



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 10⁸ 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 10⁸ 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 10⁸ 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 10⁸ 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 | | | |
| <p>Scale used to assess how a patient's disease is progressing, how the disease affects the daily living abilities of the patient:</p> <p>0 = Fully active, able to carry on all pre-disease performance without restriction;</p> <p>1 = Restricted in physically strenuous activity, ambulatory, able to carry out work of a light nature;</p> <p>2 = Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about > 50% of waking hours;</p> <p>3 = Capable of only limited self care, confined to a bed or chair > 50% of waking hours;</p> <p>4 = Completely disabled, confined to bed or chair;</p> <p>5 = Dead.</p> | | | |
| Units: Subjects | | | |
| 0 (Fully active) | 156 | | |
| 1 (Restrictive but ambulatory) | 61 | | |
| Tumor, Node, Metastasis (TNM) Disease Stage | | | |
| <p>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;</p> <p>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);</p> <p>Stage IV:</p> <p>M1a: Spread to skin, subcutaneous tissue, or lymph nodes; normal lactate dehydrogenase (LDH) level;</p> <p>M1b: Spread to lungs, normal LDH;</p> <p>M1c: Spread to all other visceral organs, normal LDH or any distant disease with elevated LDH.</p> | | | |
| Units: Subjects | | | |
| Stage IIIB - IVM1a | 115 | | |
| Stage IVM1b/c | 102 | | |
| BRAF V600 Mutation Status | | | |
| <p>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).</p> | | | |
| 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: | |
| <ul style="list-style-type: none">• 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 \geq 50% relative to baseline.

Response must have been confirmed by a repeat, consecutive assessment \geq 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 \geq 50% relative to baseline.

Response must have been confirmed by a repeat, consecutive assessment \geq 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 assessed 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 $\geq 50\%$ relative to baseline.

PD: Increase in tumor burden $\geq 25\%$ 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: Tolimogene 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 $\geq 50\%$ 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: Talinogene 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 10⁸ 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 10⁸ 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 occurrences (all) | 1 / 19 (5.26%) 2 | 1 / 95 (1.05%) 1 | 1 / 95 (1.05%) 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 occurrences (all) | 0 / 19 (0.00%) 0 | 6 / 95 (6.32%) 6 | 2 / 95 (2.11%) 2 |
| Injury, poisoning and procedural complications Radius fracture subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 95 (0.00%) 0 | 0 / 95 (0.00%) 0 |
| Nervous system disorders Brain oedema subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 1 / 95 (1.05%) 1 | 0 / 95 (0.00%) 0 |
| Cluster headache subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 95 (0.00%) 0 | 1 / 95 (1.05%) 1 |
| Dizziness subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 4 / 95 (4.21%) 4 | 10 / 95 (10.53%) 13 |
| Headache subjects affected / exposed occurrences (all) | 8 / 19 (42.11%) 17 | 22 / 95 (23.16%) 27 | 34 / 95 (35.79%) 67 |
| Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 2 / 95 (2.11%) 3 | 0 / 95 (0.00%) 0 |
| Peripheral motor neuropathy subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 95 (0.00%) 0 | 0 / 95 (0.00%) 0 |
| Speech disorder subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 95 (0.00%) 0 | 0 / 95 (0.00%) 0 |
| Tension headache subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 5 | 0 / 95 (0.00%) 0 | 0 / 95 (0.00%) 0 |
| Tremor subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 2 / 95 (2.11%) 2 | 0 / 95 (0.00%) 0 |
| Blood and lymphatic system disorders | | | |

| | | | |
|--------------------------------------------------------------------|-----------------------|------------------------|------------------------|
| Anaemia subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 5 / 95 (5.26%) 6 | 11 / 95 (11.58%) 18 |
| Lymphopenia subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 3 / 95 (3.16%) 7 | 10 / 95 (10.53%) 20 |
| Eye disorders | | | |
| Eye pain subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 95 (0.00%) 0 | 0 / 95 (0.00%) 0 |
| Uveitis subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 95 (0.00%) 0 | 0 / 95 (0.00%) 0 |
| Vision blurred subjects affected / exposed occurrences (all) | 3 / 19 (15.79%) 3 | 8 / 95 (8.42%) 8 | 6 / 95 (6.32%) 7 |
| Gastrointestinal disorders | | | |
| Abdominal pain subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 11 / 95 (11.58%) 12 | 15 / 95 (15.79%) 16 |
| Constipation subjects affected / exposed occurrences (all) | 2 / 19 (10.53%) 2 | 8 / 95 (8.42%) 8 | 14 / 95 (14.74%) 21 |
| Diarrhoea subjects affected / exposed occurrences (all) | 8 / 19 (42.11%) 13 | 33 / 95 (34.74%) 49 | 40 / 95 (42.11%) 81 |
| Dyspepsia subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 2 / 95 (2.11%) 3 | 4 / 95 (4.21%) 4 |
| Nausea subjects affected / exposed occurrences (all) | 9 / 19 (47.37%) 10 | 26 / 95 (27.37%) 27 | 36 / 95 (37.89%) 71 |
| Vomiting subjects affected / exposed occurrences (all) | 5 / 19 (26.32%) 5 | 13 / 95 (13.68%) 13 | 19 / 95 (20.00%) 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 occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 95 (0.00%) 0 | 4 / 95 (4.21%) 5 |
| Renal and urinary disorders | | | |
| Acute kidney injury subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 95 (0.00%) 0 | 1 / 95 (1.05%) 1 |
| Bladder pain subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 95 (0.00%) 0 | 0 / 95 (0.00%) 0 |
| Dysuria subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 95 (0.00%) 0 | 0 / 95 (0.00%) 0 |
| Pollakiuria subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 3 / 95 (3.16%) 3 | 3 / 95 (3.16%) 3 |
| Endocrine disorders | | | |
| Adrenal insufficiency subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 3 / 95 (3.16%) 3 | 2 / 95 (2.11%) 2 |
| Hypothyroidism subjects affected / exposed occurrences (all) | 2 / 19 (10.53%) 2 | 4 / 95 (4.21%) 4 | 4 / 95 (4.21%) 4 |
| Lymphocytic hypophysitis subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 1 / 95 (1.05%) 1 | 1 / 95 (1.05%) 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 5 | 15 / 95 (15.79%) 19 | 21 / 95 (22.11%) 33 |
| Back pain subjects affected / exposed occurrences (all) | 2 / 19 (10.53%) 2 | 8 / 95 (8.42%) 8 | 10 / 95 (10.53%) 12 |
| Muscle spasms subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 2 / 95 (2.11%) 2 | 4 / 95 (4.21%) 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 | <ul style="list-style-type: none">- 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 | <ul style="list-style-type: none">- 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 | <ul style="list-style-type: none"> - 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 | <ul style="list-style-type: none"> - 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 | <ul style="list-style-type: none"> - Added 4- and 5-year OS analysis. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported