (6.32%)
occurrences (all)	3	4	6
Hyperhidrosis			
subjects affected / exposed	0 / 19 (0.00%)	3 / 95 (3.16%)	6 / 95 (6.32%)
occurrences (all)	0	3	7
Night sweats			
subjects affected / exposed	2 / 19 (10.53%)	2 / 95 (2.11%)	2 / 95 (2.11%)
occurrences (all)	5	2	2
Pruritus			
subjects affected / exposed	8 / 19 (42.11%)	35 / 95 (36.84%)	39 / 95 (41.05%)
occurrences (all)	12	44	54
Rash			
subjects affected / exposed	9 / 19 (47.37%)	29 / 95 (30.53%)	40 / 95 (42.11%)
occurrences (all)	13	40	76
Rash erythematous			
subjects affected / exposed	2 / 19 (10.53%)	1 / 95 (1.05%)	3 / 95 (3.16%)
occurrences (all)	3	1	3
Rash maculo-papular			
subjects affected / exposed	0 / 19 (0.00%)	2 / 95 (2.11%)	6 / 95 (6.32%)
occurrences (all)	0	2	8
Skin disorder			
subjects affected / exposed	1 / 19 (5.26%)	0 / 95 (0.00%)	0 / 95 (0.00%)
occurrences (all)	1	0	0
Skin lesion			
subjects affected / exposed	1 / 19 (5.26%)	2 / 95 (2.11%)	4 / 95 (4.21%)
occurrences (all)	2	2	5

Vitiligo			
subjects affected / exposed	1 / 19 (5.26%)	0 / 95 (0.00%)	4 / 95 (4.21%)
occurrences (all)	1	0	5
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 19 (5.26%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences (all)	1	0	1
Bladder pain			
subjects affected / exposed	1 / 19 (5.26%)	0 / 95 (0.00%)	0 / 95 (0.00%)
occurrences (all)	1	0	0
Dysuria			
subjects affected / exposed	1 / 19 (5.26%)	0 / 95 (0.00%)	0 / 95 (0.00%)
occurrences (all)	1	0	0
Pollakiuria			
subjects affected / exposed	1 / 19 (5.26%)	3 / 95 (3.16%)	3 / 95 (3.16%)
occurrences (all)	1	3	3
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 19 (5.26%)	3 / 95 (3.16%)	2 / 95 (2.11%)
occurrences (all)	1	3	2
Hypothyroidism			
subjects affected / exposed	2 / 19 (10.53%)	4 / 95 (4.21%)	4 / 95 (4.21%)
occurrences (all)	2	4	4
Lymphocytic hypophysitis			
subjects affected / exposed	1 / 19 (5.26%)	1 / 95 (1.05%)	1 / 95 (1.05%)
occurrences (all)	1	1	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 19 (5.26%)	15 / 95 (15.79%)	21 / 95 (22.11%)
occurrences (all)	5	19	33
Back pain			
subjects affected / exposed	2 / 19 (10.53%)	8 / 95 (8.42%)	10 / 95 (10.53%)
occurrences (all)	2	8	12
Muscle spasms			
subjects affected / exposed	1 / 19 (5.26%)	2 / 95 (2.11%)	4 / 95 (4.21%)
occurrences (all)	1	2	4

Muscle tightness			
subjects affected / exposed	1 / 19 (5.26%)	0 / 95 (0.00%)	0 / 95 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	5 / 95 (5.26%)
occurrences (all)	0	0	12
Muscular weakness			
subjects affected / exposed	1 / 19 (5.26%)	4 / 95 (4.21%)	4 / 95 (4.21%)
occurrences (all)	1	5	5
Myalgia			
subjects affected / exposed	1 / 19 (5.26%)	4 / 95 (4.21%)	10 / 95 (10.53%)
occurrences (all)	8	5	12
Pain in extremity			
subjects affected / exposed	2 / 19 (10.53%)	7 / 95 (7.37%)	5 / 95 (5.26%)
occurrences (all)	3	8	6
Pubic pain			
subjects affected / exposed	1 / 19 (5.26%)	0 / 95 (0.00%)	0 / 95 (0.00%)
occurrences (all)	1	0	0
Soft tissue mass			
subjects affected / exposed	1 / 19 (5.26%)	0 / 95 (0.00%)	0 / 95 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Escherichia infection			
subjects affected / exposed	1 / 19 (5.26%)	0 / 95 (0.00%)	0 / 95 (0.00%)
occurrences (all)	1	0	0
Eye infection			
subjects affected / exposed	1 / 19 (5.26%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences (all)	1	0	1
Influenza			
subjects affected / exposed	1 / 19 (5.26%)	0 / 95 (0.00%)	0 / 95 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 95 (0.00%)	4 / 95 (4.21%)
occurrences (all)	1	0	6
Oral herpes			

subjects affected / exposed	0 / 19 (0.00%)	0 / 95 (0.00%)	6 / 95 (6.32%)
occurrences (all)	0	0	6
Sinusitis			
subjects affected / exposed	2 / 19 (10.53%)	0 / 95 (0.00%)	4 / 95 (4.21%)
occurrences (all)	2	0	6
Upper respiratory tract infection			
subjects affected / exposed	1 / 19 (5.26%)	5 / 95 (5.26%)	6 / 95 (6.32%)
occurrences (all)	1	5	6
Vaginal infection			
subjects affected / exposed	1 / 19 (5.26%)	0 / 95 (0.00%)	0 / 95 (0.00%)
occurrences (all)	1	0	0
Vulvovaginal mycotic infection			
subjects affected / exposed	2 / 19 (10.53%)	0 / 95 (0.00%)	0 / 95 (0.00%)
occurrences (all)	2	0	0
Wound infection			
subjects affected / exposed	1 / 19 (5.26%)	0 / 95 (0.00%)	0 / 95 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 19 (21.05%)	14 / 95 (14.74%)	12 / 95 (12.63%)
occurrences (all)	5	16	14
Dehydration			
subjects affected / exposed	2 / 19 (10.53%)	5 / 95 (5.26%)	3 / 95 (3.16%)
occurrences (all)	2	5	3
Hypercalcaemia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 95 (0.00%)	1 / 95 (1.05%)
occurrences (all)	1	0	1
Hyperglycaemia			
subjects affected / exposed	4 / 19 (21.05%)	7 / 95 (7.37%)	7 / 95 (7.37%)
occurrences (all)	5	8	9
Hyperuricaemia			
subjects affected / exposed	1 / 19 (5.26%)	1 / 95 (1.05%)	0 / 95 (0.00%)
occurrences (all)	2	1	0
Hypocalcaemia			
subjects affected / exposed	1 / 19 (5.26%)	1 / 95 (1.05%)	0 / 95 (0.00%)
occurrences (all)	1	1	0

Hypomagnesaemia			
subjects affected / exposed	1 / 19 (5.26%)	2 / 95 (2.11%)	3 / 95 (3.16%)
occurrences (all)	1	2	5
Hypokalaemia			
subjects affected / exposed	2 / 19 (10.53%)	8 / 95 (8.42%)	6 / 95 (6.32%)
occurrences (all)	2	9	7
Hyponatraemia			
subjects affected / exposed	0 / 19 (0.00%)	5 / 95 (5.26%)	4 / 95 (4.21%)
occurrences (all)	0	8	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 August 2013	- Subjects with a history of complicated herpes infection (eg, herpetic keratitis or meningoencephalitis) were excluded from the study. - Study assessments were modified to include collection and storage of blood and urine samples, and swabs of any lesions suspected of herpetic origin, for detection of talimogene laherparepvec DNA using qPCR testing. - A requirement for reporting potential or known unintended exposure to talimogene laherparepvec in a subject's household member, caregiver, or healthcare provider was added. - Optional tumor biopsy procedure for biomarker analyses was modified to allow biopsy of lesions that were not injectable. - Subjects who completed the protocol-specified long-term follow-up period for reasons other than death or full withdrawal of consent were to be followed for long-term survival under an ongoing separate registry protocol for subjects treated with talimogene laherparepvec in clinical trials. The registry protocol also monitored for late and long-term adverse events thought to be potentially related to talimogene laherparepvec. - Serious adverse event reporting procedures were updated to instruct investigators to report serious adverse events that occurred outside of the protocol-specified reporting period per the European Union CT-3 guidance. - Response criteria were clarified. - The statistical analysis was updated to include descriptive analyses of the qPCR results of talimogene laherparepvec DNA.
08 October 2014	- Requirement added that imaging studies in phase 2 were to be collected and held at an independent centralized radiology vendor for potential retrospective evaluation of tumor response by an independent centralized endpoint assessment committee. - The primary objective/endpoint in phase 2 was changed from assessment of OS to assessment of confirmed ORR. The assessment of OS was made a secondary objective/endpoint. - Eligibility criteria were modified to allow subjects who received prior treatment for melanoma to enroll into phase 2. - Sample size in phase 2 was increased from 140 to 200 subjects to allow formal testing for ORR (rather than estimating OS). - Secondary endpoints (BOR, DCR, and DDR) were added for phase 2. - Exploratory objectives were modified to remove investigation of HLA type and other genetic variations and to add PRO exploratory objectives/endpoints to the phase 2 part of the study. - Measurable disease was further defined. - Stratification factors for phase 2 were updated (stage of disease and prior therapy). - Subjects with central nervous system metastasis who had been treated and were stable were allowed to enroll. - Subjects with type I diabetes mellitus, prior splenectomy or splenic irradiation were allowed to enroll. - Coagulation function requirements at baseline were revised to align with other ongoing talimogene laherparepvec studies. - Permitted medications were updated to allow for therapeutic anticoagulants. - Additional details were added regarding the timing of biopsy procedures. - Details regarding the statistical analyses were updated to align with the changes made to the primary and secondary objectives of the study; planned interim analyses for phase 2 were added.

30 November 2015	- Study duration was increased to a maximum of 3 years follow-up from the time the last subject was randomized. - Eligibility criteria were modified: subjects who received nononcology vaccine therapies for the prevention of infectious disease were allowed to enroll; the definition of autoimmune disease was clarified, subjects who were unwilling to follow the procedures to safeguard others against the potential transmission of talimogene laherparepvec were excluded. - Permitted medications were updated to allow nononcology vaccine therapies that were used for the prevention of infectious disease. - More flexibility in the frequency of radiographic imaging was allowed for subjects who achieved CR in long-term follow-up. - The long-term follow-up survival assessment was updated to include collection of talimogene laherparepvec-related adverse events. - Response criteria were clarified. - A second updated interim analysis was added, conducted 24 weeks after the first interim analysis of efficacy and safety. - First-line analysis set was removed; testing of ORR used the ITT analysis set with an overall nominal level of 0.05. - The ability to conduct interim analyses and formal testing of OS was added.
02 March 2016	- The instructions regarding how to record responses after a tumor resection were corrected for consistency between protocol sections. - The aggregate unblinded results from the interim analyses were allowed to be shared with investigators and study team members on an as-needed basis.
05 November 2018	- Added 4- and 5-year OS analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported