**Title: 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**

Amgen Protocol Number (Talimogene Laherparepvec [AMG 678]) 20110264

EudraCT number 2012-000307-32

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**Investigator's Agreement**

I have read the attached protocol entitled 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, dated **07 November 2018**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice and applicable national or regional regulations/guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by the following:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my Subinvestigators (including, if applicable, their spouses [or legal partners] and dependent children)

at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.



Signature

Name of Investigator Date (DD Month YYYY)

## Protocol Synopsis

**Title:** 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

**Study Phase:** Phase 1b/2

**Indication:** Talimogene Laherparepvec and Ipilimumab for treatment of unresected, stages IIIB to IV melanoma

**Primary Objective:**

**Phase 1b:** 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.

**Phase 2:** 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.

**Secondary Objective(s):**

**Phase 1b:**

- To estimate the efficacy of talimogene laherparepvec in combination with ipilimumab as determined by objective response rate (ORR)
- To assess the safety of talimogene laherparepvec in combination with ipilimumab as determined by incidence of all adverse event (AE)s, grade ≥ 3 AEs (AEs), serious adverse events (SAEs), and events requiring the discontinuation of study drug, local effects on the tumor (ie, pain, inflammation and ulceration), clinically significant laboratory changes, and clinically significant changes in vital signs not defined as DLT

**Phase 2:**

- To evaluate the efficacy of talimogene laherparepvec in combination with ipilimumab versus ipilimumab alone as determined by best overall response (BOR), disease control rate (DCR), durable response rate (DRR), duration of response (DOR), time to response (TTR), progression free survival (PFS), resection rate, overall survival (OS), landmark OS by year
- To assess the safety of talimogene laherparepvec in combination with ipilimumab versus ipilimumab alone as determined by incidence of all AEs, grade ≥ 3 AEs, SAEs, and events requiring the discontinuation of study drug, local effects on the tumor (ie, pain, inflammation and ulceration), clinically significant laboratory changes, and clinically significant changes in vital signs

**Hypotheses:**

**Phase 1b:** The hypothesis is that talimogene laherparepvec in combination with ipilimumab will be safe and well tolerated in subjects with previously untreated, unresected, stages IIIB to IV melanoma.

**Phase 2:** The hypothesis is that talimogene laherparepvec in combination with ipilimumab versus ipilimumab will improve ORR in subjects with unresected, stages IIIB to IV melanoma.

**Primary Endpoint:**

**Phase 1b:** Incidence of DLT

**Phase 2:** ORR

Refer to Section 10.1.1 for the definition of the primary endpoints.

**Secondary Endpoints:**

**Efficacy:** For phase 1b, ORR. For phase 2, BOR, DCR, DRR, TTR, DOR, PFS, resection rate, and OS.

**Safety:** For phase 2, incidence of all AEs, grade ≥ 3 AEs, SAEs, and events requiring the discontinuation of study drug, local effects on the tumor (ie, pain, inflammation and ulceration),

clinically significant laboratory changes, and clinically significant changes in vital signs. For phase 1b the same safety endpoints will be evaluated as phase 2 but not including AEs and clinical laboratory abnormalities defined as DLT.

Refer to Section 10.1.1 for the definition of the secondary endpoints.

**Study Design:**

**Phase 1b:**

The phase 1b part is an open-label, multicenter, single-arm study. Talimogene laherparepvec in combination with ipilimumab will be administered to approximately 18 subjects.

Talimogene laherparepvec will be administered by intratumoral injection into the injectable cutaneous, subcutaneous, and nodal tumors initially at a dose of $10^6$ plaque forming unit/mL (PFU/mL) at day 1 of week 1 followed by a dose of $10^8$ PFU/mL at day 1 of week 4, and every 2 weeks (± 3 days) thereafter. Ipilimumab will be administered intravenously at a dose of 3 mg/kg every 3 weeks (± 3 days) for 4 infusions starting at day 1 of week 6 (ie, at the time of the third dose of talimogene laherparepvec), day 1 of week 9, day 1 of week 12, and day 1 of week 15. When talimogene laherparepvec and ipilimumab are administered on the same day, talimogene laherparepvec must be administered first.

Subjects will be treated with talimogene laherparepvec until complete response (CR), all injectable tumors have disappeared, confirmed disease progression per the modified Immune-Related Response Criteria (irRC; Wolchok et al, 2009 [Appendix E]), or intolerance of study treatment, whichever occurs first. Due to the mechanism of action, subjects may experience growth in existing tumors or the appearance of new tumors prior to maximal clinical benefit of talimogene laherparepvec. Therefore, talimogene laherparepvec dosing should be continued provided that the subject has no evidence of confirmed disease progression per modified irRC (Appendix E) and is able to tolerate the treatment.

Subjects will be followed for safety approximately 30 (+ 7) days after the last dose of talimogene laherparepvec or 60 (+ 7) days after the last dose of ipilimumab, whichever is later, and survival for approximately **60** months after the last subject is randomized in phase 2.

A Dose Level Review Team (DLRT) consisting of the Amgen study team, including at least one clinician, safety representative, and biostatistician, and at least one investigator participating in the study who has recruited subjects into the phase 1b part of the study, will review the safety data to evaluate possible drug effects and DLT. This team will recommend either to enroll more subjects for DLT evaluation in the phase 1b, to stop enrollment into phase 1b, or to declare the combination appears to be tolerable and open the phase 2 part of the study.

The rules of the DLT evaluation and the definition of DLT are provided in Section 3.1.1.

**Phase 2:**

The phase 2 part of the study is an open-label, multicenter, randomized study to further assess the safety and to evaluate the efficacy of the talimogene laherparepvec in combination with ipilimumab. Approximately 200 subjects will be randomized 1:1 to receive the following:

- **arm 1:** talimogene laherparepvec plus ipilimumab
- **arm 2:** ipilimumab

Subjects randomized before amendment 2 will be stratified by stage of disease (stage IIIB/C, IVM1a, and stage IVM1b vs IVM1c) and *BRAF* V600E (mutation vs mutation not present). Subjects randomized after amendment 2 will be stratified by stage of disease (stage IIIB/C and IVM1a vs stage IVM1b and IVM1c) and prior therapy (treatment naïve vs previously treated with systemic anticancer immunotherapy vs previously treated with systemic anticancer treatment other than immunotherapy).

Talimogene laherparepvec will be administered by intratumoral injection into the injectable cutaneous, subcutaneous, and nodal tumors initially at a dose of $10^6$ PFU/mL at day 1 of week 1 followed by a dose of $10^8$ PFU/mL at day 1 of week 4, and every 2 weeks (± 3 days) thereafter. Ipilimumab will be administered intravenously at a dose of 3 mg/kg every 3 weeks

(± 3 days) for 4 infusions. Subjects randomized to arm 1 will receive ipilimumab starting at day 1 of week 6 (ie, at the time of the third dose of talimogene laherparepvec), day 1 of week 9, day 1 of week 12, and day 1 of week 15. When talimogene laherparepvec and ipilimumab are administered on the same day, talimogene laherparepvec must be administered first. Subjects randomized to arm 2 will receive ipilimumab starting at day 1 of week 1, day 1 of week 4, day 1 of week 7, and day 1 of week 10.

Subjects will be treated with talimogene laherparepvec until CR, all injectable tumors have disappeared, confirmed disease progression per the modified irRC (Appendix E), or intolerance of study treatment, whichever occurs first. Due to the mechanism of action, subjects may experience growth in existing tumors or the appearance of new tumors prior to maximal clinical benefit of talimogene laherparepvec. Therefore, talimogene laherparepvec dosing should be continued provided that the subject has no evidence of confirmed disease progression per modified irRC and is able to tolerate the treatment.

Subjects will be followed for safety approximately 30 (+ 7) days after the last dose of talimogene laherparepvec or 60 (+ 7) days after the last dose of ipilimumab, whichever is later, and survival for approximately **60** months after the last subject is randomized in phase 2.

Prior to starting the phase 2 part of the study, a Data Review Team (DRT) internal to Amgen but external to the talimogene laherparepvec product team will be formed. The DRT, governed by a detailed DRT charter, will review accumulating safety data from the phase 2 at regular intervals to safeguard the interests of trial participants (see Section 10.4.3).

The overall study design is described by a study schema at the end of the protocol synopsis section.

**Sample Size:** Approximately 218 subjects are planned to be enrolled in the study (approximately 18 subjects will enroll in the phase 1b and approximately 200 subjects will enroll in the phase 2).

**Summary of Subject Eligibility Criteria:**

**Key Inclusion Criteria:**

- Subject has provided informed consent.
- Histologically confirmed diagnosis of malignant melanoma
- Stage IIIB, IIIC, IVM1a, IVM1b, or IVM1c disease that is not suitable for surgical resection
- **Phase 1b:** Treatment naïve: Must not have received any prior systemic anticancer treatment consisting of chemotherapy, immunotherapy, or targeted therapy for unresected stage IIIB to IV melanoma. Note: Subjects who received prior adjuvant therapy for melanoma will not be excluded. However, if the subject received adjuvant therapy, the subject must have completed therapy at least 6 months prior to enrollment. No prior talimogene laherparepvec, ipilimumab, other Cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) inhibitors, programmed death-1 (PD-1) inhibitors, or tumor vaccine is allowed, even if given in the adjuvant setting.
- **Phase 2:**
  - Either treatment naïve or received only one line of systemic anticancer therapy if *BRAF* wild-type or up to two lines of systemic anticancer therapy including one *BRAF* inhibitor-containing regimen if *BRAF* mutant. Treatments given in an adjuvant setting (eg, interferon, radiotherapy, isolated limb perfusion, or investigational agents) are not considered as prior lines of therapy. No prior talimogene laherparepvec, other oncolytic virus therapies, or tumor vaccines are allowed, even if given in the adjuvant setting.
  - Subjects treated with prior ipilimumab must have had PR, CR, or at least 6 months of stable disease followed by disease progression.
  - Subjects previously treated with anti-PD1 or anti-CTLA-4 antibodies must not have discontinued therapy due to any treatment-related adverse events including immune-related adverse events. Prior treatment-related adverse events should also be fully resolved and not requiring treatment for at least 28 days prior to randomization.

- Measurable disease defined as one or both of the following:
  - at least 1 melanoma lesion that can be accurately and serially measured in at least 2 dimensions and for which the longest diameter is ≥ 10 mm and with perpendicular diameter ≥ 5 mm as measured by contrast-enhanced or spiral computed tomography (CT) scan for visceral or soft tissue disease. Lymph nodes must measure > 15 mm in their short axis to be considered measurable by CT scan.
  - at least 1 superficial cutaneous or subcutaneous melanoma lesion that can be accurately and serially measured in at least 2 dimensions and for which the short axis is ≥ 5 mm as measured by calipers
- Injectable disease (ie, suitable for direct injection or through the use of ultrasound [US] guidance) defined as follows:
  - at least 1 injectable cutaneous, subcutaneous, or nodal melanoma lesion ≥ 5 mm in longest diameter.
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
- Male or female, age ≥ 18 years
- Adequate hematologic, hepatic, renal, and coagulation functions as described in Section 4.1.

**Key Exclusion Criteria:**

- Primary uveal or mucosal melanoma
- History or evidence of melanoma associated with immunodeficiency states (eg, hereditary immune deficiency, organ transplant, or leukemia)
- **Phase 1b**: History or evidence of central nervous system (CNS) metastases
- **Phase 2**: Clinically active cerebral melanoma metastases. Subjects with up to 3 cerebral metastases, and neurological performance status of 0 may be enrolled, provided that all lesions have been adequately treated with stereotactic radiation therapy, craniotomy, or Gamma knife therapy, with no evidence of progression, and have not required steroids, for at least 2 months prior to enrollment.
- History or evidence of symptomatic autoimmune disease (such as pneumonitis, glomerulonephritis, vasculitis, rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, scleroderma, or other), or history of autoimmune disease that required systemic treatment (ie, use of corticosteroids, immunosuppressive drugs or biological agents used for treatment of autoimmune diseases) in past 2 months prior to enrollment. Replacement therapy (eg, thyroxine for hypothyroidism, insulin for diabetes mellitus) is not considered a form of systemic treatment for autoimmune disease.
- Evidence of clinically significant immunosuppression for any reason such as:
  - organ transplant
  - any severe congenital or acquired cellular and/or humoral immune deficiency
  - concurrent opportunistic infection
  - requires concomitant treatment with immunosuppressive agents, including CTLA-4 agonists or chronic oral or systemic steroid medication use at a dose of > 7.5 mg/day of prednisone or equivalent (except for management of AEs or CNS metastases during the course of the study)
- Active herpetic skin lesions or prior complications of HSV-1 infection (eg, herpetic keratitis or encephalitis)
- Requires intermittent or chronic systemic (intravenous or oral) treatment with an antiherpetic drug (eg, acyclovir), other than intermittent topical use

- Known human immunodeficiency virus (HIV) disease (if clinically suspected HIV infection, subject requires negative test)
- Known acute or chronic hepatitis B or hepatitis C infection (if clinically suspected hepatitis B or hepatitis infection, subject requires negative test. However, if results are not indicative of true active or chronic infection, the subject may be enrolled/randomized after approval is obtained from the Amgen medical monitor)
- Phase 1b: Prior talimogene laherparepvec, ipilimumab, other Cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) inhibitors, programmed death-1 (PD-1) inhibitors, or tumor vaccine
- Phase 2: Prior talimogene laherparepvec, other oncolytic virus therapies, or tumor vaccines
- Currently receiving or less than 28 days since ending systemic anticancer treatment for unresected stage IIIB to IV melanoma

For a full list of eligibility criteria, please refer to Section 4.1 and Section 4.2.

**Talimogene Laherparepvec Dosage and Administration:**

Talimogene laherparepvec will be administered to subjects enrolled in the phase 1b or randomized to arm 1 of phase 2. Talimogene laherparepvec will be only administered by intratumoral injection into injectable cutaneous, subcutaneous, and nodal tumors with or without image US guidance. Talimogene laherparepvec must not be administered into visceral organ metastases. The initial dose of talimogene laherparepvec is up to 4.0 mL of $10^6$ PFU/mL. Subsequent doses of talimogene laherparepvec up to 4.0 mL of $10^8$ PFU/mL will be given every 2 weeks ± 3 days.

Refer to Section 6.1 for additional information regarding talimogene laherparepvec dosage and administration.

**Ipilimumab Dosage and Administration:**

Ipilimumab at a dose of 3 mg/kg will be administered intravenously over 90 (± 15) minutes through an intravenous line containing a sterile, nonpyrogenic, low-protein-binding in-line filter every 3 weeks (± 3 days) for a total of 4 infusions at the following visits:

- phase 1b and arm 1 of phase 2: day 1 week 6, day 1 week 9, day 1 week 12, and day 1 week 15
- arm 2 of phase 2: day 1 week 1, day 1 week 4, day 1 week 7, and day 1 week 10

Refer to Section 6.2 for additional information regarding ipilimumab dosage and administration.

**Procedures:**

**Screening, Enrollment (Phase 1b), Randomization (Phase 2):**

The following key procedures will be performed during the screening period (for a full list of screening procedures, including the timing of each procedure please refer to Section 7.2.1):

- confirmation that the Informed Consent Form has been signed
- review of inclusion and exclusion criteria
- demographic data including sex, age, race and ethnicity
- medication and medical history review, concomitant medication(s)
- physical examination, including weight, vital signs, and ECOG performance status assessment (Appendix F)
- a 12-lead electrocardiogram (ECG)
- radiographic tumor imaging and clinical tumor assessment
- record any SAEs that occur after subject signs informed consent

- local laboratory assessments:
  - HIV test, hepatitis B and hepatitis C tests (only if indicated for clinically suspected HIV, hepatitis B or hepatitis C infection, respectively)
  - hematology panel
  - chemistry panel
  - LDH
  - coagulation: prothrombin time (PT) or international normalization ratio (INR) and partial thromboplastin time (PTT) or partial thromboplastin time (aPTT)
  - thyroid function tests: thyroid stimulating hormone (TSH), free thyroxine (T4)
  - serum or urine pregnancy test for female subjects of childbearing potential.
- Archived tumor tissue for v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) V600E testing and biomarker analyses

**Treatment:**

The following key procedures will be completed during the treatment period (for a full list of treatment procedures, including the timing of each procedure please refer to Section 7.2.2):

- recording of concomitant medication(s) and AE(s)/SAE(s) at each visit.
- physical examination including weight, vital signs, and ECOG performance status assessment (Appendix F)
- local laboratory tests:
  - hematology panel
  - chemistry panel
  - thyroid function tests: TSH, free T4
- blood samples for biomarker analysis, including herpes simplex type-1 virus (HSV-1) antibody serostatus and flow cytometry analysis of lymphocyte subsets including B cells, T cells and Natural Killer (NK) cells
- For phase 2 arm 1: blood and urine will be collected, stored, and ultimately tested for detection of talimogene laherparepvec DNA using qPCR
- optional tumor biopsy
- For phase 1b and phase 2 arm 1: swabs of cold sore, vesicles, and other lesions suspected to be of herpetic origin (if any) will be collected, stored, and ultimately tested for detection of talimogene laherparepvec DNA using real-time polymerase chain reaction (qPCR)
- radiographic tumor imaging, clinical tumor assessment, and tumor response
- For phase 2: completion of patient reported outcome (PRO) questionnaires: EuroQoL-5D (EQ-5D) and the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) **until no longer than 3 years after the last subject is randomized.**
- Administration of study treatment (refer to Section 6)

**Safety Follow-up:**

The following key procedures will be completed during the safety follow-up (for a full list of safety follow-up procedures, including the timing of each procedure please refer to Section 7.2.3):

- recording of concomitant medication(s) and AE(s)/SAE(s).
- physical examination including weight, vital signs, and ECOG performance status assessment (Appendix F)
- a 12-lead ECG

- local laboratory tests, including the following:
  - hematology panel
  - chemistry panel
  - thyroid function tests: TSH, Free T4
  - serum or urine pregnancy test for female subjects of childbearing potential
- blood samples for biomarker analysis, including HSV-1 antibody serostatus
- blood and urine will be collected, stored, and ultimately tested for detection of talimogene laherparepvec DNA using qPCR
- swabs of cold sore, vesicles, and other lesions suspected to be of herpetic origin (if any) will be collected, stored, and ultimately tested for detection of talimogene laherparepvec DNA using qPCR
- radiographic tumor imaging, clinical tumor assessment and tumor response assessment
- For phase 2: completion of PRO questionnaires: EQ-5D and EORTC QLQ-C30

**Reporting Exposure to Talimogene Laherparepvec in Phase 1b and Phase 2 Arm 1:**

Reporting potential or known unintended exposure to talimogene laherparepvec, suspected related signs or symptoms, and detection of talimogene laherparepvec DNA in a swab taken from a lesion, if any, in a subject's household member, caregiver, or healthcare provider as specified in Section 9.4.

**Long-term follow-up:**

All subjects who permanently discontinue study drug for any reason other than withdrawal of full consent will be contacted by clinic visit or telephone every 12 weeks (± 28 days) following the safety follow-up to assess survival, initiation of additional melanoma therapy, and whether any talimogene laherparepvec-related AEs have occurred until death, subject withdraws full consent, or up to **60** months after the last subject is randomized in phase 2.

Radiographic imaging, clinical tumor assessment, and tumor response assessment as detailed in Section 7.2.2 will be performed every 12 weeks (± 1 week) until documentation of confirmed disease progression per modified irRC (Appendix E) for subjects discontinuing study treatment for any reason other than progressive disease (PD). Completion of PRO questionnaires (EQ-5D and EORTC QLQ-C30) **will be performed until no longer than 3 years after the last subject is randomized.**

Subjects who have received talimogene laherparepvec and completed the long-term follow-up for any reason other than death or withdrawal of full consent and who provide consent will continue follow-up for survival under a separate ongoing registry protocol which is in place for the long-term follow-up of subjects treated with talimogene laherparepvec in clinical trials. The registry protocol will also monitor for late and long-term adverse events thought to be potentially related to talimogene laherparepvec.

For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedule of Assessments for the phase 1b and phase 2, (Table 2, Table 3, and Table 4 respectively).

**Statistical Considerations:**

Approximately 200 subjects will be randomized in a ratio of 1:1 to the two treatment arms in the phase 2 part of the study. This sample size was based on comparing the treatment arms with respect to ORR as primary efficacy endpoint within the Intent-to-treat (ITT) Analysis Set with 90% power and a 2-sided 5% significance level (see Table 6). Superiority will not be declared at the interim analysis and therefore the significance levels will not be adjusted for the interim analysis.

For primary analysis the incidence of AEs and clinical laboratory abnormalities defined as DLT will be summarized for the phase 1b part. All statistical testing will be performed at a 2-sided significance level of 0.05, unless otherwise stated. For the phase 2 part a Chi square test with

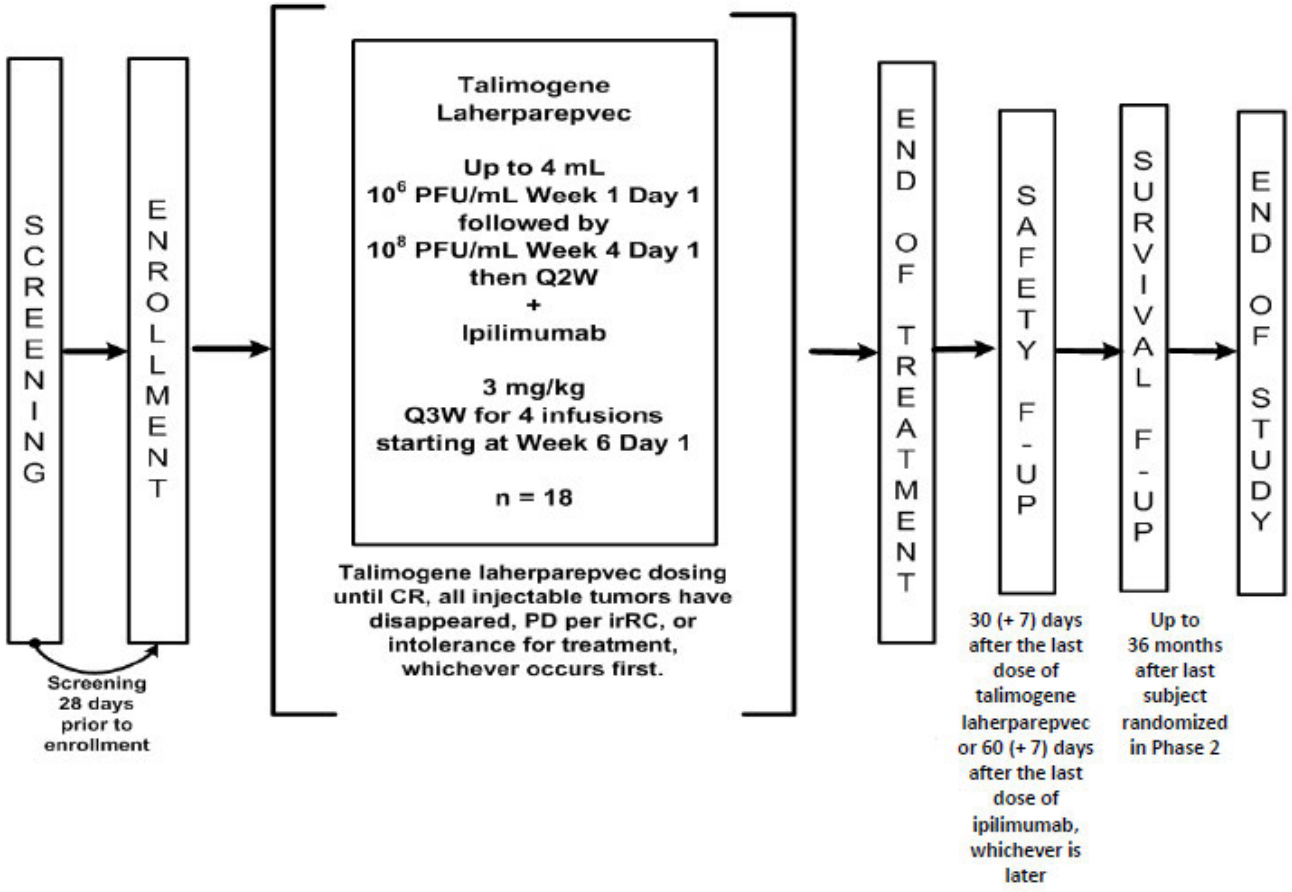
continuity correction (Fleiss, et al 1980) will be used to test whether there is difference in the ORR between treatment arms with talimogene laherparepvec in combination with ipilimumab relative to ipilimumab alone. For each treatment arm, exact binomial 2-sided 95% confidence intervals (CI) (Clopper and Pearson, 1934) will be generated for ORR. Wilson's score method with continuity correction will be used to calculate a 95% CI for the between-arm difference in rates (Newcombe, 1998). The similar approaches will also be used for disease control rate, durable response rate**,** and resection rate but the p-values will be descriptive. If, at the primary analysis of ORR, the null hypothesis of no treatment effect in comparing ORR between the two treatment arms is rejected, OS will be compared with an un-stratified log-rank test at the study's Final Analysis. The OS treatment hazard ratio and its 2-sided 95% CI will be estimated using an un-stratified Cox proportional hazards model. Kaplan-Meier (KM) curves for OS will be generated by treatment arm in the ITT Analysis Set. KM estimates and the 95% CIs for within each treatment and between treatment differences of annual OS rates will be provided. The CI for treatment annual rate differences will be based on variance estimates using Greenwood's formula (Kalbfleisch and Prentice, 1980). CIs for the KM quartiles will be provided by treatment arm (Brookmeyer and Crowley, 1982). **D**escriptive interim analyses **for** OS will be performed at the time of **primary analysis for** ORR and at 2 years**, 3 years, and 4 years** after the last subject is randomized **in phase 2.** Analysis of TTR, PFS and DOR will follow the same method as described for OS, but all p-values will be descriptive.

Subject incidence rates of treatment-emergent AEs (including all AEs, grade ≥ 3 AEs, SAEs, AEs of interest and events requiring the discontinuation of study drug, and local effects on the tumor [ie, pain, inflammation and ulceration]) will be summarized. Talimogene laherparepvec-related AEs reported during the long-term follow-up period will be listed separately. In addition, clinically significant laboratory changes and clinically significant changes in vital signs will be summarized with descriptive statistics. Summary statistics will also be provided for concomitant medications, study drug dose delay and discontinuation, overall exposure, and changes in ECOG performance status. In addition appropriate summary of qPCR analysis results of talimogene laherparepvec DNA in swab samples taken from lesions suspected to be herpetic in origin and in the blood and urine will be provided. Potential or known unintended exposure to talimogene laherparepvec, related suspected signs or symptoms, and detection of talimogene laherparepvec DNA in a subject's household member, caregiver, or healthcare provider will be reported. Summary scores at each assessment and changes from baseline of PROs in phase 2 as assessed by EQ-5D and the EORTC QLQ-C30 questionnaires will be reported by randomized treatment group.

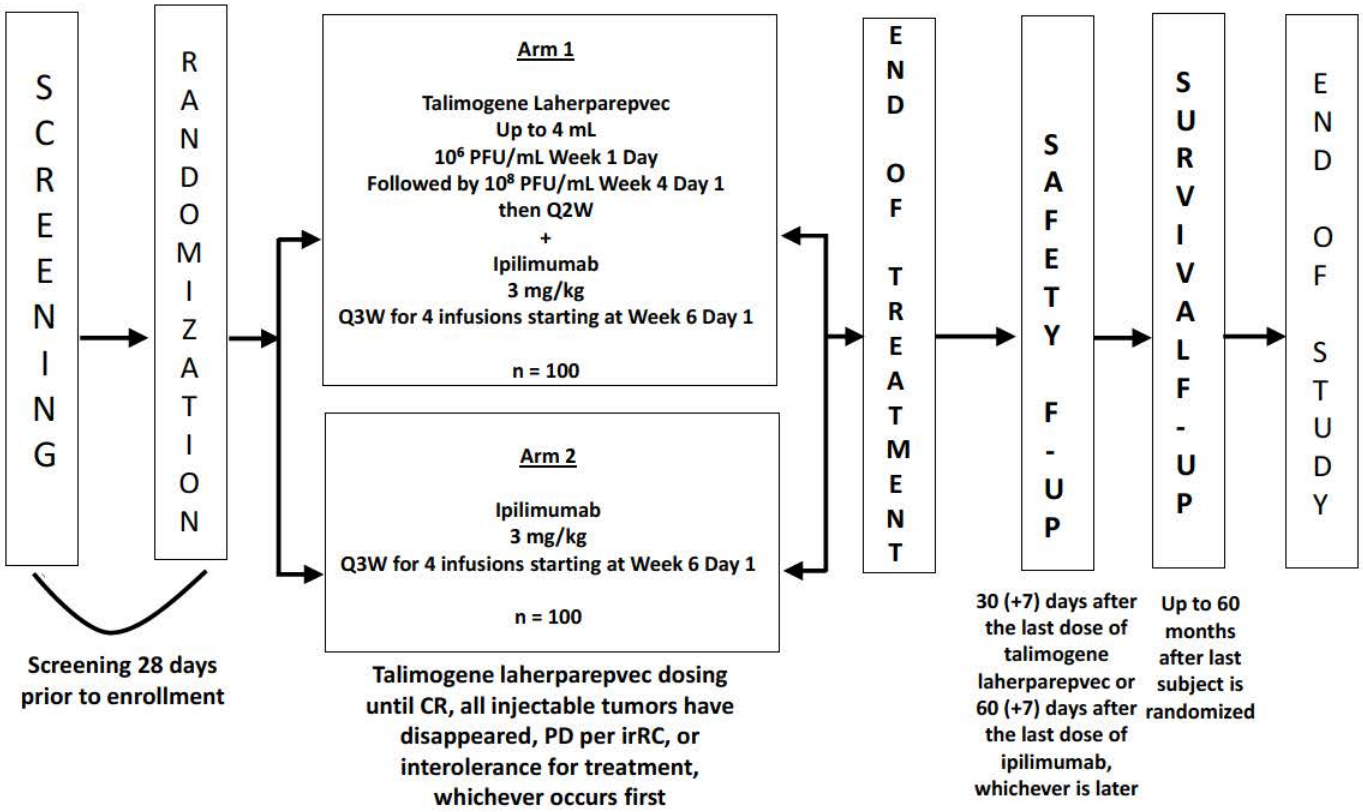


**Sponsor:** Amgen, Inc.

**Study Design and Treatment Schema for Phase 1b**



**Study Design and Treatment Schema for Phase 2**



## Study Glossary

| Abbreviation or Term | Definition/Explanation |
|---|---|
| AE | adverse event |
| ALT | alanine aminotransferase |
| ANC | absolute neutrophil count |
| ANOVA | analysis of variance |
| AST | aspartate aminotransferase |
| BOR | best overall response |
| *BRAF* | v-raf murine sarcoma viral oncogene homolog B1 |
| CNS | central nervous system |
| CR | complete response |
| CRF | case report form |
| CSR | clinical study report |
| CT | computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTLA-4 | cytotoxic T-lymphocyte associated antigen 4 |
| DCR | disease control rate |
| DLRT | Dose Level Review Team |
| DLT | dose-limiting toxicity |
| DNA | deoxyribonucleic acid |
| DOR | duration of response |
| DRR | durable response rate |
| DRT | Data Review Team |
| EAC | Endpoint Assessment Committee |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| EDC | electronic data capture |
| end of study for individual subject | defined as date the subject withdraws full consent from the study, completes the safety follow-up visit or the long-term survival follow-up whichever is later, or death |
| end of study (primary completion) | defined as **the date** when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary analysis of phase 2**, whether the study concluded as planned in the protocol or was terminated early**. |
| end of study (end of trial) | defined as when the last subject **across all sites** is assessed or receives an intervention for evaluation in the study **(ie, last subject last visit), following any additional parts in the study (ie, long-term follow-up), as applicable**. |
| EORTC | European Organization for Research and Treatment of Cancer |

| Abbreviation or Term | Definition/Explanation |
|---|---|
| ETO System | Electronic Trial Operation System: An electronic system that is used to facilitate the operations of a clinical trial through the collection of study related data. |
| EQ-5D | EuroQoL-5D |
| GCP | Good Clinical Practice |
| GM-CSF | granulocyte macrophage colony stimulating factor |
| HIV | human immunodeficiency virus |
| HLA | human leukocyte antigen |
| HSV-1 | herpes simplex type-1 virus |
| ICH | International Conference on Harmonisation |
| IgG1 | immunoglobulin G1 |
| INR | international normalization ratio |
| IPIM | Investigational Product Instruction Manual |
| IRB/IEC | Institutional Review Board/Institutional Ethics Committee |
| irRC | Immune Related Response Criteria |
| ITT | intent-to-treat |
| K-M | Kaplan-Meier |
| LDH | lactate dehydrogenase |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MHC | major histocompatibility complex |
| MPR | minor partial response |
| MRI | magnetic resonance imaging |
| NK | natural killer |
| ORR | objective response rate |
| OS | overall survival |
| PD | progressive disease |
| PD-1 | program death-1 |
| PET | positron emission tomography |
| PFS | progression free survival |
| PFU | plaque forming unit |
| **PI** | **Principal Investigator** |
| POR | Proof of Receipts |
| PR | partial response |
| PRO | patient reported outcomes |
| PT | prothrombin time |
| PTT/aPTT | partial thromboplastin time/activated partial thromboplastin time |

| Abbreviation or Term | Definition/Explanation |
|---|---|
| QLQ-C30 | Quality of Life Questionnaire Core 30 |
| qPCR | real-time polymerase chain reaction |
| RBC | red blood cells |
| REMS | risk evaluation and mitigation strategy |
| RNA | ribonucleic acid |
| SAE | serious adverse event |
| SD | stable disease |
| SOC | system organ class |
| Source Data | Information from an original record or certified a copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline (E6)). Examples of source data include Subject identification, Randomization identification, and Stratification Value. |
| SPD | sum of the products of the two largest perpendicular diameters |
| SRS | stereotactic radiotherapy |
| T4 | Thyroxine |
| TSH | thyroid stimulating hormone |
| TTR | time to response |
| UE | unable to evaluate |
| ULN | upper limit of normal |
| US | Ultrasound |
| USA | United States of America |
| WBC | white blood cells |
| VAS | visual analogue scale |
| VGPR | very good partial response |

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# 1. OBJECTIVES

## 1.1 Primary

The primary objectives are as follows:

- phase 1b: 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
- phase 2: 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

## 1.2 Secondary

The secondary objectives are as follows:

- phase 1b:
  - to estimate the efficacy of talimogene laherparepvec in combination with ipilimumab as determined by objective response rate (ORR)
  - to assess the safety of talimogene laherparepvec in combination with ipilimumab as determined by incidence of all adverse event (AE)s, grade ≥ 3 AEs, serious adverse event (SAEs), and events requiring the discontinuation of study drug, local effects on the tumor (ie, pain, inflammation and ulceration), clinically significant laboratory changes, and clinically significant changes in vital signs not defined as DLT
- phase 2:
  - to evaluate the efficacy of talimogene laherparepvec in combination with ipilimumab versus ipilimumab alone as determined by best overall response (BOR), disease control rate (DCR), durable response rate (DRR), duration of response (DOR), time to response (TTR), progression free survival (PFS), resection rate, overall survival (OS), landmark OS by year
  - to assess the safety of talimogene laherparepvec in combination with ipilimumab versus ipilimumab alone as determined by incidence of all AEs, grade ≥ 3 AEs, SAEs, and events requiring the discontinuation of study drug, local effects on the tumor (ie, pain, inflammation and ulceration), clinically significant laboratory changes, and clinically significant changes in vital signs

## 1.3 Exploratory

The exploratory objectives are as follows:

[redacted]

[redacted]

- to evaluate patient reported outcomes (PRO) in phase 2 as assessed by the EuroQoL-5D (EQ-5D) and the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30)

## 2. BACKGROUND AND RATIONALE

### 2.1 Melanoma

Melanoma is a tumor of melanocytes, cells derived from the neural crest. Although most melanomas occur in the skin, they may also arise from mucosal surfaces or at other sites to which neural crest cells migrate. Many melanomas originate on sun-exposed regions, leading to the conclusion that sunlight is the main environmental cause of most cutaneous melanomas (Welch et al, 2005). Other risk factors include geographical location and ethnicity. White Australians have the greatest risk of melanoma worldwide (Goldstein and Tucker, 1993), and white populations have a 10-fold higher risk of developing melanoma than black, Asian, or Hispanic populations, assumed to be due to the degree of skin pigmentation (Stevens et al, 1990). Within the white populations, fair skin and blue eyes are associated with a greater risk of developing melanoma. Approximately 5% to 10% of all cutaneous melanomas occur in families with hereditary melanoma predisposition (familial melanoma). Approximately 40% to 60% of cutaneous melanoma harbor mutations in the v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) gene that lead to activation of downstream signaling through the RAF-MEK-MAPK pathways (Davies et al, 2002; Curtin et al, 2005). Approximately 90% of these mutations result in substitution of glutamic acid for valine at codon 600 (*BRAF* V600E) (Chapman et al, 2011; Zelboraf™ Prescribing Information, 2011).

Melanoma is the fifth most common cancer in men and the sixth most common cancer in women in the United States of America (USA), with an estimated 76,250 new cases and 9,180 deaths expected in 2012 (Siegel et al, 2012). In Europe, the annual incidence of melanoma is somewhat lower than that in the USA, at approximately 7 per 100,000 as compared to 18 per 100,000 in the USA (Ries et al, 2000). In Europe, approximately 83,729 new cases were diagnosed in 2008 and approximately 85,086 new cases were expected in 2010 (GLOBOCAN 2008, 2010). The incidence of melanoma is increasing rapidly worldwide, with a 270% increase in the USA between 1973 and 2002. This increase is the most rapid of any cancer with the exception of lung cancer in women (Jemal et al, 2006; Ries et al, 2000).

Melanoma that has not spread beyond the initial site is highly curable. Most of these cases are thin tumors that have not invaded beyond the papillary dermis (Stage II; thickness, 1.0 mm or less). Melanoma that has spread to regional lymph nodes (Stage III) may be curable with wide (2 to 4 cm) excision of the primary tumor and removal of the involved regional lymph nodes (Karakousis et al, 2006; Balch et al, 2009). Melanoma that has spread to distant sites (Stage IV) is infrequently curable with standard therapy, although long-term survival is occasionally achieved by resection of metastasis (Overett and Shiu, 1985).

Until very recently, the traditional nonsurgical therapies for unresectable or advanced melanoma in adults included, chemotherapy (dacarbazine, temozolomide, or other agents either alone or in combination), or interleukin-2. Although some regimens produced objective responses, they were usually short-lived. For example, dacarbazine or temozolomide achieved a 7% to 12% objective response rate but an objective response did not appear to be associated with a prolongation in survival (Anderson et al, 1995; Chapman et al, 1999; Wagner et al, 2000; Middleton et al, 2000). Response rates for interleukin-2 ranged from 10% to 20% (Rosenberg et al, 1994; Sparano et al, 1993; Atkins et al, 1999), with a small proportion achieving prolonged response, but its administration requires specialized facilities and well-trained staff.

Recently, the United States Food and Drug Administration and other regulatory authorities approved two novel therapies for advanced melanoma: a *BRAF* inhibitor, vemurafenib (Zelboraf™ Prescribing Information, 2011), and an immune stimulatory agent, ipilimumab (Yervoy®, 2013). The trials upon which approval for these agents were based demonstrated improved survival compared to control treatments. The pivotal vemurafenib study showed improved rates of OS and PFS in subjects with previously untreated metastatic melanoma with the *BRAF* V600E mutation who received vemurafenib versus standard dacarbazine (Chapman et al, 2011). The pivotal trial of ipilimumab showed an OS improvement in subjects with HLA-A2*0201 genotype, previously treated metastatic melanoma as compared with a peptide vaccine (Hodi et al, 2010). Another trial showed improved OS for metastatic melanoma subjects treated with ipilimumab and dacarbazine versus placebo and dacarbazine (Robert et al, 2011).

In 2013, regulatory agencies also approved the *BRAF* inhibitor dabrafenib (Tafinlar™, 2013) and the *MEK* inhibitor trametinib (Mekinist™, 2013), both in *BRAF* V600 mutant advanced melanoma. Each agent showed a benefit in progression-free

survival compared to dacarbazine in phase 3 trials (Hauschild et al, 2012; Flaherty et al, 2012a), though cross-over and short duration of follow-up to date limits interpretation of overall survival. Additionally, dabrafenib and trametinib were approved recently as a combination therapy for *BRAF*-mutant unresectable or metastatic melanoma (Flaherty et al, 2012b).

In 2014, the United States Food and Drug Administration granted accelerated approval to pembrolizumab (Keytruda®, 2014), a programmed death receptor 1 (PD-1) inhibitor, for treatment of patients with advanced or unresectable melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. The efficacy of pembrolizumab was established in 173 clinical trial participants with advanced melanoma whose disease progressed after prior treatment. In the half of the participants who received pembrolizumab at the recommended dose of 2 mg/kg every 3 weeks, approximately 24% (95% CI: 15; 34) had overall objective response with 1 complete response (CR) and 20 partial responses (PRs). At the time of analysis, 86% (18/21) of patients with objective responses had ongoing responses with durations ranging from 1.4+ to 8.5+ months, including 8 patients with ongoing responses of 6 months or longer.

In 2015, the United States Food and Drug Administration granted approval to talimogene laherparepvec (IMLYGIC™, 2015) for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery. This included the limitation that it has not been shown to improve overall survival or have an effect on visceral metastases.



### 2.2 Talimogene Laherparepvec Background

Talimogene laherparepvec (previously known as OncoVEX$^{GM-CSF}$) is an intratumorally delivered oncolytic immunotherapy comprised of an immune-enhanced herpes simplex virus type-1 (HSV-1) that selectively replicates in solid tumors (Talimogene Laherparepvec Investigator's Brochure). The HSV-1 viral genes encoding ICP34.5 (the so-called neurovirulence factor) and ICP47 (which blocks viral antigen presentation to major histocompatibility complex [MHC] class I and II molecules) have been functionally deleted. The deletion of ICP47 also leads to earlier expression of US11, a gene that promotes virus growth in tumor cells without decreasing tumor selectivity. The coding sequence for human granulocyte macrophage colony stimulating factor (GM-CSF), a cytokine involved in the stimulation of immune responses, has been inserted into the viral genome. Extensive experimental studies of the biological activity

of GM-CSF established its having a major role in promoting the generation of dendritic cells from blood monocytes (Demir et al, 2003; Lonial, 2004; Conti and Gessani, 2008). Dendritic cells have the capacity to capture antigens, migrate in response to chemotactic stimuli, and induce proliferative responses and Th1 cytokine production in CD4+ and CD8+ T-lymphocytes (Hart, 1997; Steinman, 2001; Ikeda, et al, 2004; Paul, 2007). Th1-type cytokines have the capacity to produce proinflammatory responses, eradicate tumors, and perpetuate autoimmune responses (Nishimura et al, 2000; Ikeda, et al, 2004; Knutson and Disis, 2005).

Thus, the dual mechanisms of action of talimogene laherparepvec comprise a direct oncolytic effect achieved by infection and replication of the virus in the tumor, resulting in tumor cell lysis and enhancement of antitumor immune response by expression of GM-CSF in the tumor microenvironment. This therapeutic strategy intended to induce antitumor effects through both direct tumor lysis and secondary initiation of systemic tumor-specific immune responses.

Talimogene laherparepvec was tested in an open-label ascending-dose study (Study 001-01) with single doses of either $10^6$, $10^7$, or $10^8$ plaque forming units/mL (PFU/mL) (up to 4 mL), injected directly into a single metastatic skin or subcutaneous tumor of breast cancer, head and neck cancer, gastrointestinal cancer, or melanoma (Talimogene Laherparepvec Investigator's Brochure; Hu et al, 2006).

In that study, subjects who were seronegative at study entry experienced more AEs, including flu-like syndromes consisting of malaise, rigors, pyrexia, and erythema around the injected tumor. Erythematous skin rash with scattered vesicles in the skin were noted in some seronegative subjects who received $10^7$ PFU/mL as their first dose. Virus was also detected on the surface of some of the injected nodules; however, virus was not detected outside of the dressing covering the injection site. The events were transient and self-limiting, and no long-term sequelae were noted.

In the subsequent multidose part of the study, talimogene laherparepvec was well tolerated in seronegative or seropositive subjects who received a lower initial dose of $10^6$ PFU/mL, followed by two doses of $10^8$ PFU/mL. Febrile responses were minimal, there was no further detection of virus on the surface of the injected tumors, and vesicles were not seen. Additionally, all seronegative subjects seroconverted within 3 weeks following the first dose of talimogene laherparepvec. Necrosis of injected tumors, confirmed on histopathology, was observed in both seropositive and seronegative subjects. These data supported the conclusion that an initial dose of $10^6$ PFU/mL,

followed by doses of $10^8$ PFU/mL, was appropriate for use in further trials. This dose regimen has been used in the ongoing phase 3 of trial of talimogene laherparepvec for treatment of subjects with advanced stage melanoma that completed enrollment with 439 subjects (OPTiM Study [005-05]).

Clinical data currently available indicate that talimogene laherparepvec has the potential to provide overall clinical benefit to patients with advanced melanoma (Talimogene Laherparepvec Investigator's Brochure). In particular, a 20% rate of complete response (CR) was achieved in a phase 2 study with talimogene laherparepvec in stage IIIC to IV melanoma (Senzer et al, 2009). Response was still ongoing for all but 2 subjects at the time of the last tumor evaluation, with a median duration of longest response of 223 days (Talimogene Laherparepvec Investigator's Brochure). In addition, responses were observed in both injected and uninjected sites, including visceral sites.

Talimogene laherparepvec was tested in an open-label randomized phase 3 study versus subcutaneously administered GM-CSF in Stage IIIB, IIIC, and Stage IV unresectable melanoma (OPTiM Study). Primary results of this study were presented in June of 2013, and showed a statistically significant difference between the rate of durable response among subjects treated with talimogene laherparepvec (16%; 95% CI: 12%, 21%) versus those treated with GM-CSF (2%; 95% CI: 0%, 5%) (p-value< 0.0001). A difference in the secondary endpoint of OS was also seen with an HR of 0.79 (95% CI: 0.62-1.00), p = 0.051. Median OS of subjects treated with talimogene laherparepvec was 4.4 months longer than those treated with GM-CSF (23.3. months for talimogene laherparepvec versus 18.9 months for GM-CSF) (Kaufman et al, 2014). Survival at 12, 24, 36 and 48 months in the talimogene laherparepvec arm was estimated to be 74%, 50%, 39% and 33%, respectively, and 69%, 40%, 30% and 21% in the GM-CSF arm, respectively. Median (range) time to response among the 78 subjects in the talimogene laherparepvec arm with a response was 4.1 (1.2 to 16.7) months, whereas among the 8 in the GM-CSF arm with a response, it was 3.7 (1.9 to 9.1) months. Fifty-four percent of talimogene laherparepvec objective responders and 48% of talimogene laherparepvec durable responders exhibited "interval progression", which is transient locoregional or distant progression including appearance of new lesions, before ultimately achieving response (Kaufman et al, 2013, Ross et al, 2014).

The most common side effects in the OPTiM study were chills (talimogene laherparepvec, 49%; GM-CSF, 9%), pyrexia (43%; 9%), injection-site pain (28%; 6%), nausea (36%; 20%), influenza-like illness (30%; 15%), and fatigue (50%; 36%) (all treatment-emergent). Grade ≥ 3 adverse events occurred in 36% of subjects receiving talimogene laherparepvec and 21% of subjects receiving GM-CSF. The only grade 3/4 adverse events occurring in ≥ 5 of subjects was cellulitis (talimogene laherparepvec, n = 6 [2.1%]; GM-CSF, n =1[< 1%]). Of 10 fatal adverse events in the talimogene laherparepvec arm, 8 were attributable to disease progression. The remaining 2 fatal adverse events (sepsis in the setting of salmonella infection; myocardial infarction) were not considered treatment-related per investigator (Andtbacka et al, 2013).

Refer to the Talimogene Laherparepvec Investigator's Brochure for additional information.

### 2.3 Ipilimumab Background

Ipilimumab, a fully human monoclonal antibody (immunoglobulin G1 [IgG1]), binds to cytotoxic T-lymphocyte associated antigen 4 (CTLA-4), a negative regulator of T-cell activation, and blocks the interaction of CTLA-4 with its ligands, CD80/CD86 (Yervoy®, 2013). CTLA-4 is an immune checkpoint molecule that down-regulates pathways of T-cell activation (Fong et al, 2009; Weber, 2009). Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation.

Ipilimumab was investigated in a randomized (3:1:1), double-blind, double-dummy study that included 676 randomized subjects with previously treated, unresectable or metastatic melanoma (Hodi et al, 2010; Yervoy®, 2013). Of these 676 subjects, 403 were randomized to receive ipilimumab at 3 mg/kg in combination with peptide vaccine (gp100), 137 were randomized to receive ipilimumab at 3 mg/kg, and 136 were randomized to receive gp100 alone. The study enrolled only subjects with HLA-A2*0201 genotype because this HLA genotype facilitates the immune presentation of the investigational peptide vaccine. The median OS was 10.0 months among subjects receiving ipilimumab plus gp100, as compared with 6.4 months among subjects receiving gp100 alone (hazard ratio for death, 0.68; P<0.001). The median OS with ipilimumab alone was 10.1 months (hazard ratio for death compared with gp100 alone, 0.66; P = 0.003). No difference in OS was detected between the ipilimumab groups (hazard ratio with ipilimumab plus gp100, 1.04; P = 0.76). Grade 3 or 4 immune-related AEs occurred in 10% to 15% of subjects treated with ipilimumab and in 3% treated with

gp100 alone. There were 14 deaths related to the study drugs (2.1%), and 7 were associated with immune-related AEs.

In another study, 503 subjects with previously untreated metastatic melanoma were randomly assigned in a 1:1 ratio, to ipilimumab (10 mg/kg) plus dacarbazine (850 mg/m$^2$ of body-surface area) or dacarbazine (850 mg/m$^2$) plus placebo, given at weeks 1, 4, 7, and 10, followed by dacarbazine alone every 3 weeks through week 22. Subjects with stable disease (SD) or an objective response and no dose-limiting toxic effects received ipilimumab or placebo every 12 weeks thereafter as maintenance therapy (Robert et al, 2011). Survival was significantly longer in the group receiving ipilimumab plus dacarbazine than in the group receiving dacarbazine plus placebo (11.2 months vs 9.1 months, with higher survival rates in the ipilimumab-dacarbazine group at 1 year (47.3% vs 36.3%), 2 years (28.5% vs 17.9%), and 3 years (20.8% vs 12.2%) (hazard ratio for death, 0.72; P < 0.001). Grade 3 or 4 AEs occurred in 56.3% of subjects treated with ipilimumab plus dacarbazine, as compared with 27.5% treated with dacarbazine and placebo (P < 0.001). The most common immune related AEs in the ipilimumab-dacarbazine group were elevated liver-function values, with grade 3 or 4 elevations in liver-function values noted in 17.4% to 20.7% of the subjects. No drug-related deaths occurred in the ipilimumab-dacarbazine group; one fatal gastrointestinal hemorrhage was reported in the dacarbazine group.

Ipilimumab can result in immune-mediated adverse reactions due to T-cell activation and proliferation. Inhibition of CTLA-4 characteristically induces toxicities for which the definition "immune-related AEs" has been proposed. Immune-related AEs mainly include colitis/diarrhea, dermatitis, hepatitis, and endocrinopathies; uveitis, nephritis, and inflammatory myopathy also have been reported occasionally (Di Giacomo et al, 2011). Using specific treatment guidelines that include symptomatic therapies or systemic corticosteroids, CTLA-4 treatment-related side effects were generally mild, reversible, and manageable. However, severe or fatal immune-mediated adverse reactions have also been observed in patients treated with ipilimumab (Yervoy®, 2013). These immune-mediated reactions may involve any organ system; however, the most common severe immune-mediated reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy and endocrinopathy. The majority of these immune-mediated reactions manifested during treatment; however, a minority occurred weeks to months after discontinuation of ipilimumab. Therefore, it is critical that

immune-mediated adverse reactions be treated early during the course of treatment to avoid major complications.

Refer to the regional manufacturer package insert of ipilimumab (Yervoy®, 2013) for additional information.

### 2.4 Combination of Talimogene Laherparepvec and Ipilimumab

The phase 1b portion of this study enrolled 19 patients of which 18 were treated with the combination of both talimogene laherparepvec and ipilimumab (Puzanov et al, 2014). One subject withdrew consent after one dose of talimogene laherparepvec. There were no reported dose limiting toxicities (DLT) during the DLT evaluation period (the 6 weeks following the first administration of ipilimumab). The most common AEs were chills, fatigue, and pyrexia occurring in 11 subjects (58%) each. Grade 3 or 4 AEs of any kind occurred in 6 subjects (32%). The only grade 3 or 4 event occurring in more than one subject was grade 3 nausea in two subjects. Two subjects (11%) experienced possible immune-related grade 3 or 4 AEs attributed either ipilimumab or the combination of ipilimumab and talimogene laherparepvec. There were no unexpected AEs attributable to the combination therapy that have not been seen previously with either ipilimumab or talimogene laherparepvec individually. Of the subjects who experienced possible immune-related grade 3 or 4 AEs, 1 subject experienced grade 3 hypophysitis attributed to ipilimumab and grade 3 adrenal insufficiency and grade 3 diarrhea, both of which were attributed to the combination of products. The other subject experienced grade 4 amylase and lipase elevations which were attributed to ipilimumab (Puzanov et al, 2014). These grade 3/4 AE rates and possible immune-related AEs are consistent with what has been reported with ipilimumab alone (Hodi et al, 2010). One grade 5 event of metastases to the central nervous system occurred during the treatment and safety follow-up period. Analysis performed at a median tumor follow-up time of 15.6 months revealed 9 confirmed responses out of 18 evaluable subjects (50%) with 4 complete responses (22%) by immune-related response criteria, and DRR was 44% (Puzanov et al, 2015). Median time to response was 4.1 months, and median duration of treatment was 3.1 months (Puzanov et al, 2014).

### 2.5 Rationale

This protocol rationally combines talimogene laherparepvec with ipilimumab looking to achieve an increased magnitude of tumor specific T cell responses as compared to the ipilimumab alone. Talimogene laherparepvec and CTLA-4 blockade are intended to enhance T-cell activation through different mechanisms, respectively augmenting

dendritic cell-mediated tumor antigen presentation (Kaufman et al, 2010) following the release of tumor antigens by lytic virus replication, enhanced through the local expression of GM-CSF, and antagonizing immune tolerance by blocking inhibitory signals mediated by CTLA-4 on T lymphocytes (Kapadia and Fong, 2005). A pre-clinical study demonstrated an injected oncolytic viral therapy and CTLA-4 blockade in combination had enhanced activity in local and distant tumors compared to either agent alone (Zamarin et al, 2014).

Although the current clinical data characterizing the clinical outcome of talimogene laherparepvec is not fully mature, monotherapy with the oncolytic immunotherapy has been shown to demonstrate a substantial proportion of responses and durable responses in phase 2 and is anticipated to demonstrate a clinically meaningful improvement in OS (Senzer et al, 2009). Ipilimumab monotherapy is known to provide a clinically meaningful but relatively modest increase in OS (approximately 2 to 3 months compared to dacarbazine or peptide vaccine), and complete and partial responses only occurred in a small subset of subjects (about 10.9%). Additionally, responses with ipilimumab often occurred late, with up to 10% of patients having responses after initial progression on therapy (Hodi et al, 2010; Robert et al, 2011).

This phase 1b/2, multicenter, open-label study is intended to provide proof of concept that a regimen of an oncolytic immunotherapy (talimogene laherparepvec) and an immune checkpoint inhibitor (ipilimumab) is tolerable and that the combination treatment might enhance the clinical efficacy shown when ipilimumab is administered alone. The study will evaluate the safety and estimate the efficacy of talimogene laherparepvec in combination with ipilimumab compared to ipilimumab alone in subjects with unresected, stages IIIB to IV melanoma. As this is the first use of talimogene laherparepvec with ipilimumab, the phase 1b part of this study is intended to evaluate the safety of talimogene laherparepvec in combination with ipilimumab in the target population before the phase 2 part of study is used to further evaluate the safety and evaluate the preliminary efficacy of the combination.

The addition of ipilimumab to talimogene laherparepvec is intended to enhance the systemic anti-tumor response to tumor antigens released following the lytic replication of talimogene laherparepvec in tumors. Therefore, this combination therapy may result in the enhanced destruction of injected tumors as well as uninjected/distant tumors, including micrometastatic disease to improve the rate of overall tumor response and duration of response. Overall, these effects may contribute to an improvement in OS.

Ipilimumab is approved for use in untreated and previously treated advanced melanoma patients (Yervoy®, 2013). Results with another checkpoint inhibitor, pembrolizumab, have shown that similar response rates in subjects with advanced or unresectable melanoma whether or not the subjects were previously treated with ipilimumab (Hamid et al, 2013). Therefore, the study will now allow subjects previously treated with other systemic therapies to enroll in order to adapt to the changing landscape of melanoma treatment and to study the combination therapy in a second line or greater setting. The response rate in the treatment naïve subjects enrolled on the phase 1b portion of this study was higher than what would be expected for talimogene laherparepvec or ipilimumab alone, but whether the combination is equally effective in previously treated subjects is unknown. Therefore an increase in population size to 200 subjects in the phase 2 part of the study is being implemented to ensure sufficient statistical power to detect an improvement in ORR for the treatment naïve subjects only (refer to Section 10.2 for sample size considerations).

### 2.6 Clinical Hypotheses

Phase 1b: The hypothesis is that talimogene laherparepvec in combination with ipilimumab will be safe and well tolerated in subjects with previously untreated, unresected, stages IIIB to IV melanoma.

Phase 2: The hypothesis is that talimogene laherparepvec in combination with ipilimumab versus ipilimumab will improve ORR in subjects with unresected, stages IIIB to IV melanoma.

## 3. EXPERIMENTAL PLAN

### 3.1 Study Design

#### 3.1.1 Study Design of Phase 1b

The phase 1b part is an open-label, multicenter, single-arm study. Talimogene laherparepvec in combination with ipilimumab will be administered to approximately 18 subjects.

Talimogene laherparepvec will be administered by intratumoral injection into the injectable cutaneous, subcutaneous, and nodal tumors initially at a dose of $10^6$ PFU/mL at day 1 of week 1 followed by a dose of $10^8$ PFU/mL at day 1 of week 4, and every 2 weeks (± 3 days) thereafter. Ipilimumab will be administered intravenously at a dose of 3 mg/kg every 3 weeks (± 3 days) for 4 infusions starting at day 1 of week 6 (ie, at the time of the third dose of talimogene laherparepvec), day 1 of week 9, day 1 of

week 12, and day 1 of week 15. When talimogene laherparepvec and ipilimumab are administered on the same day, talimogene laherparepvec must be administered first.

Subjects will be treated with talimogene laherparepvec until complete response (CR), all injectable tumors have disappeared, confirmed disease progression per the modified Immune-Related Response Criteria (irRC; Wolchok et al, 2009 [Appendix E]), or intolerance of study treatment, whichever occurs first. Due to the mechanism of action, subjects may experience growth in existing tumors or the appearance of new tumors prior to maximal clinical benefit of talimogene laherparepvec. Therefore, talimogene laherparepvec dosing should be continued provided that the subject has no evidence of confirmed disease progression per modified irRC (Appendix E) and is able to tolerate the treatment.

Subjects will be followed for safety approximately 30 (+ 7) days after the last dose of talimogene laherparepvec or 60 (+ 7) days after the last dose of ipilimumab, whichever is later, and survival for approximately **60** months after the last subject is randomized in phase 2.

A Dose Level Review Team (DLRT) consisting of the Amgen study team, including at least one clinician, safety representative, and biostatistician, and at least one investigator participating in the study who has recruited subjects into the phase 1b part of the study, will review the safety data to evaluate possible drug effects and DLT. This team will recommend either to enroll more subjects for DLT evaluation in the phase 1b, to stop enrollment into phase 1b, or to declare that the combination appears to be tolerable and open the phase 2 part of the study.

The DLT evaluation period is 6 weeks from the initial administration of ipilimumab (ie, week 6 to 12). To be evaluable for a DLT subjects must have had the opportunity to be on treatment for at least 6 weeks from the initial dosing of ipilimumab and received at least 1 dose of talimogene laherparepvec and 1 dose of ipilimumab. Subjects may be replaced if they are not evaluable for DLT (ie, either a subject did not receive study treatment, permanently discontinued talimogene laherparepvec prior to receiving the first dose of ipilimumab for any reason, or ended the study treatment prior to week 12 for reason other than experiencing a DLT).

The DLRT will initially meet when 6 subjects are evaluable for DLT. The DLRT will declare the combination of talimogene laherparepvec and ipilimumab tolerable if

incidence of DLT is < 33% during the DLT evaluation period subject to the following rules:

- If ≤ 1 subject among the initial 6 evaluable subjects in the phase 1b experience DLT during the DLT evaluation period, then combination of talimogene laherparepvec and ipilimumab will be declared as safe.
- If 2 subjects among the initial 6 evaluable subjects in the phase 1b experience DLT during the DLT evaluation period, an additional 3 evaluable subjects will be enrolled to the phase 1b.
- If ≤ 2 subjects among the expanded cohort of 9 evaluable subjects in the phase 1b experience DLT during the DLT evaluation period, then combination of talimogene laherparepvec and ipilimumab will be declared as safe.
- If ≥ 3 subjects among the initial 6 evaluable subjects or among the expanded cohort of 9 evaluable subjects in the phase 1b experience DLT during the DLT evaluation period, then combination of talimogene laherparepvec and ipilimumab will be declared as not safe, the enrollment into phase 1b will end, and the phase 2 will not be opened for enrollment.

The DLT evaluation will be based on the initial 6 to 9 subjects meeting the DLT evaluation criteria as outlined above. However, the enrollment will not be halted while the DLT evaluation is still ongoing. Approximately 18 subjects in total may be enrolled in the phase 1b part of the study. Additional subjects enrolled beyond the DLT evaluation may be needed to help assess the overall safety profile of talimogene laherparepvec in combination with ipilimumab before proceeding to the phase 2 part of the study.



**Dose-Limiting Toxicities:**

DLT is defined as any toxicity related to talimogene laherparepvec or the combination of talimogene laherparepvec and ipilimumab that occurs among the 6 to 9 DLT evaluable subjects enrolled during the DLT evaluation period of the phase 1b, which meets any of the following criteria (Note: Toxicity will be assessed using the Common Terminology Criteria for Adverse Events [CTCAE] version 3.0 [Appendix A]:

- any treatment-related non-laboratory AEs of grade 4 or greater
- grade 4 or greater immune-mediated dermatitis
- grade 4 or greater immune-mediated endocrinopathy (except autoimmune thyroiditis- see below)
- grade 3 or greater immune-mediated enterocolitis
- grade 3 or greater immune-mediated hepatitis with the exception of grade 3 immune-mediated hepatitis that resolves to grade 1 or baseline within 28 days of onset

- grade 3 or greater immune-mediated neuropathy
- grade 3 or greater other immune-mediated AEs including any of the following;
  - hemolytic anemia
  - angiopathy, myocarditis, pericarditis, temporal arteritis, or vasculitis
  - autoimmune thyroiditis with the exception of grade 3 autoimmune thyroiditis that resolves to grade 1 or baseline within 28 days of onset
  - blepharitis, conjunctivitis, episcleritis, iritis, scleritis, or uveitis
  - pancreatitis
  - meningitis
  - arthritis or polymyalgia rheumatica
  - nephritis
  - pneumonitis
  - psoriasis or leukocytoclastic vasculitis

Of note, unless an alternative etiology has been identified, signs and symptoms of any disease process described above as a DLT should be considered immune-mediated.

In addition to DLT defined above, the DLRT will review all available safety data and will base its decision on its members' clinical judgment and/or area expertise considering all relevant safety information.

All DLTs should be documented on the AE case report forms (CRF).

The overall study design of the phase 1b is described by a study schema at the end of the protocol synopsis section.

The study endpoints of the phase 1b are defined in Section 10.1.1.

### 3.1.2 Study Design of Phase 2

The phase 2 part of the study is an open-label, multicenter, randomized study to further assess the safety and to evaluate the efficacy of the talimogene laherparepvec in combination with ipilimumab. Approximately 200 subjects will be randomized 1:1 to receive the following:

- arm 1: talimogene laherparepvec plus ipilimumab
- arm 2: ipilimumab

Subjects randomized before amendment 2 will be stratified by stage of disease (stage IIIB/C, IVM1a, and stage IVM1b vs IVM1c) and *BRAF* V600E (mutation vs mutation not present). Subjects randomized after amendment 2 will be stratified by stage of disease (stage IIIB/C and IVM1a vs stage IVM1b and IVM1c) and prior therapy

(treatment naïve vs previously treated with systemic anticancer immunotherapy vs previously treated with systemic anticancer treatment other than immunotherapy).

Talimogene laherparepvec will be administered by intratumoral injection into the injectable cutaneous, subcutaneous, and nodal tumors initially at a dose of $10^6$ PFU/mL at day 1 of week 1 followed by a dose of $10^8$ PFU/mL at day 1 of week 4, and every 2 weeks (± 3 days) thereafter. Ipilimumab will be administered intravenously at a dose of 3 mg/kg every 3 weeks (± 3 days) for 4 infusions. Subjects randomized to arm 1 will receive ipilimumab starting at day 1 of week 6 (ie, at the time of the third dose of talimogene laherparepvec), day 1 of week 9, day 1 of week 12, and day 1 of week 15. When talimogene laherparepvec and ipilimumab are administered on the same day, talimogene laherparepvec must be administered first. Subjects randomized to arm 2 will receive ipilimumab starting at day 1 of week 1, day 1 of week 4, day 1 of week 7, and day 1 of week 10.

Subjects will be treated with talimogene laherparepvec until CR, all injectable tumors have disappeared, confirmed disease progression per the modified irRC (Appendix E), or intolerance of study treatment, whichever occurs first. Due to the mechanism of action, subjects may experience growth in existing tumors or the appearance of new tumors prior to maximal clinical benefit of talimogene laherparepvec. Therefore, talimogene laherparepvec dosing should be continued provided that the subject has no evidence of confirmed disease progression per modified irRC and is able to tolerate the treatment.

Subjects will be followed for safety approximately 30 (+ 7) days after the last dose of talimogene laherparepvec or 60 (+ 7) days after the last dose of ipilimumab, whichever is later, and survival for approximately **60** months after the last subject is randomized in phase 2.

Prior to starting the phase 2 part of the study, a Data Review Team (DRT) internal to Amgen but external to the talimogene laherparepvec product team will be formed. The DRT will consist of one biostatistician and two clinicians (one from Global Development Therapeutic Area Development and one from Global Safety) that collectively have experience in the management of subjects with cancer and in the conduct of randomized clinical trials. The DRT, governed by a detailed DRT charter, will review accumulating safety data from the phase 2 at regular intervals to safeguard the interests of trial participants (see Section 10.4.3).

The overall study design of the phase 2 is described by a study schema at the end of the protocol synopsis section.

The study endpoints of the phase 2 are defined in Section 10.1.1.

### 3.2 Number of Sites

For the phase 1b portion, the study will be conducted at approximately 10 to 15 sites in the USA. Other countries may also participate in the phase 1b. For the phase 2 portion, the study will be conducted at approximately 50 sites globally including USA and Europe, if feasible. Additional sites and countries may be added.

Sites that do not enroll subjects within 4 months of site initiation may be closed.

### 3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as “subjects”.

Approximately 218 subjects will be enrolled in this study; approximately 18 subjects will be enrolled in phase 1b, and approximately 200 subjects will be enrolled in the phase 2.

Refer to Section 10.2 for sample size considerations.

### 3.4 Estimated Study Duration

#### 3.4.1 Study Duration for Participants

##### 3.4.1.1 Phase 1b Study Duration for Participants

The duration for the phase 1b is approximately 44 months. The duration of screening for each subject will be approximately 28 days. The subject accrual period is planned for approximately 7 months. The duration of treatment will vary for each subject. Subjects will be treated until CR, all injectable tumors have disappeared, confirmed disease progression per the modified irRC (Appendix E), or intolerance of study treatment, whichever occurs first. Subjects will be followed for safety approximately 30 (+ 7) days after the last dose of talimogene laherparepvec or 60 (+ 7) days after the last dose of ipilimumab, whichever is later, and survival for approximately **60** months after the last subject is randomized in phase 2.

The end of phase 1b study for each subject is defined as the date the subject withdraws full consent from the study, completes the long-term survival follow-up, whichever is later, or death.

##### 3.4.1.2 Phase 2 Study Duration for Participants

Accrual in the phase 2 is planned to start approximately 6 months after the end of enrollment in the phase 1b.

The duration for the phase 2 is approximately **60** months. The duration of screening for each subject will be approximately 28 days. The subject accrual period is planned for approximately 18 months. The duration of treatment will vary for each subject. Subjects randomized to arm 1 will be treated until CR, all injectable tumors have disappeared, confirmed disease progression per the modified irRC (Appendix E), or intolerance of study treatment, whichever occurs first. Subjects randomized to arm 2 will be treated for approximately 4 months. Subjects will be followed for safety approximately 30 (+ 7) days after the last dose of talimogene laherparepvec or 60 (+ 7) days after the last dose of ipilimumab, whichever is later, and survival for approximately **60** months after the last subject is randomized in phase 2.

The end of the phase 2 study for each subject is defined as the date the subject withdraws full consent from the study, the long-term survival follow-up, whichever is later, or death.

### 3.4.2 End of Study

Primary Completion: The time when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary analysis of phase 2**, whether the study concluded as planned in the protocol or was terminated early**. The primary completion is anticipated to occur approximately 6 months after the date the last subject is randomized in the phase 2.

**End of Study: The end of study date is defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up) as applicable.**



## 4. SUBJECT ELIGIBILITY

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening).

Before any study-specific procedure, the appropriate written informed consent must be obtained (see Section 11.1).

### 4.1 Inclusion Criteria

4.1.1 Subject has provided informed consent

4.1.2 Histologically confirmed diagnosis of malignant melanoma

4.1.3 Stage IIIB, IIIC, IVM1a, IVM1b, or IVM1c disease that is not suitable for surgical resection

4.1.4 Phase 1b: Treatment naïve: Must not have received any prior systemic anticancer treatment consisting of chemotherapy, immunotherapy, or targeted therapy for unresected stage IIIB to IV melanoma. Note: Subjects who received prior adjuvant therapy for melanoma will not be excluded. However, if the subject received adjuvant therapy, the subject must have completed therapy at least 6 months prior to enrollment. No prior talimogene laherparepvec, ipilimumab, other CTLA-4 inhibitors, programmed death-1 (PD-1) inhibitors, or tumor vaccine is allowed, even if given in the adjuvant setting.

4.1.5 Phase 2:

- Either treatment naïve or received only one line of systemic anticancer therapy if *BRAF* wild-type or up to two lines of systemic anticancer therapy including one *BRAF* inhibitor-containing regimen if *BRAF* mutant. Treatments given in an adjuvant setting (eg, interferon, radiotherapy, isolated limb perfusion, or investigational agents) are not considered as prior lines of therapy. No prior talimogene laherparepvec, other oncolytic virus therapies, or tumor vaccines are allowed, even if given in the adjuvant setting.
- Subjects treated with prior ipilimumab must have had PR, CR, or at least 6 months of stable disease followed by disease progression
- Subjects previously treated with anti-PD1 or anti-CTLA-4 antibodies must not have discontinued therapy due to any treatment-related adverse events including immune-related adverse events. Prior treatment-related adverse events should also be fully resolved and not requiring treatment for at least 28 days prior to randomization.

4.1.6 Measurable disease defined as one or both of the following:

- at least 1 melanoma lesion that can be accurately and serially measured in at least 2 dimensions and for which the longest diameter is ≥ 10 mm and with perpendicular diameter ≥ 5 mm as measured by contrast-enhanced or spiral computed tomography (CT) scan for visceral or nodal/soft tissue disease. Lymph nodes must measure > 15 mm in their short axis to be considered measurable by CT scan.
- at least 1 superficial cutaneous or subcutaneous melanoma lesion that can be accurately and serially measured in at least 2 dimensions and for which the short axis is ≥ 5 mm as measured by calipers

4.1.7 Injectable disease (ie, suitable for direct injection or through the use of ultrasound [US] guidance) defined as follows:

- at least 1 injectable cutaneous, subcutaneous, or nodal melanoma lesion ≥ 5 mm in longest diameter

4.1.8 Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1

4.1.9 Male or female, age ≥ 18 years

4.1.10 Adequate hematologic function as follows:

- absolute neutrophil count (ANC) ≥ 1.5 x $10^9$/L
- platelet count ≥ 100 x $10^9$/L
- hemoglobin ≥ 9 g/dL (without need for hematopoietic growth factor or transfusion support)

4.1.11 Adequate renal function as follows:

- serum creatinine ≤ 1.5 x upper limit of normal (ULN), or 24-hour creatinine clearance ≥ 50 cc/min. (Note: Creatinine clearance need not be determined if the baseline serum creatinine is within normal limits)

4.1.12 Adequate hepatic function as follows:

- serum bilirubin ≤ 1.5 x ULN
- aspartate amino transferase (AST) ≤ 2.5 x ULN
- alanine amino transferase (ALT) ≤ 2.5 x ULN

4.1.13 Coagulation:

- international normalization ratio (INR) or prothrombin time (PT) ≤ 1.5 x ULN unless the subject is receiving anticoagulant therapy as long as PT and partial thromboplastin time (PTT)/ activated PTT (aPTT) is within therapeutic range of intended use of anticoagulants
- PTT or aPTT ≤ 1.5 x ULN unless the subject is receiving anticoagulant therapy as long as PT and PTT/aPTT is within therapeutic range of intended use of anticoagulants



**4.2 Exclusion Criteria**

4.2.1 Primary uveal or mucosal melanoma

4.2.2 History or evidence of melanoma associated with immunodeficiency states (eg, hereditary immune deficiency, organ transplant, or leukemia)

4.2.3 Phase 1b: History or evidence of central nervous system (CNS) metastases

4.2.4 Phase 2: Clinically active cerebral melanoma metastases. Subjects with up to 3 cerebral metastases, and neurological performance status of 0 may be enrolled, provided that all lesions have been adequately treated with stereotactic radiation therapy, craniotomy, or Gamma knife therapy, with no evidence of progression, and have not required steroids, for at least 2 months prior to enrollment.

4.2.5 History of other malignancy within the past 3 years with the following exceptions:

- malignancy treated with curative intent and with no known active disease present and has not received chemotherapy for ≤ 3 years before enrollment or randomization and felt to be at low risk for recurrence by the treating physician
- adequately treated non-melanoma skin cancer without evidence of disease at the time of enrollment or randomization

- adequately treated cervical carcinoma in situ without evidence of disease at the time of enrollment or randomization
- adequately treated breast ductal carcinoma in situ without evidence of disease at the time of enrollment or randomization
- prostatic intraepithelial neoplasia without evidence of prostate cancer at the time of enrollment or randomization
- adequately treated superficial or in-situ carcinoma of the bladder without evidence of disease at the time of enrollment or randomization

4.2.6 History or evidence of symptomatic autoimmune disease (such as pneumonitis, glomerulonephritis, vasculitis, rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, scleroderma, or other), or history of autoimmune disease that required systemic treatment (ie, use of corticosteroids, immunosuppressive drugs or biological agents used for treatment of autoimmune diseases) in past 2 months prior to enrollment. Replacement therapy (eg, thyroxine for hypothyroidism, insulin for diabetes mellitus) is not considered a form of systemic treatment for autoimmune disease.

4.2.7 Evidence of clinically significant immunosuppression for any reason such as:

- organ transplant
- any severe congenital or acquired cellular and/or humoral immune deficiency
- concurrent opportunistic infection
- requires concomitant treatment with immunosuppressive agents, including CTLA-4 agonists, or chronic oral or systemic steroid medication use at a dose of > 7.5 mg/day of prednisone or equivalent (except for management of AEs or CNS metastases during the course of the study)



4.2.8 Active herpetic skin lesions or prior complications of HSV-1 infection (eg, herpetic keratitis or encephalitis)

4.2.9 Requires intermittent or chronic systemic (intravenous or oral) treatment with an antiherpetic drug (eg, acyclovir), other than intermittent topical use

4.2.11 Known human immunodeficiency virus (HIV) disease (if clinically suspected HIV infection, subject requires negative test)

4.2.12 Known acute or chronic hepatitis B or hepatitis C infection (if clinically suspected hepatitis B or hepatitis C infection, subject requires negative test. However, if positive results are not indicative of true active or chronic infection, the subject may be enrolled/randomized after approval is obtained from the Amgen medical monitor).

4.2.13 Female subject is pregnant or breast-feeding, or planning to become pregnant during study treatment and through 3 months after the last dose of study treatment

4.2.14 Female subject of childbearing potential who is unwilling to use acceptable methods of effective contraception during study treatment and through 3 months after the last dose of talimogene laherparepvec or ipilimumab, whichever is later. (Note: Women not of childbearing potential are defined as: Any female who is post-menopausal [age $\geq$ 55 years with cessation of

menses for 12 or more months or less than 55 years with postmenopausal status confirmed by follicle-stimulating hormone [FSH] in the postmenopausal range] or who have had a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy).

4.2.15 Male subject who is unwilling to use acceptable method of effective contraception during ipilimumab treatment and through 3 months after the last dose of ipilimumab

4.2.16 Phase 1b: Prior talimogene laherparepvec, ipilimumab, other CTLA-4 inhibitors, programmed death-1 (PD-1) inhibitors, or tumor vaccine

4.2.17 Phase 2: Prior talimogene laherparepvec, other oncolytic virus therapies, or tumor vaccines

4.2.18 Currently receiving or less than 28 days since ending systemic anticancer treatment consisting of chemotherapy, immunotherapy, or targeted therapy for unresected stage IIIB to IV melanoma

4.2.19 Currently receiving treatment in another investigational device or drug study, or less than 30 days since ending treatment on another investigational device or drug study(s)

4.2.20 Other investigational procedures while participating in this study are excluded

4.2.21 Subject has known sensitivity to any of the products or components to be administered during dosing

4.2.22 Subject previously has entered this study

4.2.23 Subject likely to not be available to complete all protocol-required study visits or procedures and/or to comply with all required study procedures to the best of the subject and investigator's knowledge

4.2.24 History or evidence of any other clinically significant disorder, condition, or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion

4.2.25 Sexually active subject who is unwilling to use a barrier method (preferably latex condom) to avoid potential viral transmission during sexual contact during and within 30 days after treatment with talimogene laherparepvec

4.2.26 Subject who is unwilling to minimize exposure with his/her blood or other body fluids to individuals who are at higher risks for HSV-1 induced complications (immunosuppressed individuals, HIV-positive individuals, pregnant women, or children under the age of 1 year) during talimogene laherparepvec treatment and through 30 days after the last dose of talimogene laherparepvec

## 5. SUBJECT ENROLLMENT

Before subjects may be entered into the study, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form, and all other subject information and/or recruitment material (see Section 11.2). All subjects must personally sign and date the consent form





Chesney JA, *et al. J Immunother Cancer* 2023; 11:e006270. doi: 10.1136/jitc-2022-006270

before commencement of study-specific procedures (ie, non-standard of care procedures).

All subjects who enter into the screening period for the study (defined as the point when the subject signs the informed consent) must be registered as screened subjects in the electronic trial operation (ETO) system and will receive a unique subject identification number before any study-specific procedures are performed. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject. The subject identification number will not be the same as the randomization number assigned for subjects participating in the phase 2. The subject identification number must remain constant throughout the entire clinical study; it must not be changed at the time of rescreening, enrollment, or randomization.

Subjects that are determined not eligible after screening must be screen-failed in the ETO system and the reason for the screen-failure provided. Subjects who do not meet all eligibility criteria may be rescreened once at the discretion of the investigator. If a subject is being rescreened, he or she may need to reconsent to the study to ensure that the IRB/IEC approved main informed consent form is signed within 28 days of enrollment or randomization. Subjects that are determined not eligible after rescreen must be screen-failed in the ETO system and the reason for the screen-failure provided. Subjects may only be enrolled or randomized once into this study.

Upon confirmation of eligibility, the site staff will use the ETO system to enroll or randomize a subject. For the phase 1b portion the subjects will be considered enrolled upon registering the subject as enrolled in the ETO system. For the phase 2 portion the subjects will be considered enrolled upon randomization in the ETO system.



### 5.1 Randomization During Phase 2

Upon confirmation of eligibility, the site staff will use the ETO system to randomize a subject.

The ETO system will assign a randomization number. Approximately 200 subjects will be randomized in phase 2. Subjects randomized before amendment 2 will be stratified according to stage of disease (stage IIIB/C, stage IVM1a, and stage IVM1b vs stage IVM1c) and *BRAF* V600E (mutation vs mutation not present). Subjects randomized after amendment 2 will be stratified according to stage of disease (stage IIIB/C and IVM1a vs stage IVM1b and IVM1c) and prior therapy (treatment naïve vs previously treated with



Chesney JA, *et al. J Immunother Cancer* 2023; 11:e006270. doi: 10.1136/jitc-2022-006270

systemic anticancer immunotherapy vs previously treated with systemic anticancer treatment other than immunotherapy).

Subjects will be randomized with a 1:1 ratio to receive the following:

- arm 1: talimogene laherparepvec plus ipilimumab
- arm 2: ipilimumab

Following randomization via the ETO system, study treatment must commence within 5 days.

Eligible subjects must be registered as a randomized subject in the ETO system before the administration of protocol-specified therapy.

This is an open label trial. The investigator, site staff, and subject will be aware of the treatment to which the subject was randomized.

## 6. TREATMENT PROCEDURES

Talimogene laherparepvec is the investigational product administered in this study and will be provided by Amgen. Ipilimumab is approved in some countries for treatment of, unresectable or metastatic melanoma but may be considered an investigational product in other countries. Ipilimumab will be supplied by Amgen when required by local regulations.

An Investigational Product Instruction Manual (IPIM) containing detailed information regarding the storage, preparation, administration, and destruction of talimogene laherparepvec and ipilimumab will be provided separately.

### 6.1 Talimogene Laherparepvec

Talimogene laherparepvec will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures.

#### 6.1.1 Talimogene Laherparepvec Dosage, Administration, and Schedule

Talimogene laherparepvec will be administered to subjects enrolled in the phase 1b or randomized to arm 1 of the phase 2 study. Talimogene laherparepvec must be prepared and administered by a qualified and, where applicable, licensed healthcare professional. Subjects should be assessed clinically for toxicity prior to each dose using the CTCAE version 3 (Appendix A). Complete blood count with differential and chemistry panels including liver function laboratory tests (ALT, AST, and total bilirubin) must be obtained according to the schedule of assessments (see Sections 7.1 and 7.2), and the results

should be checked before each treatment. Dosing will occur only if these test values are acceptable, per Section 6.1.2.

Talimogene laherparepvec will be only administered by intratumoral injection into injectable cutaneous, subcutaneous, and nodal tumors with or without image US guidance. Talimogene laherparepvec must not be administered into visceral organ metastases. The initial dose of talimogene laherparepvec is up to 4.0 mL of $10^6$ PFU/mL. Subsequent doses of talimogene laherparepvec are up to 4.0 mL of $10^8$ PFU/mL. When talimogene laherparepvec and ipilimumab are administered on the same day, talimogene laherparepvec must be administered before ipilimumab.

On day 1 of week 1 the first dose of talimogene laherparepvec will be up to 4.0 mL of $10^6$ PFU/mL. The second injection up to 4.0 mL of $10^8$ PFU/mL should be administered 3 weeks after the initial injection (ie, no sooner than day 1 of week 4 but should not be delayed more than 5 days after the 3 week time point). Subsequent injections up to 4.0 mL of $10^8$ PFU/mL should be given every 2 weeks $\pm$ 3 days.

The maximum volume of talimogene laherparepvec administered at any dose is 4.0 mL for any individual lesion. The maximum dose in any one treatment is 4.0 mL. Investigators are encouraged to use the maximum amount whenever lesions allow. Dose reduction for AEs is not allowed. However if in the course of administration of talimogene laherparepvec the subject cannot tolerate the full dose due to an injection-related AE such as pain, the total volume given should be recorded, and the reason for intolerance should be documented as an AE.

The recommended volume of talimogene laherparepvec to be injected into the tumor(s) is dependent on the size of the tumor(s) and should be determined according to the injection volume guideline in Table 1:

**Table 1. Talimogene Laherparepvec Injection Volume Guideline Based on Tumor Size**

| Tumor Size (longest dimension) | Maximum Injection Volume |
|---|---|
| > 5.0 cm | 4.0 mL |
| > 2.5 cm to 5.0 cm | 2.0 mL |
| > 1.5 cm to 2.5 cm | 1.0 mL |
| > 0.5 cm to 1.5 cm | 0.5 mL |
| $\leq$ 0.5 cm | 0.1 mL |

All reasonably injectable lesions (cutaneous, subcutaneous and nodal disease that can be injected with or without ultrasound [US] guidance) should be injected with the maximum dosing volume available on an individual dosing occasion. On each treatment day, prioritization of injections is recommended as follows:

- any new injectable tumor that has appeared since the last injection
- by tumor size, beginning with the largest tumor
- any previously uninjectable tumor(s) that is now injectable

It is recommended that each lesion should receive the maximum amount possible to inject due to tumor properties at each visit before moving on to the next lesion, using the prioritization model above and the injection volume guideline based on tumor size per Table 1. Lesions should be injected until the maximum volume per day (4.0 mL) has been reached or there are no further injectable lesions, whichever comes first.

Subjects will be treated with talimogene laherparepvec until CR, all injectable tumors have disappeared, confirmed disease progression per the modified irRC (Appendix E), or intolerance of study treatment, whichever occurs first. Due to the mechanism of action, subjects may experience growth in existing tumors or the appearance of new tumors prior to maximal clinical benefit of talimogene laherparepvec. Therefore, talimogene laherparepvec dosing should be continued provided that the subject has no evidence of confirmed disease progression per modified irRC and is able to tolerate the treatment.

The dose, start date, stop date, and lot number of talimogene laherparepvec are to be recorded on the electronic CRF.



### 6.1.2 Talimogene Laherparepvec Dosage Delays, Withholding, and Restarting

Dose reductions of talimogene laherparepvec are not permitted, other than with respect to a reduction in the volume injected due to a disease response. If a subject experiences a toxicity that meets the DLT definition in the phase 1b or any of the following treatment-related toxicities in the phase 2, talimogene laherparepvec administration should be delayed until the DLT has resolved to at least CTCAE grade 1 or baseline:

- grade 2 or greater immune-mediated adverse events, with the exception of vitiligo
- grade 2 or greater allergic reactions
- any other grade 3 or greater hematologic or non-hematologic toxicity

Subjects who are receiving talimogene laherparepvec may not receive systemic antiherpetic drugs (eg, acyclovir, valacyclovir, famciclovir), but may receive a topically administered antiherpetic drug more than 20 cm from a talimogene laherparepvec injection site. Treatment with talimogene laherparepvec should be permanently discontinued if, in the opinion of the investigator, the subject develops clinical evidence of any systemic herpes infection (such as encephalitis or disseminated infection).

If talimogene laherparepvec treatment was delayed by > 1 week, that dose will be deemed to have been missed and the subject will proceed to the next scheduled treatment visit. If the subject requires corticosteroid dosing of > 7.5 mg prednisone daily (or equivalent) and/or other immunosuppressive medication for ipilimumab related toxicities, talimogene laherparepvec dosing must be held until the corticosteroid dose has decreased to 7.5 mg prednisone daily (or equivalent) and the administration of the other immunosuppressive medication has discontinued.

If talimogene laherparepvec dosing is delayed by more than 4 weeks from the date of the planned dose (ie, approximately 6 weeks from the previous dose) due to the occurrence of a DLT or AE that is considered related to talimogene laherparepvec, the subject must be permanently taken off talimogene laherparepvec treatment. In the event talimogene laherparepvec is delayed or permanently discontinued for talimogene laherparepvec-related toxicity, ipilimumab will continue to be administered until a total of 4 infusions, confirmed disease progression per the modified irRC (Appendix E), or unacceptable ipilimumab-related toxicity, whichever occurs first. However, in the event talimogene laherparepvec is permanently discontinued prior to the administration of the first dose of ipilimumab during the phase 1b part of the study, the subject must be permanently taken off study treatment and will not receive ipilimumab as part of the study.

If talimogene laherparepvec dosing is delayed by more than 4 weeks from the date of the planned dose (ie, approximately 6 weeks from the previous dose) for reasons other than treatment-related toxicity, the case must be reviewed by the Amgen medical monitor in conjunction with the investigator to determine if the subject can resume talimogene laherparepvec therapy as long as the subject's disease has not progressed per the modified irRC (Appendix E).

Talimogene laherparepvec is to be permanently discontinued for subjects meeting any of the following criteria:

- The subject, for any reason, requires treatment with another anticancer therapeutic agent for treatment of the study disease (other than the exceptions noted in Section 6.6). In this case, discontinuation from the treatment occurs immediately upon introduction of the new agent.
- Confirmed **progressive disease (**PD**)** occurs as defined per the modified irRC (Appendix E).
- A grade 2 or greater immune-mediated adverse event (with the exception of vitiligo) or allergic reactions attributed to talimogene laherparepvec that would require a dose delay of greater than 4 weeks from the date of the planned dose (ie, approximately 6 weeks from the previous dose).

  NOTE: immune-mediated glomerulonephritis, vasculitis, and pneumonitis and exacerbation of psoriasis have been observed in subjects receiving talimogene laherparepvec in clinical trials. Most of these subjects had a history of other autoimmune disease and/or prior treatment with agents that offered plausible alternative etiologies, however, immune-mediated adverse events can potentially involve any organ system.
- Any other talimogene laherparepvec-related non-hematologic or hematologic toxicities grade 3 or greater occur that, in the opinion of the investigator, would require a dose delay of greater than 4 weeks from the date of the planned dose (ie, approximately 6 weeks from the previous dose).
- The subject develops clinical evidence of any systemic herpes infection (such as encephalitis or disseminated infection).
- A female subject becomes pregnant or fails to use acceptable method(s) of effective contraception (for those subjects who are able to conceive).
- A female subject breast feeds while on study treatment.
- Concurrent medical illness that, in the judgment of the investigator, would make continued treatment with talimogene laherparepvec dangerous for the subject.

For additional information related special warnings and precautions for the use of talimogene laherparepvec please refer to the latest version of the Talimogene Laherparepvec Investigator's Brochure.

### 6.2 Ipilimumab

Ipilimumab is commercially available in some countries and may be provided by Amgen as required by local regulation. The investigator may be responsible for obtaining supplies of ipilimumab if approved by a regulatory authority and commercially available in the respective country for treatment of the target study population. For complete prescribing information, please see the most current package or prescribing inserts.

Additional details regarding the storage, preparation, administration, and destruction of ipilimumab will be provided in the IPIM separately.

### 6.2.1 Ipilimumab Dosage, Administration, and Schedule

Ipilimumab must be prepared and administered by a qualified and, where applicable, licensed healthcare professional. Subjects should be assessed clinically for toxicity prior to each dose of ipilimumab using the CTCAE version 3 (Appendix A). Complete blood count with differential, chemistry panels including liver function laboratory tests (ALT, AST, and total bilirubin), and thyroid function tests (thyroid stimulating hormone [TSH], and free thyroxine [free T4]) must be obtained according to the schedule of assessments (see Sections 7.1 and 7.2) or more frequently if clinically indicated, and the results should be checked before each ipilimumab treatment. Dosing will occur only if these test values are acceptable, per Section 6.2.2.

Ipilimumab at a dose of 3 mg/kg will be administered intravenously over 90 (± 15) minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein-binding in-line filter every 3 weeks (± 3 days) for a total of 4 infusions at following visits:

- phase 1b and arm 1 of phase 2: day 1 week 6, day 1 week 9, day 1 week 12, and day 1 week 15
- arm 2 of phase 2: day 1 week 1, day 1 week 4, day 1 week 7, and day 1 week 10

When talimogene laherparepvec and ipilimumab are administered on the same day, ipilimumab must be administered after talimogene laherparepvec. In the event talimogene laherparepvec is delayed or permanently discontinued for talimogene laherparepvec-related toxicity, ipilimumab will continue to be administered until a total of 4 infusions, disease progression per the modified irRC (Appendix E), or unacceptable ipilimumab-related toxicity, whichever occurs first. However, in the event talimogene laherparepvec is permanently discontinued prior to the administration of the first dose of ipilimumab during the phase 1b part of the study, the subject must be permanently taken off study treatment and will not receive ipilimumab as part of the study.

The dose, start date, and stop date of ipilimumab are to be recorded on the electronic CRF.

### 6.2.2 Ipilimumab Dosage Withholding and Restarting

This section describes the guidelines for the management of ipilimumab related immune-mediated toxicities. These guidelines are not intended to be all inclusive. For additional information regarding the management of ipilimumab related toxicities, please refer to the most current regional package or prescribing inserts. In addition, please

consult the most recent regional risk evaluation and mitigation strategy (REMS) for ipilimumab, if applicable to your region.

Ipilimumab can result in severe and fatal immune-mediated adverse reactions due to T-cell activation and proliferation. These immune-mediated reactions may involve any organ system; however, the most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathies. The majority of these immune-mediated reactions initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of ipilimumab (Yervoy®, 2013). It is important to recognize and address the immune-mediated symptoms early during the course of ipilimumab treatment. Assess subjects for signs and symptoms of enterocolitis, dermatitis, neuropathy and endocrinopathy, and evaluate complete blood count with differential and chemistry panel including liver function tests (ALT, AST, and total bilirubin) and thyroid function tests (TSH and free T4) at screening and before each dose of ipilimumab as described in Section 7 and more frequently if clinically indicated.

Dose reductions of ipilimumab are not permitted.

The ipilimumab dose must be withheld for the following:

- grade 2 or grade 3 immune-mediated dermatitis
- grade 2 immune-mediated enterocolitis
- grade 2 immune-mediated hepatotoxicity (ie, AST or ALT > 2.5 to 5 x ULN or total bilirubin > 1.5 to 3 x ULN)
- grade 2 immune-mediated neuropathy
- grade 2 or grade 3 immune-mediated endocrinopathy or any symptomatic endocrinopathy (until complete resolution or stable on hormone therapy)

For subjects with complete or partial resolution of adverse reactions (grade 0 - 1), and who are receiving 7.5 mg or less prednisone or equivalent per day, resume ipilimumab at a dose of 3 mg/kg every 3 weeks until administration of all 4 planned doses or 16 weeks from first dose, whichever occurs earlier (except immune-mediated endocrinopathy, which requires either complete resolution or stability on non-steroid hormonal therapy as described in Section 6.2.2.5).

Of note, unless an alternative etiology has been identified, signs and symptoms consistent with any of the above disease processes should be considered immune-mediated.

Permanently discontinue ipilimumab for any of the following:

- grade 3 or greater immune-mediated enterocolitis
- grade 3 or greater immune-mediated hepatitis (ie, AST or ALT > 5 x ULN or total bilirubin > 3 x ULN)
- grade 4 immune-mediated dermatitis (including Stevens-Johnson syndrome, toxic epidermal necrolysis or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations)
- grade 3 or greater immune-mediated neuropathy (including motor or sensory neuropathy, Guillain-Barré syndrome, or myasthenia gravis)
- grade 3 or greater, or otherwise clinically significant other immune-mediated reactions including any of the following:
  - hemolytic anemia
  - angiopathy, myocarditis, pericarditis, temporal arteritis, or vasculitis
  - autoimmune thyroiditis
  - blepharitis, conjunctivitis, episcleritis, iritis, scleritis, or uveitis
  - pancreatitis
  - meningitis
  - arthritis or polymyalgia rheumatica
  - nephritis
  - pneumonitis
  - psoriasis or leukocytoclastic vasculitis
- Persistent grade 2 immune-mediated adverse reactions that do not resolve within 16 weeks from administration of first dose of ipilimumab
- Inability to reduce corticosteroid dose to 7.5 mg or less of prednisone or equivalent per day within 16 weeks from administration of first dose of ipilimumab
- Failure to complete full treatment course within 16 weeks from administration of first dose
- Any grade 3 or greater bronchospasm or other hypersensitivity reaction
- Any other non-laboratory grade 4 treatment-related AE
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued ipilimumab dosing

For subjects enrolled in the phase 1b or randomized to arm 1 of phase 2: In the event ipilimumab is skipped or permanently discontinued for ipilimumab-related toxicity, talimogene laherparepvec will continue to be administered every 2 weeks until CR, all injectable tumors have disappeared, disease progression per the modified irRC (Appendix E), or intolerance of study treatment, whichever occurs first. However, if the subject requires corticosteroid dosing of > 7.5 mg prednisone daily (or equivalent) for

ipilimumab related toxicities, talimogene laherparepvec dosing must be held until the corticosteroid dose has decreased to ≤ 7.5 prednisone daily (or equivalent).

#### 6.2.2.1 Management of Ipilimumab-related Enterocolitis

Ipilimumab can result in severe or fatal inflammation of the gastrointestinal tract (with potential risk of bowel perforation) most commonly manifested as diarrhea or colitis. Advice subjects to immediately report changes in bowel movements. Monitor subjects for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, mucus or blood in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic subjects, rule out infectious etiologies and consider endoscopic evaluation for persistent or severe symptoms.

Permanently discontinue ipilimumab in subjects with ≥ grade 3 enterocolitis (≥ 7 stools/day over baseline, peritoneal signs consistent with bowel perforation, ileus, fever). Consider endoscopic evaluation to rule out bowel perforation; if bowel perforation is present, do not administer corticosteroid. Initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. Upon improvement to grade 1 or less, initiate corticosteroid taper and continue to taper over at least one month. In clinical trials, rapid corticosteroid tapering resulted in recurrence or worsening symptoms of enterocolitis in some subjects (Yervoy®, 2013). Subjects with ongoing ≥ grade 3 enterocolitis despite systemic corticosteroid should be continually evaluated for evidence of gastrointestinal perforation or peritonitis. Consider repeat endoscopy and alternative immunosuppressive therapy.

Withhold ipilimumab dosing for grade 2 enterocolitis (4 to stools/day over baseline, abdominal pain, blood or mucus in stool); administer antidiarrheal treatment and, if persistent for more than one week, initiate systemic corticosteroids at a dose of 0.5 mg/kg/day prednisone or equivalent. Continue steroids until improvement to mild severity (grade 1) or resolution (grade 0). For subjects with complete or partial resolution of adverse reactions (grade 0 - 1), and who are receiving 7.5 mg or less prednisone or equivalent per day, resume ipilimumab per Section 6.2.2.

#### 6.2.2.2 Management of Ipilimumab-related Hepatitis

Ipilimumab can result in severe and fatal inflammation of the liver most commonly manifested as elevations of transaminases and hyperbilirubinemia (Yervoy®, 2013). Monitor liver function tests (hepatic transaminase [AST and ALT] and total bilirubin levels) and assess subjects for signs and symptoms of hepatotoxicity before each dose

of ipilimumab. In subjects with hepatotoxicity, rule out infectious or malignant causes and increase frequency of liver function test monitoring, if clinically indicated, until resolution. Unless an alternative etiology has been identified, laboratory abnormalities consistent with hepatitis should be considered immune-mediated.

Permanently discontinue ipilimumab in subjects with ≥ grade 3 hepatotoxicity (ie, AST or ALT > 5 x ULN or total bilirubin > 3 x ULN) and administer systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When liver function tests show sustained improvement or return to baseline, initiate corticosteroid tapering and continue to taper over 1 month. For ongoing ≥ grade 3 hepatitis consider alternative immune-suppressive therapy. Across the clinical development program for ipilimumab, mycophenolate treatment has been administered in subjects who have persistent ≥ grade 3 hepatitis despite high-dose corticosteroids (Yervoy®, 2013).

Withhold ipilimumab in subjects with grade 2 hepatotoxicity (ie, AST or ALT > 2.5 to 5 x ULN or bilirubin > 1.5 to 3.0 x ULN). For subjects with complete or partial resolution of adverse reactions (grade 0 - 1) (ie, AST or ALT ≤ 2.5 x ULN or return to baseline and bilirubin ≤ 1.5 or return to baseline), and who are receiving 7.5 mg or less prednisone or equivalent per day, resume ipilimumab per Section 6.2.2.

#### 6.2.2.3 Management of Ipilimumab-related Dermatitis

Ipilimumab can result in severe and fatal inflammation of the skin, including Stevens-John syndrome and toxic epidermal necrolysis (Yervoy®, 2013). Advise subjects to report skin-related changes. Monitor subjects for signs and symptoms of dermatitis such as rash and pruritus. Unless an alternate etiology has been identified, signs or symptoms of dermatitis should be considered immune-mediated.

Permanently discontinue ipilimumab in subjects with ≥ grade 4 immune-mediated dermatitis including Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations. Administer systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When dermatitis is controlled, corticosteroid tapering should occur over a period of at least 1 month.

Withhold ipilimumab dosing in subjects with grade 2 or 3 signs and symptoms of dermatitis (ie, non-localized or diffuse rash covering ≤ 50% of skin surface). Administer topical or systemic corticosteroids if there is no improvement of symptoms within 1 week. For subjects with complete or partial resolution of adverse reactions (grade 0-1), and

who are receiving 7.5 mg or less prednisone or equivalent per day, resume ipilimumab per Section 6.2.2.

#### 6.2.2.4 Management of Ipilimumab-related Neuropathies

Ipilimumab can cause serious and fatal immune-mediated neurological adverse reactions, including sensory and motor neuropathy, Guillain-Barré syndrome, and myasthenia gravis (Yervoy®, 2013). Subjects should be advised to immediately report signs and symptoms, such as muscle weakness or sensory alterations. Monitor subjects for symptoms of motor or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, or paresthesia. Unless an alternative etiology has been identified, signs and symptoms of neuropathy should be considered immune-mediated.

Permanently discontinue ipilimumab in subjects with ≥ grade 3 motor or sensory neuropathy (interfering with daily activities or life threatening) such as Guillain-Barré-like syndrome or myasthenia gravis. Institute appropriate medical intervention for management of ≥ grade 3 neuropathies. Consider initiation of systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent for ≥ grade 3 neuropathies.

Withhold ipilimumab dosing in subjects with grade 2 neuropathy (not interfering with daily activities). Introduce medical intervention for grade 2 neuropathy as appropriate. Resume ipilimumab when symptoms resolved or return to baseline per Section 6.2.2.

#### 6.2.2.5 Management of Ipilimumab-related Endocrinopathies

Ipilimumab can cause severe to life threatening endocrinopathies, most commonly manifested as hypopituitarism, adrenal insufficiency (including adrenal crisis), and hyper- or hypothyroidism (Yervoy®, 2013). Monitor subjects for clinical signs and symptoms of hypophysitis, adrenal insufficiency (including adrenal crisis), and hyper-or hypothyroidism. Subjects may present with fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms which may resemble other causes such as brain metastasis or underlying disease. Unless an alternate etiology has been identified, signs or symptoms of endocrinopathies should be considered immune-mediated.

Monitor thyroid function tests and clinical chemistries at the start of treatment, before each dose, and as clinically indicated based on signs and symptoms. In a limited number of subjects, hypophysitis was diagnosed by imaging studies through enlargement of the pituitary gland (Yervoy®, 2013).

Withhold ipilimumab dosing for ≥ grade 2 immune-mediated adverse reactions or any symptomatic endocrinopathy until complete resolution or stable on hormonal therapy such as levothyroxine for thyroid hormone replacement. Initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent, and initiate appropriate hormone replacement therapy. For subjects with complete or partial resolution of adverse reactions (grade 0 - 1) or who are stable on hormone replacement therapy, and who are receiving 7.5 mg or less prednisone or equivalent per day, resume ipilimumab per Section 6.2.2.

#### 6.2.2.6 Management of Other Ipilimumab-related AEs, Including Ocular Manifestations

Across the clinical development program for ipilimumab, the following likely immune- mediated adverse reactions were also reported with less than 1% incidence: myocarditis, angiopathy, temporal arteritis, vasculitis, polymyalgia rheumatica, conjunctivitis, blepharitis, episcleritis, scleritis, leukocytoclastic vasculitis, erythema multiforme, psoriasis, pancreatitis, arthritis, and autoimmune thyroiditis (Yervoy®, 2013).

Permanently discontinue ipilimumab for other clinically significant or ≥ grade 3 immune-mediated AEs, including ocular manifestations, angiopathy and arteritis. Initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent for clinical significant or ≥ grade 3 immune-mediated adverse reactions.

Administer corticosteroid eye drops to subjects who develop uveitis, iritis, or episcleritis. Permanently discontinue ipilimumab for immune-mediated ocular disease that, in the judgment of the investigator, is unresponsive to local immunosuppressive therapy.

### 6.3 Other Protocol-required Therapies

All other protocol-required therapies including, topical anesthetic or an injectable local anesthetic medications used for pretreatment of the talimogene injection site and oral or systemic steroids for management of ipilimumab immune-mediated AEs that are commercially available are not provided or reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies of these protocol-required therapies.

Additional details regarding these protocol-required therapies are provided in the IPIM.

### 6.4 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.5.

All prescription and nonprescription concomitant medication administered up to 28 days prior to enrollment/randomization, on an ongoing basis at enrollment/randomization, as well as changes in such concomitant medication, and, any new concomitant medication taken while the subject is on study, should be recorded on the appropriate CRF either the 30 days after the last dose of talimogene laherparepvec or 60 days after the last dose of ipilimumab, whichever is later. The therapy name, indication, dose, unit, frequency, start date and stop date will be collected.

Investigators should use supportive care agents in compliance with their respective regional label. Investigators may not use supportive care agents as part of a separate clinical trial.

### 6.5 Excluded Treatments During Study Period

Subjects must not use any of the following therapies during screening or treatment period:

- other investigational agents or procedures
- concurrent experimental or approved anti-tumor therapies other than study drugs and radiation therapy required for palliation
- any other CTLA-4 inhibitors or agonists
- PD-1 and PD-L1 inhibitors
- immunosuppressive agents (with the exception of treatment for AEs [see Section 6.2.2] and CNS metastases [see Section 6.6])
- antiherpetic drugs, other than if topically administered > 20 cm from a talimogene laherparepvec injection site
- any surgery or radiotherapy for melanoma (other than the exceptions noted in Section 6.6)
- Subjects must not schedule any elective surgeries (other than the exceptions noted in Section 6.6) during the treatment period and for at least 30 days after the last administration of study drugs. If a subject undergoes any unexpected surgery during the course of the study, all study treatments must be withheld and the investigator or designee should notify the sponsor medical monitor as soon as possible. A subject may be allowed to resume study drugs if both the investigator and sponsor medical monitor agree to restart study therapy.

The eligibility criteria describe other medications and procedures which are prohibited in this study (refer to Section 4).

Progression should be confirmed in otherwise clinically stable subjects before switching to alternative therapies.

### 6.6 Other Treatment Procedures

Investigators may choose to resect lesions which become suitable for resection to render the subject free of macroscopic disease. Additionally, biopsies may be taken of cutaneous or subcutaneous lesions for tumor analysis during study. However, resection of lesions may only occur following the final ipilimumab dose and the subsequent tumor assessment. Tumor resections in which melanoma is contained within the resected tissue will render subjects unevaluable for response assessments post-operatively (Appendix E).

Local radiation treatment to the site of bone and other metastasis will be permitted for palliative pain management at any time during the study. If a subject undergoes local radiation, the investigator or designee should notify the sponsor medical monitor as soon as possible and the treatment should be recorded in the source document and CRF.

If a subject demonstrates evidence of new or worsening CNS metastases, all study treatments should be withheld and the investigator or designee should notify the sponsor medical monitor as soon as possible. Subjects may be allowed to remain on study after discussion between the sponsor medical monitor and the investigator to determine the appropriateness of treatment resumption provided CNS lesions can be treated with stereotactic radiotherapy (SRS), GammaKnife, or craniotomy. After approval is obtained from the sponsor medical monitor, subjects may be allowed to reinitiate talimogene laherparepvec and/or ipilimumab treatment per Sections 6.1 and 6.2, respectively, following SRS only when dosing of corticosteroid is below 1.1 mg dexamethasone, 7.5 mg prednisone or equivalent. If higher doses of a corticosteroid are used, talimogene laherparepvec and/or ipilimumab must be held until that dose level is reached during the period of steroid tapering.

## 7. STUDY PROCEDURES

### 7.1 Schedule of Assessments

The schedule of the assessments for the phase 1b and phase 2 are summarized in Table 2, Table 3 and Table 4 respectively.

## Table 2. Schedule of Assessments for Phase 1b

| | Screening | | | Study Treatment[d,w] (week number) | | | | | | | | | | | | | | | | | Follow-up | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study Procedures | ≤ 28 days[a] | ≤ 10 days[b] | ≤ 72 hour[c] | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18[v] | Safety[e] | Survival[f] |
| **General Assessments** | | | | | | | | | | | | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | | | | | | | | | | | |
| Review of Eligibility Criteria | X | | | | | | | | | | | | | | | | | | | | | | |
| Demographics (sex, age, race, and ethnicity) | X | | | | | | | | | | | | | | | | | | | | | | |
| Medical and Medication History | X | | | | | | | | | | | | | | | | | | | | | | |
| Recording of Concomitant Medication[i] | X | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | X | X[t] |
| Vital Signs[g] | X | | | X | | | X | | X | | X | X | X | | X | | X | X | X | | X | X | |
| Physical Exam, including weight | X | | | X | | | X | | X | | | X | | | X | | | X | | | X | X | |
| ECOG Performance Status | X | | | X | | | X | | X | | | X | | | X | | | X | | | X | X | |
| 12-lead ECG[h] | X | | | | | | | | | | | | | | | | | | | | | X | |
| Review of AEs and SAEs[i] | X | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | X | X[f] |
| Survival Assessment | | | | | | | | | | | | | | | | | | | | | | | X |
| **Local Laboratory Tests** | | | | | | | | | | | | | | | | | | | | | | | |
| Chemistry[j] | | X | | X | | | X | | X | | | X | | | X | | | X | | | X | X | |
| Hematology[k] | | X | | X | | | X | | X | | | X | | | X | | | X | | | X | X | |
| LDH | | X | | | | | | | | | | | | | | | | | | | | | |
| Coagulation (PT or INR and PTT or aPTT) | | X | | | | | | | | | | | | | | | | | | | | | |
| Thyroid function Tests[l] | | X | | | | | | | X | | | X | | | X | | | X | | | | X | |
| Urine or Serum Pregnancy Test[m] | | | X | | | | | | | | | | | | | | | | | | | X | |
| HIV, Hepatitis B, Hepatitis C[u] | X | | | | | | | | | | | | | | | | | | | | | | |



Footnotes defined on last page of the table

**Table 2. Schedule of Assessments for Phase 1b**

| | Screening | | | Study Treatment[d,w] (week number) | | | | | | | | | | | | | | | | | | Follow-up | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Procedures** | ≤ 28 days[a] | ≤ 10 days[b] | ≤ 72 hour[c] | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18[v] | Safety[e] | Survival[f] |
| **Central Laboratory Tests** | | | | | | | | | | | | | | | | | | | | | | | |
| Archived Tumor Tissue for *BRAF* V600E testing & Biomarker Analyses[n] | X | | | | | | | | | | | | | | | | | | | | | | |
| Blood for Biomarker Analyses[o] | | | | X | | | X | | X | | | X | | | | | | X | | | | X | |
| Tumor biopsy (Optional)[p] | | | | X | | | | | X | | | | | | | | | X | | | | | |
| Blood and Urine for qPCR[y] | | | | | | | | | | | | | | | | | | | | | | X | |
| Swab of Herpetic Lesion for qPCR[z] | | | | X | Within 3 days of occurrence of suspected lesion of herpetic origin | | | | | | | | | | | | | | | | | X | |
| **Clinical & Radiographic Tumor/Response Assessments** | | | | | | | | | | | | | | | | | | | | | | | |
| Clinical Tumor Assessment[q] | X | | | | | | | | | | | | | | X | | | | | | | X | X |
| Radiographic (CT, PET/CT, MRI, or US) scans & Tumor Assessment[r,s] | X | | | | | | | | | | | | | | X | | | | | | | X | X |
| **Treatment Administration** | | | | | | | | | | | | | | | | | | | | | | | |
| Talimogene laherparepvec[w] | | | | X | | | X | | X | | X | | X | | X | | X | | X | | X | | |
| Ipilimumab[x] | | | | | | | | | X | | | X | | | X | | | X | | | | | |
| Reporting Exposure to Talimogene Laherparepvec | | | | | | | | | | | | | | | | | | | | | | | |
| Exposure of Subject's Household member or Caregiver[aa] | | | | → | | | | | | | | | | | | | | | | | | → | |
| Exposure of Subject's Healthcare Provider[aa] | | | | → | | | | | | | | | | | | | | | | | | → | |



Footnotes defined on next page of the table

[a] Procedures to be performed ≤ 28 days prior to enrollment.

[b] Procedures to be performed ≤ 10 days prior to enrollment.

[c] Procedures to be performed ≤ 72 hours prior to enrollment.

[d] Talimogene laherparepvec treatment should begin as soon as possible after enrollment via IVRS but no later than 5 days after enrollment. During treatment, assessments and procedures will be performed within ± 3 days of the planned visit.

[e] Safety follow-up will be performed approximately 30 (+ 7) days after the last dose of talimogene laherparepvec or 60 (+ 7) days after the last dose of ipilimumab, whichever is later.

[f] Subjects will be followed for survival by clinic visit or telephone contact every 12 weeks ± 28 days from the date of the safety follow-up visit until up to **60** months after the last subject is randomized in phase 2. Subsequent cancer treatments for melanoma and whether any talimogene laherparepvec-related AEs have occurred will be collected as part of the long-term follow-up survival assessment.

[g] Vital signs (blood pressure, resting pulse, respiration rate, and temperature) must be performed prior to the study treatment (talimogene laherparepvec and/or ipilimumab) administration.

[h] A single 12-lead ECG will be performed ≤ 28 days before enrollment and the safety follow-up visit.

[i] All SAEs that occur after the subject has signed the main informed consent through 30 days after the last administration of talimogene laherparepvec or 60 days after the last dose of ipilimumab, whichever is later, will be reported to Amgen and recorded in the case report form. SAEs must be reported to Amgen within 24 hours of discovery. All nonserious AEs that occur and concomitant medications that are administered after enrollment through 30 days after the last administration of talimogene laherparepvec or 60 days after the last dose of ipilimumab, whichever is later, will be recorded in the case report form. AEs and concomitant medications should be assessed on an ongoing basis and recorded at each subject visit.

[j] Blood samples for chemistry will be collected at screening and prior to study treatment administration at day 1 of weeks 1, 4, 6, 9, 12, 15, 18 then every 4 weeks until end of study treatment. Results should be reviewed prior to the administration of scheduled dose of study drugs. Blood sample will also be collected at the safety follow-up visit.

[k] Blood samples for hematology will be collected at screening and at prior to study treatment administration at day 1 of weeks 1, 4, 6, 9, 12, 15, 18 then every 4 weeks until end of study treatment. Results should be reviewed prior to the administration of scheduled dose of study drugs. Blood sample will also be collected at the safety follow-up visit.

[l] Blood samples for thyroid function tests will be collected at screening and prior to study treatment administration on day 1 of weeks 6, 9, 12, and 15. During treatment the thyroid function tests can be performed within 3 days of the planned visit. Results should be reviewed prior to the administration of the scheduled dose of study drugs. Blood sample will also be collected at the safety follow-up visit.

[m] Urine or serum pregnancy test to be performed on female of childbearing potential.

[n] Formalin-fixed paraffin-embedded tumor tissue from either the primary tumor or a metastatic lesion (block or unstained tumor slides) and the associated pathology reports) must be submitted for *BRAF* V600E mutation testing to either a local laboratory, if the test can be performed locally per standard of care, or a central laboratory. Tumor sample *BRAF* V600E mutation testing should be submitted to the local or central laboratory within 28 days after enrollment. *BRAF* V600E tumor mutation status obtained prior to screening from a local laboratory will be acceptable. The local laboratory report supporting local *BRAF* V600E tumor testing results must be available at the site within 28 days of enrollment. In addition, tumor sample will be submitted to a central laboratory for archiving for other biomarker analyses within 4 weeks after enrollment.

[o] Blood samples for biomarker analyses including testing for HSV-1 antibody serostatus will be collected prior to study treatment administration on day 1 of week 1, day 1 of week 4, day 1 of week 6, day 1 of week 9, day 1 of week 15 and safety follow up visit.

[p] Optional Tumor biopsy (only for subjects who consent to the tumor biopsy): At least one injected lesion and/or one uninjected lesion will be biopsied according to the following scheduled: within 3 days prior to the subject receiving the first dose of study treatment on day 1 and within 3 days prior to the dose of week 6, week 15, and week 24. Refer to Laboratory Manual for tumor biopsy procedures.

[q] Investigator's clinical measurement of cutaneous, subcutaneous, or nodal tumor measurement by caliper and response assessment per a modification of irRC (Appendix E). The screening measurement must be done within 28 days prior to enrollment and will be used as baseline. During treatment, the clinical tumor assessments will performed independent of treatment cycle at week 12 (± 1 week) and then every 12 weeks (± 1 week) until disease progression per the modified irRC (Appendix E).Clinical tumor assessment is required at the safety follow up visit if the subject ended treatment prior to disease progression per irRC and has not had clinical tumor assessment performed within 12 weeks (± 1 week) of the visit. Every effort should be made to complete clinical tumor assessments during the long-term follow-up until documentation of disease progression per the modified irRC (Appendix E) for subjects discontinuing treatment for any reason other than progressive disease (PD).

[r] Radiographic imaging (CT, PET/CT, MRI or US) of the chest, abdomen, and pelvis, and CT or MRI of the brain are required at screening. Tumor assessments must also include all other sites of disease. The screening scans must be done within 28 days prior to enrollment and will be used as baseline. During treatment, radiographic imaging (CT or MRI) of the abdomen, pelvis, and chest, along with tumor assessments of all other sites of disease, (and CT scan or MRI of the brain if a subject has symptoms or signs suggestive of CNS metastasis), will be performed independent of treatment cycle at week 12 (± 1 week) and then every 12 weeks (± 1 week) until clinically relevant disease progression. Abdomen and pelvis MRI/CT scans or CT scans performed with PET must be with contrast if they are to be used for radiographic tumor imaging assessments. Radiographic imaging is required at the safety follow up visit if the subject ended treatment prior to clinically relevant disease progression and has not had radiographic tumor imaging performed within 12 weeks (± 1 week) of the visit. Every effort should be made to complete radiographic assessments during the long-term follow-up until documentation of disease progression per the modified irRC (Appendix E) for subjects discontinuing treatment for any reason other than PD. Subjects who have reached a confirmed CR may increase their interval of radiographic assessments up to 6 months after the first 2 years beyond confirmed **complete response** (CR) and up to 12 months after the first 5 years beyond confirmed CR as **per Principal Investigator (PI) discretion**. **Subjects without CR will be assessed radiographically every 6 months after the first 2 years until the subject is 5 years off of therapy, then as per PI discretion.**

[s] Response (CR, or PR) or disease progression to be confirmed by second consecutive clinical and radiographic assessments no less than 4 weeks from the date of the first documented response or disease progression. Note: Confirmation of disease progression is required only in the absence of rapid clinical deterioration (rapid decline in performance status or rapid disease progression requiring other therapy).

[t] Only subsequent treatment for melanoma will be recorded.

[u] HIV, Hepatitis B and/or Hepatitis C test required if clinically indicated.

[v] Repeat week 18 procedures and assessments every 2 weeks except physical exam, ECOG performance status, and blood samples for chemistry and hematology which will be repeated every 4 weeks after week 18 until end of study treatment.

[w] Talimogene laherparepvec will be administered on day 1 of week 1, day 1 of week 4, and Q2W (± 3 days) thereafter. The initial dose of talimogene laherparepvec is up to 4.0 mL of $10^6$ PFU/mL. Subsequent doses of talimogene laherparepvec are up to 4.0 mL of $10^8$ PFU/mL. Dosing of talimogene laherparepvec should be continued until CR, disease progression per the modified irRC (Appendix E), or intolerance of study treatment, whichever occurs first. Due to the mechanism of action, subjects may experience growth in existing tumors or the appearance of new tumors prior to maximal clinical benefit of talimogene laherparepvec. Therefore, dosing should be continued for at least 6 months from the time of initial dose provided that the subject has no evidence of disease progression per the modified irRC (Appendix E) and is able to tolerate the treatment. Assessments and procedures are to be performed within 3 days of the planned visit and results available prior to study drug administration, unless otherwise specified. It is recommended that dosing occur on the same day of the week (eg, if first dose is administered on a Monday, all subsequent doses should be administered on a Monday), however, a ± 3 day dosing window is allowed.

[x] Ipilimumab will be administered intravenously at a dose of 3 mg/kg every 3 weeks (± 3 days) for 4 infusions starting at day 1 of week 6 (at the time of the third dose of Talimogene laherparepvec), day 1 of week 9, day 1 of week 12, and day 1 of week 15. When talimogene laherparepvec and ipilimumab are administered on the same day, talimogene laherparepvec must be administered first.

[y] Blood and urine samples will be collected at the safety follow-up visit, stored, and ultimately tested for detection of talimogene laherparepvec DNA using qPCR.

[z] Swab of any lesion of herpetic origin for qPCR testing: Subject should return to clinic within 3 days of the occurrence of reportable lesion suspected to be herpetic in origin such as cold sores or vesicles. The lesion should be evaluated by the investigator and swabbed if HSV infection is suspected. The sample will be collected, stored, and ultimately tested for detection of talimogene laherparepvec DNA using qPCR.

[aa] Reporting potential or known unintended exposure to talimogene laherparepvec: If a household member, caregiver, or healthcare provider who has had close contact with the subject is suspected to have been exposed to talimogene laherparepvec (eg, have or who have had signs or symptoms suspected to be herpetic origin or accidentally exposed to talimogene laherparepvec), report the potential or known unintended exposure to talimogene laherparepvec, suspected related signs or symptoms, and detection of talimogene laherparepvec DNA by qPCR testing in a swab taken from a lesion, if any, in a subject's household member, caregiver, or healthcare provider as specified in Section 9.4.

## Table 3. Schedule of Assessments for Phase 2 - Arm 1

| | Screening | | | Study Treatment[d,w] (week number) | | | | | | | | | | | | | | | | | | Follow-up | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study Procedures | ≤ 28 days[a] | ≤ 10 days[b] | ≤ 72 hour[c] | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18[v] | 24 | Safety[e] | Survival[f] |
| **General Assessments** | | | | | | | | | | | | | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | | | | | | | | | | | | |
| Review of Eligibility Criteria | X | | | | | | | | | | | | | | | | | | | | | | | |
| Demographics (sex, age, race, and ethnicity) | X | | | | | | | | | | | | | | | | | | | | | | | |
| Medical and Medication History | X | | | | | | | | | | | | | | | | | | | | | | | |
| Recording of Concomitant Medication[i] | X | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | X | X[t] |
| Vital Signs[g] | X | | | X | | | X | | X | | X | X | X | | X | | X | X | X | | X | | X | |
| Physical Exam, including weight | X | | | X | | | X | | X | | | X | | | X | | | X | | | X | | X | |
| ECOG Performance Status | X | | | X | | | X | | X | | | X | | | X | | | X | | | X | | X | |
| 12-lead ECG[h] | X | | | | | | | | | | | | | | | | | | | | | | X | |
| Review of AEs and SAEs[i] | X | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | X | X[f] |
| Survival Assessment | | | | | | | | | | | | | | | | | | | | | | | | X |
| **Local Laboratory Tests** | | | | | | | | | | | | | | | | | | | | | | | | |
| Chemistry[j] | | X | | X | | | X | | X | | | X | | | X | | | X | | | X | | X | |
| Hematology[k] | | X | | X | | | X | | X | | | X | | | X | | | X | | | X | | X | |
| LDH | | X | | | | | | | | | | | | | | | | | | | | | | |
| Coagulation PT or INR and PTT or aPTT | | X | | | | | | | | | | | | | | | | | | | | | | |
| Thyroid function tests[l] | | X | | | | | | | X | | | X | | | X | | | X | | | | | X | |
| Urine or Serum Pregnancy Test[m] | | | X | | | | | | | | | | | | | | | | | | | | X | |
| HIV, Hepatitis B, Hepatitis C Tests[u] | X | | | | | | | | | | | | | | | | | | | | | | | |



Footnotes defined on last page of the table.

**Table 3. Schedule of Assessments for Phase 2 - Arm 1**

| | Screening | | | Study Treatment[d,w] (week number) | | | | | | | | | | | | | | | | | | Follow-up | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study Procedures | ≤ 28 days[a] | ≤ 10 days[b] | ≤ 72 hour[c] | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18[v] | 24 | Safety[e] | Survival[f] |
| **Central Laboratory Tests** | | | | | | | | | | | | | | | | | | | | | | | | |
| Archived Tumor Tissue for *BRAF* V600E testing & Biomarker Analyses[n] | X | | | | | | | | | | | | | | | | | | | | | | | |
| Blood for Biomarker Analyses[o] | | | | X | | | X | | X | | | X | | | | | | X | | | | X | X | |
| Tumor Biopsy (Optional)[p] | | | | X | | | | | X | | | | | | | | | | | | | X | | |
| Blood and Urine for qPCR[y] | | | | X | | | X | | X | | X | | | | | | | | | | | | X | |
| Swab of Herpetic Lesion for qPCR[z] | | | | X | Within 3 days of occurrence of suspected lesion of herpetic origin | | | | | | | | | | | | | | | | | | X | |
| **Clinical & Radiographic Tumor/Response Assessments** | | | | | | | | | | | | | | | | | | | | | | | | |
| Clinical Tumor Assessment[q] | X | | | | | | | | | | | | | | X | | | | | | | X | X | X |
| Radiographic (CT, PET/CT, MRI, or US) scans & Tumor Assessment[r,s] | X | | | | | | | | | | | | | | X | | | | | | | X | X | X |
| **Treatment Administration** | | | | | | | | | | | | | | | | | | | | | | | | |
| Talimogene laherparepvec[w] | | | | X | | | X | | X | | X | | X | | X | | X | | X | | X | X | | |
| Ipilimumab[x] | | | | | | | | | X | | | X | | | X | | | X | | | | | | |
| Reporting Exposure to Talimogene Laherparepvec | | | | | | | | | | | | | | | | | | | | | | | | |
| Exposure of Subject's Household member or Caregiver[aa] | | | | → | | | | | | | | | | | | | | | | | | | | |
| Exposure of Subject's Healthcare Provider[aa] | | | | → | | | | | | | | | | | | | | | | | | | | |
| **PRO Questionnaires** | | | | | | | | | | | | | | | | | | | | | | | | |
| EQ-D5 Questionnaire[bb] | | | | X | | | X | | X | | | X | | | X | | | X | | | X | X | X | X |
| EORTC QLQ-C30 Questionnaire[bb] | | | | X | | | X | | X | | | X | | | X | | | X | | | X | X | X | X |

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Footnotes defind on next page of the table

[a] Procedures to be performed ≤ 28 days prior to randomization.
[b] Procedures to be performed ≤ 10 days prior to randomization.
[c] Procedures to be performed ≤ 72 hours prior to randomization.
[d] Talimogene laherparepvec treatment should begin as soon as possible after enrollment via IVRS but no later than 5 days after enrollment. During treatment, assessments and procedures will be performed within ± 3 days of the planned visit.
[e] Safety follow-up will be performed approximately 30 (+ 7) days after the last dose of talimogene laherparepvec or 60 (+ 7) days after the last dose of ipilimumab, whichever is later.
[f] Subjects will be followed for survival by clinic visit or telephone contact every 12 weeks ± 28 days from the date of the safety follow-up visit until up to **60** months after the last subject is randomized in phase 2. Subsequent cancer treatments for melanoma and whether any talimogene laherparepvec-related AEs have occurred will be collected as part of the long-term follow-up survival assessment.
[g] Vital signs (blood pressure, resting pulse, respiration rate, and temperature) must be performed prior to the study treatment (talimogene laherparepvec and/or ipilimumab) administration.
[h] A single 12-lead ECG will be performed ≤ 28 days before enrollment and the safety follow-up visit.
[i] All SAEs that occur after the subject has signed the main informed consent through 30 days after the last administration of talimogene laherparepvec or 60 days after the last dose of ipilimumab, whichever is later, will be reported to Amgen and recorded in the case report form. SAEs must be reported to Amgen within 24 hours of discovery. All non-serious AEs that occur and concomitant medications that are administered after enrollment through 30 days after the last administration of talimogene laherparepvec or 60 days after the last dose of ipilimumab, whichever is later, will be recorded in the case report form. AEs and concomitant medications should be assessed on an ongoing basis and recorded at each subject visit.
[j] Blood samples for chemistry will be collected at screening. During treatment blood samples will be collected prior to study treatment administration at day 1 of weeks 1, 4, 6, 9, 12, 15, 18 then every 4 weeks until end of study treatment. Results should be reviewed prior to the administration of schedule dose of study drugs. Blood sample will also be collected at the safety follow-up visit.
[k] Blood samples for hematology will be collected at screening. During treatment blood samples will be collected prior to study treatment administration at day 1 of weeks 1, 4, 6, 9, 12, 15, 18 then every 4 weeks until end of study treatment. Results should be reviewed prior to the administration of scheduled dose of study drugs. Blood sample will also be collected at the safety follow-up visit.
[l] Blood samples for thyroid function tests will be collected at screening. Samples will be collected prior to study treatment administration on day 1 of weeks 6, 9, 12, and 15. Results should be reviewed prior to the administration of scheduled dose of study drugs. Blood sample will also be collected at the safety follow-up visit.
[m] Urine or serum pregnancy test to be performed on female of childbearing potential.
[n] Formalin-fixed paraffin-embedded tumor tissue from either the primary tumor or a metastatic lesion (block or unstained tumor slides) and the associated pathology reports) must be submitted for *BRAF* V600E mutation testing to either a local laboratory, if the test can be performed locally per standard of care, or a central laboratory. Tumor sample for *BRAF* V600E mutation testing should be submitted to the local or central laboratory within 28 days after randomization. *BRAF* V600E tumor mutation status obtained prior to screening from a local laboratory will be acceptable. The local laboratory report supporting local *BRAF* V600E tumor testing results must be available at the sites within 28 days after randomization. In addition, tumor sample will be submitted within 4 weeks after randomization to a central laboratory for archiving for other biomarker analyses.
[o] Blood samples for biomarker analyses including testing for HSV-1 antibody serostatus will be collected prior to study treatment administration at the following time points: day 1 of week 1, day 1 of week 4, day 1 of week 6, day 1 of week 9, day 1 of week 15, and either at the time of initial unconfirmed PR, confirmed PD per modified irRC (Appendix D), or at weeks 24 for subjects with SD, whichever comes first, and safety follow-up visit.

[p] Optional Tumor biopsy (only for subjects who consent to the tumor biopsy): At least one injected lesion and/or one uninjected lesion will be biopsied according to the following schedule: within 3 days prior to the subject receiving the first dose of study treatment on day 1 (archival biopsy tissue may be substituted if prior biopsy was performed within 1 month prior to day 1, and no systemic anticancer therapies were given 1 month prior to the biopsy) and within 3 days prior to the dose of week 6, and either at the time of initial unconfirmed PR, confirmed PD per modified irRC (Appendix D), or at week 24 for subjects with SD, whichever comes first. Refer to Laboratory Manual for tumor biopsy procedures.

[q] Investigator's clinical measurement of cutaneous, subcutaneous, or nodal tumor measurement by caliper and response assessment per a modification of irRC (Appendix E). The screening measurement must be done within 28 days prior to randomization and will be used as baseline. During treatment, the clinical tumor assessments will performed independent of treatment cycle at week 12 (± 1 week) and then every 12 weeks (± 1 week) until disease progression per the modified irRC (Appendix E). Clinical tumor assessment is required at the safety follow up visit if the subject ended treatment prior to disease progression per the modified irRC (Appendix E) and has not had clinical tumor assessment performed within 12 weeks (± 1 week) of the visit. Every effort should be made to complete clinical tumor assessments during the long-term follow-up until documentation of disease progression per the modified irRC (Appendix E) for subjects discontinuing treatment for any reason other than PD.

[r] Radiographic imaging (CT, PET/CT, MRI or US) of the chest, abdomen, and pelvis, and CT or MRI of the brain are required at screening. Tumor assessments must also include all other sites of disease. The screening scans must be done within 28 days prior to randomization and will be used as baseline. During treatment, radiographic imaging (CT or MRI) of the abdomen, pelvis, and chest, along with tumor assessments of all other sites of disease, (and CT or MRI of the brain with contrast if a subject has symptoms or signs suggestive of CNS metastases), will be performed independent of treatment cycle at week 12 (± 1 week) and then every 12 weeks (± 1 week) until clinically relevant disease progression. Abdomen and pelvis MRI/CT scans or CT scans performed with PET must be with contrast if they are to be used for radiographic tumor imaging assessments. Radiographic imaging is required at the safety follow up visit if the subject ended treatment prior to clinically relevant disease progression and has not had radiographic tumor imaging performed within 12 weeks (± 1 week) of the visit. Every effort should be made to complete radiographic assessments during the long-term follow-up until documentation of disease progression per the modified irRC (Appendix E) for subjects discontinuing treatment for any reason other than PD. Subjects who have reached a confirmed CR may increase their interval of radiographic assessments up to 6 months after the first 2 years beyond confirmed **complete response (**CR**)** and up to 12 months after the first 5 years beyond confirmed CR as **per Principal Investigator (PI) discretion**. **Subjects without CR will be assessed radiographically every 6 months after the first 2 years until the subject is 5 years off of therapy, then as per PI discretion.**

[s] Response (CR, or PR) or disease progression to be confirmed by second consecutive clinical and radiographic assessments no less than 4 weeks from the date of the first documented response or disease progression. Note: Confirmation of disease progression is required only in the absence of rapid clinical deterioration (rapid decline in performance status or rapid disease progression requiring other therapy).

[t] Only subsequent treatment for melanoma will be recorded.

[u] HIV, hepatitis B and/or hepatitis C test required only if indicated for clinically suspected HIV, hepatitis B, or hepatitis C infection, respectively.

[v] Repeat week 18 procedures and assessments every 2 weeks except physical exam, ECOG performance status and blood sample for chemistry and hematology which will be repeated every 4 weeks after week 18 until end of study treatment.

[w] Talimogene laherparepvec will be administered to subjects randomized to arm 1 on day 1 of week 1, day 1 of week 4, and Q2W (± 3 days) thereafter. The initial dose of talimogene laherparepvec is up to 4.0 mL of $10^6$ PFU/mL. Subsequent doses of talimogene laherparepvec are up to 4.0 mL of $10^8$ PFU/mL Dosing of talimogene laherparepvec should be continued until CR, disease progression per the modified irRC (Appendix E), or intolerance of study treatment, whichever occurs first. Due to the mechanism of action, subjects may experience growth in existing tumors or the appearance of new tumors prior to maximal clinical benefit of talimogene laherparepvec. Therefore, dosing should be continued for at least 6 months from the time of initial dose provided that the subject has no evidence of disease progression per the modified irRC (Appendix E) and is able to tolerate the treatment. Assessments and procedures are to be performed within 3 days of the planned visit and results available prior to study drug administration, unless otherwise specified. It is recommended that dosing occur on the same day of the week (eg, if first dose is administered on a Monday, all subsequent doses should be administered on a Monday), however, a ± 3 day dosing window is allowed.

[x] Ipilimumab will be administered intravenously to subjects randomized to arm 1 at a dose of 3 mg/kg every 3 weeks (± 3 days) for 4 infusions starting at day 1 of week 6 (at the time of the third dose of talimogene laherparepvec), day 1 of week 9, day 1 of week 12, and day 1 of week 15. When talimogene laherparepvec and ipilimumab are administered on the same day, talimogene laherparepvec must be administered first.

[y] Blood and urine samples will be collected prior to study treatment administration at day 1 of weeks 1, 4, 6, and 8, and at the safety follow-up visit. Sample will stored and ultimately tested for detection of talimogene laherparepvec DNA using qPCR.

[z] Swab of any lesion of herpetic origin for qPCR testing: Subject should return to clinic within 3 days of the occurrence of reportable lesion suspected to be herpetic in origin such as cold sores or vesicles. The lesion should be evaluated by the investigator and swabbed if HSV infection is suspected. The sample will be collected, stored, and ultimately tested for the detection of talimogene laherparepvec DNA using qPCR.

[aa] Reporting potential or known unintended exposure to talimogene laherparepvec: If a household member, caregiver, or healthcare provider who has had close contact with the subject is suspected to have been exposed to talimogene laherparepvec (eg, have or who have had signs or symptoms suspected to be herpetic origin or accidentally exposed to talimogene laherparepvec), report the potential or known unintended exposure to talimogene laherparepvec, suspected related signs or symptoms, and detection of talimogene laherparepvec DNA by qPCR testing in a swab taken from a lesion, if any, in a subject's household member, caregiver, or healthcare provider as specified in Section 9.4.

[bb] Completion of PRO (EQ-D5 and EORTC QLQ-C30) questionnaires prior to study treatment administration at day 1 of weeks 1, 4, 6, 9, 12, 15, 18, 22, 24, then every 4 weeks until end of study treatment, and at the safety follow-up visit. For subjects who have discontinued treatment for any reason other than confirmed PD, every effort should be made to complete PRO (EQ-D5 and EORTC QLQ-C30) questionnaires every 12 weeks (+1 week) during the long-term follow-up until **no longer than 3 years after the last subject is randomized.**

## Table 4. Schedule of Assessments for Phase 2 - Arm 2

| | Screening | | | Study Treatment[d,w] (week number) | | | | | | | | | | | | | | | | | | Follow-up | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Procedures** | ≤ 28 days[a] | ≤ 10 days[b] | ≤ 72 hour[c] | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 24 | Safety[e] | Survival[f] |
| **General Assessments** | | | | | | | | | | | | | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | | | | | | | | | | | | |
| Review of Eligibility Criteria | X | | | | | | | | | | | | | | | | | | | | | | | |
| Demographics (sex, age, race, and ethnicity) | X | | | | | | | | | | | | | | | | | | | | | | | |
| Medical and Medication History | X | | | | | | | | | | | | | | | | | | | | | | | |
| Recording of Concomitant Medication[i] | X | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | X | X[t] |
| Vital Signs[g] | X | | | X | | | X | | | X | | | X | | | | | | | | | | X | |
| Physical Exam, including weight | X | | | X | | | X | | | X | | | X | | | | | | | | | | X | |
| ECOG Performance Status | X | | | X | | | X | | | X | | | X | | | | | | | | | | X | |
| 12-lead ECG[h] | X | | | | | | | | | | | | | | | | | | | | | | X | |
| Review of AEs and SAEs[i] | X | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | → | X | X[f] |
| Survival Assessment | | | | | | | | | | | | | | | | | | | | | | | | X |
| **Local Laboratory Tests** | | | | | | | | | | | | | | | | | | | | | | | | |
| Chemistry[j] | | X | | X | | | X | | | X | | | X | | | | | | | | | | X | |
| Hematology[k] | | X | | X | | | X | | | X | | | X | | | | | | | | | | X | |
| LDH | | X | | | | | | | | | | | | | | | | | | | | | | |
| Coagulation PT or INR and PTT or aPTT | | X | | | | | | | | | | | | | | | | | | | | | | |
| Thyroid function tests[l] | | X | | X | | | X | | | X | | | X | | | | | | | | | | X | |
| Urine or Serum Pregnancy Test[m] | | | X | | | | | | | | | | | | | | | | | | | | X | |
| HIV, Hepatitis B, Hepatitis C Tests[u] | X | | | | | | | | | | | | | | | | | | | | | | | |
| **Central Laboratory Tests** | | | | | | | | | | | | | | | | | | | | | | | | |
| Archived Tumor Tissue for *BRAF* V600E testing & Biomarker Analyses[n] | X | | | | | | | | | | | | | | | | | | | | | | | |
| Blood for Biomarker Analyses[o] | | | | X | | | X | | | | | | X | | | | | | | | | X | X | |
| Tumor Biopsy (Optional)[p] | | | | X | | | | | | | | | | | | | | | | | | X | | |



Footnotes defined on last page of the table.

## Table 4. Schedule of Assessments for Phase 2 - Arm 2

| | Screening | | | Study Treatment[d,w] (week number) | | | | | | | | | | | | | | | | | | Follow-up | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study Procedures | ≤ 28 days[a] | ≤ 10 days[b] | ≤ 72 hour[c] | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 24 | Safety[e] | Survival[f] |
| **Clinical & Radiographic Tumor/Response Assessments** | | | | | | | | | | | | | | | | | | | | | | | | |
| Clinical Tumor Assessment[q] | X | | | | | | | | | | | | | | X | | | | | | | X | X | X |
| Radiographic (CT, PET/CT, MRI, or US) scans & Tumor Assessment[r,s] | X | | | | | | | | | | | | | | X | | | | | | | X | X | X |
| **Treatment Administration** | | | | | | | | | | | | | | | | | | | | | | | | |
| Ipilimumab[v] | | | | X | | | X | | | X | | | X | | | | | | | | | | | |
| PRO Questionnaires | | | | | | | | | | | | | | | | | | | | | | | | |
| EQ-D5 Questionnaire[w] | | | | X | | | X | | | X | | | X | | X | | | | | | | X | X | X |
| EORTC QLQ-C30 Questionnaire[w] | | | | X | | | X | | | X | | | X | | X | | | | | | | X | X | X |

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Footnotes defined on next page of the table

[a] Procedures to be performed ≤ 28 days prior to randomization.
[b] Procedures to be performed ≤ 10 days prior to randomization.
[c] Procedures to be performed ≤ 72 hours prior to randomization.
[d] Treatment should begin as soon as possible after enrollment via IVRS but no later than 5 days after enrollment. During treatment, assessments and procedures will be performed within ± 3 days of the planned visit.
[e] Safety follow-up will be performed approximately 60 (+ 7) days after the last dose of ipilimumab.
[f] Subjects will be followed for survival by clinic visit or telephone contact every 12 weeks ± 28 days from the date of the safety follow-up visit until up to **60** months after the last subject is randomized in phase 2. Subsequent cancer treatments for melanoma will be collected as part of the long-term follow-up survival assessment.
[g] Vital signs (blood pressure, resting pulse, respiration rate, and temperature) must be performed prior to ipilimumab administration.
[h] A single 12-lead ECG will be performed ≤ 28 days before enrollment and the safety follow-up visit.
[i] All SAEs that occur after the subject has signed the main informed consent through 60 days after the last dose of ipilimumab will be reported to Amgen and recorded in the case report form. SAEs must be reported to Amgen within 24 hours of discovery. All non-serious AEs that occur and concomitant medications that are administered after enrollment through 60 days after the last dose of ipilimumab will be recorded in the case report form. AEs and concomitant medications should be assessed on an ongoing basis and recorded at each subject visit.
[j] Blood samples for chemistry will be collected at screening. During treatment blood samples will be collected prior to study treatment administration at day 1 of weeks 1, 4, 7, and 10. Results should be reviewed prior to administration of scheduled dose of study drug. Blood sample will also be collected at the safety follow-up visit.
[k] Blood samples for hematology will be collected at screening. During treatment blood samples will be collected prior to study treatment administration at day 1 of weeks 1, 4, 7, and 10. Results should be reviewed prior to scheduled dose of administration of study drugs. Blood samples will also be collected at the safety follow-up visit.
[l] Blood samples for thyroid function tests will be collected at screening. Samples will be collected prior to study treatment administration on day 1 of weeks 1, 4, 7, and 10. Thyroid function tests can be performed within 3 days of the planned visit. Results should be reviewed prior to the administration of the scheduled dose of study drug. Blood sample will also be collected at the safety follow-up visit.
[m] Urine or serum pregnancy test to be performed on female of childbearing potential.
[n] Formalin-fixed paraffin-embedded tumor tissue from either the primary tumor or a metastatic lesion (block or unstained tumor slides) and the associated pathology reports) must be submitted for *BRAF* V600E mutation testing to either a local laboratory, if the test can be performed locally per standard of care, or a central laboratory. Tumor sample for *BRAF* V600E mutation testing should be submitted to the local or central laboratory within 28 days after randomization. *BRAF* V600E tumor mutation status obtained prior to screening from a local laboratory will be acceptable. The local laboratory report supporting local *BRAF* V600E tumor testing results must be available at the site within 28 days after randomization. In addition, tumor sample will be submitted within 4 weeks after randomization to a central laboratory for archiving for other biomarker analyses.
[o] Blood samples for biomarker analyses including testing for HSV-1 antibody serostatus will be collected prior to study treatment administration at the following time points: day 1 of week 1, day 1 of week 4, day 1 of week 10, and either at the time of initial unconfirmed PR, confirmed PD per modified irRC (Appendix D), or at weeks 24 for subjects with SD, whichever comes first, and the safety follow up visit.
[p] Optional Tumor biopsy (only for subjects who consent to the tumor biopsy): At least one lesion will be biopsied according to the following scheduled: within 3 days prior to the subject receiving the first dose of study treatment on day 1 (archival biopsy tissue may be substituted if prior biopsy was performed within 1 month prior to day 1, and no systemic anticancer therapies were given 1 month prior to the biopsy) and either at the time of time of initial unconfirmed PR, confirmed PD per modified irRC (Appendix D), or at week 24 for subjects with SD, whichever comes first. Refer to Laboratory Manual for tumor biopsy procedures.

[q] Investigator's clinical measurement of cutaneous, subcutaneous, or nodal tumor measurement by caliper and response assessment per a modification of irRC (Appendix E). The screening measurement must be done within 28 days prior to randomization and will be used as baseline. During treatment, the clinical tumor assessments will performed independent of treatment cycle at week 12 (± 1 week) and then every 12 weeks (± 1 week) until disease progression per the modified irRC (Appendix E).. Clinical tumor assessment is required at the safety follow up visit if the subject ended treatment prior to disease progression per the modified irRC (Appendix E). and has not had clinical tumor assessment performed within 12 weeks (± 1 week) of the visit. Every effort should be made to complete clinical tumor assessments during the long-term follow-up until documentation of disease progression per the modified irRC for subjects discontinuing treatment for any reason other than PD.

[r] Radiographic imaging (CT, PET/CT, MRI or US) of the chest, abdomen, and pelvis, and CT or MRI of the brain are required at screening. Tumor assessments must also include all other sites of disease. The screening scans must be done within 28 days prior to randomization and will be used as baseline. During treatment, radiographic imaging (CT or MRI) of the abdomen, pelvis, and chest, along with tumor assessments of all other sites of disease, (and CT or MRI of the brain with contrast if a subject has symptoms or signs suggestive of CNS metastases), will be performed independent of treatment cycle at week 12 (± 1 week) and then every 12 weeks (± 1 week) until clinically relevant disease progression. Abdomen and pelvis MRI/CT scans or CT scans performed with PET must be with contrast if they are to be used for radiographic tumor imaging assessments. Radiographic imaging is required at the safety follow up visit if the subject ended treatment prior to clinically relevant disease progression and has not had radiographic tumor imaging performed within 12 weeks (± 1 week) of the visit. Every effort should be made to complete radiographic assessments during the long-term follow-up until documentation of disease progression per the modified irRC (Appendix E) for subjects discontinuing treatment for any reason other than PD. Subjects who have reached a confirmed CR may increase their interval of radiographic assessments up to 6 months after the first 2 years beyond confirmed **complete response (**CR**)** and up to 12 months after the first 5 years beyond confirmed CR as long as **per Principal Investigator (PI) discretion**. **Subjects without CR will be assessed radiographically every 6 months after the first 2 years until the subject is 5 years off of therapy, then as per PI discretion.**

[s] Response (CR, or PR) or disease progression to be confirmed by second consecutive clinical and radiographic assessments no less than 4 weeks from the date of the first documented response or disease progression. Note: Confirmation of disease progression is required only in the absence of rapid clinical deterioration (rapid decline in performance status or rapid disease progression requiring other therapy).

[t] Only subsequent treatment for melanoma will be recorded.

[u] HIV, hepatitis B and/or hepatitis C test required only if indicated for clinically suspected HIV, hepatitis B, or hepatitis C infection, respectively.

[v] Ipilimumab will be administered intravenously to subjects randomized to arm 2 at a dose of 3 mg/kg every 3 weeks (± 3 days) for 4 infusions starting at day 1 of week 1, day 1 of week 4, day 1 of week 7, and day 1 of week 10.

[W] Completion of PRO (EQ-D5 and EORTC QLQ-C30) questionnaires prior to study treatment administration at day 1 of weeks 1, 4, 7, 10, and during weeks 12 and 24 for subjects who have discontinued treatment for any reason other than confirmed PD, and at the safety follow-up visit. For subjects who have discontinued treatment for any reason other than confirmed PD, every effort should be made to complete PRO (EQ-D5 and EORTC QLQ-C30) questionnaires every 12 weeks (+1 week) during the long-term follow-up until **no longer than 3 years after the last subject is randomized.**

### 7.2 General Study Procedures

A signed and dated IRB/IEC-approved informed consent must be obtained before any study specific procedures are performed. Procedures that are part of routine care are not considered study specific procedures and may be used at screening to determine eligibility. All subjects will be screened for eligibility before enrollment/randomization. Only eligible subjects will be enrolled/randomized into the study.

During treatment, assessments and procedures can be performed within 3 days of the planned visit. It is recommended that dosing occur on the same day of the week (eg, if first dose is administered on Monday, all subsequent doses should be administered on a Monday), however a ± 3 day dosing and study procedure window is allowed.

The sponsor reserves the right to have all imaging studies performed at screening and on study during the phase 2 to be reviewed by an independent centralized endpoint assessment committee (EAC) for evaluation of response. Copies of all imaging studies, including those performed before the implementation of amendment 2, will be collected and held at an independent centralized radiology vendor for potential retrospective evaluation of response by an EAC.

Procedures deemed necessary as part of standard of care or as required by local laws and regulations may be performed at the Investigator's discretion.

The following laboratory analytes in Table 5 will be assessed at various times throughout the study:



**Table 5. Laboratory Analytes**

| **Chemistry** | **Coagulation** | **Thyroid Function** | **Hematology** | **Other Labs** |
|---|---|---|---|---|
| Sodium | PT or INR | TSH | RBC | *BRAF* V600E mutation |
| Potassium | PTT or aPTT | Free T4 | Hemoglobin | Pregnancy |
| Chloride | | | Hematocrit | Biomarkers |
| Total protein | | | Platelets | HSV-1 antibody |
| Albumin | | | WBC | Optional tumor biopsy |
| Calcium | | | Differential* | HIV** |
| Creatinine | | | • Neutrophils | Hepatitis B** |
| Total bilirubin | | | • Eosinophils | Hepatitis C** |
| Alkaline-phosphatase | | | • Basophils | LDH |
| AST (SGOT) | | | • Lymphocytes | |
| ALT (SGPT) | | | • Monocytes | |
| | | | *3-part differential if 5-part unable to be performed | **Required only if clinically indicated |

### 7.2.1 Screening, Enrollment (Phase 1b) or Randomization (Phase 2)

All subjects must have the following procedures completed within 28 days (unless otherwise noted) prior to enrollment/randomization:

- confirmation that the Informed Consent Form has been signed
- review of inclusion and exclusion criteria
- demographic data including sex, age, race, and ethnicity
- medication and medical history review, concomitant medication(s)
- physical examination as per standard of care including weight
- vital signs: systolic/diastolic blood pressure, resting pulse, respiration rate, temperature. Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign CRF. Record all measurements on the vital signs CRF. The temperature measurement selected for a subject should be from the same location throughout the study and documented on the vital signs CRF.
- ECOG performance status assessment (see Appendix F)
- a 12-lead electrocardiogram (ECG): Subject must be in supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The ECG must include the following measurements: Heart Rate, PR, QRS, QT, and QTc intervals. The investigator will review all ECGs. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to Amgen.
- radiographic tumor imaging (including CT scan, positron emission tomography [PET]/CT scan, magnetic resonance imaging [MRI] or US) of the chest, abdomen, pelvis and all other sites of disease, and CT scan or MRI of the brain with contrast); to be used as baseline imaging. Abdomen and pelvis MRI/CT scans or CT scans performed with PET must be with contrast if they are to be used for radiographic tumor imaging assessments.
- clinical tumor assessments, including clinical measurement of cutaneous, subcutaneous, or nodal tumor measurement by caliper to be used as baseline assessment.
- record of any SAEs that occur after subject signs informed consent
- local laboratory tests, as follows:
  - within ≤ 28 days prior to enrollment/randomization:
    - HIV test: required only if indicated for clinically suspected HIV infection
    - hepatitis B and/or hepatitis C tests: required only if indicated for clinically suspected hepatitis B or hepatitis C infection, respectively

- within ≤ 10 days prior to enrollment/randomization:
  - hematology panel: hemoglobin, hematocrit, white blood cell (WBC) count, with 5-part differential (3-part differential if 5-part unable to be performed), red blood cell (RBC) count, platelets
  - coagulation: PT or INR and PTT or aPTT
  - chemistry panel: sodium, potassium, chloride, total protein, albumin, calcium, creatinine, total bilirubin, alkaline phosphatase, AST, ALT
  - lactate dehydrogenase (LDH)
  - thyroid function tests: TSH, free T4
- within ≤ 3 days prior to enrollment/randomization
  - serum or urine pregnancy test for female subjects of childbearing potential

- Archived tumor tissue for *BRAF* V600E testing and biomarker analyses:
  - *BRAF* V600E mutation testing may be obtained in a number of ways as listed below:
    - Previously Known *BRAF* V600E Tumor Status: *BRAF* V600E tumor status result, obtained prior to screening for this study, from a local laboratory will be acceptable. The local laboratory report supporting the local *BRAF* V600E tumor testing result must be available at the site within 28 days after enrollment (phase 1b) or randomization (phase 2).
    - Previously Unknown *BRAF* V600E Tumor Status: Archived formalin-fixed paraffin-embedded tumor tissue (block or unstained tumor slide) from either the primary tumor or a metastatic lesion should be analyzed at a local laboratory or submitted to the central laboratory within 28 days after enrollment (phase 1b) or randomization (phase 2).
  - Archived formalin-fixed paraffin-embedded tumor tissue (block or unstained tumor slide) from either the primary tumor or a metastatic lesion, and the associated pathology reports must be submitted to the central laboratory during screening or within 4 weeks after enrollment/randomization for biomarker analyses.



### 7.2.2 Treatment

The following procedures will be completed during the treatment period. Treatment begins when the first dose of protocol treatment is administered to a subject. Study treatment should begin as soon as possible after enrollment/randomization via ETO but no later than 5 days after enrollment/randomization. Study treatment is to be administered after all other procedures are completed during each visit unless otherwise stated. Treatment procedures include the following:

- recording of concomitant medication(s) at each visit
- recording of AE(s)/SAE(s) at each visit SAEs will be reported within 24 hours of discovery of the event

- physical examination as per standard of care, including weight
  - phase 1b and phase 2 arm 1: day 1 of weeks 1, 4, 6, 9, 12, 15, 18, then every 4 weeks until end of study treatment
  - phase 2 arm 2: day 1 of weeks 1, 4, 7, 10
- vital signs: systolic/diastolic blood pressure, resting pulse, respiration rate and temperature. Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign CRF. Record all measurements on the vital signs CRF. The temperature measurement for a subject should be from the same location throughout the study and documented on the vital signs CRF.
  - phase 1b and phase 2 arm 1: day 1 of weeks 1, 4, 6, 8, 9, 10, 12, 14, 15, 16, 18, then every 2 weeks until end of study treatment
  - phase 2 arm 2: day 1 of weeks 1, 4, 7, 10
- ECOG performance status assessment (Appendix F)
  - phase 1b and phase 2 arm 1: day 1 of weeks 1, 4, 6, 9, 12, 15, 18 then every 4 weeks until end of study treatment
  - phase 2 arm 2: day 1 of weeks 1, 4, 7, 10
- local laboratory tests: Screening laboratory values may be used for day 1 week 1 assessment if completed within 3 days of study treatment initiation. On treatment tests can be performed within 3 days of the planned visit. Results should be reviewed prior to the administration of study treatment.
  - hematology panel: hemoglobin, hematocrit, WBC with 5-part differential (3-part differential if 5-part unable to be performed), RBC, platelet
    - phase 1b and phase 2 arm 1: day 1 of weeks 1, 4, 6, 9, 12, 15, 18 then every 4 weeks until end of study treatment
    - phase 2 arm 2: day 1 of weeks 1, 4, 7, 10
  - chemistry panel: sodium, potassium, chloride, total protein, albumin, calcium, creatinine, total bilirubin, alkaline phosphatase, AST, ALT
    - phase 1b and phase 2 arm 1: day 1 of weeks 1, 4, 6, 9, 12, 15, 18 then every 4 weeks until end of study treatment
    - phase 2 arm 2: day 1 of weeks 1, 4, 7, 10
  - thyroid function tests: TSH, free T4
    - phase 1b and phase 2 arm 1: day 1 of weeks 6, 9, 12, 15
    - phase 2 arm 2: day 1 of weeks 1, 4, 7, 10

- Blood samples will be drawn for biomarker analysis, including HSV-1 antibody serostatus and flow cytometry analysis of lymphocyte subsets including B cells, T cells and Natural Killer (NK) cells at the following time points (Refer to Laboratory Manual for biomarker sample procedures):
    - phase 1b: day 1 of weeks 1, 4, 6, 9, and 15
    - phase 2 arm 1: day 1 of weeks 1, 4, 6, 9, and 15 and either at the time of initial unconfirmed PR, confirmed PD per modified irRC (Appendix D), or at weeks 24 for subjects with SD, whichever comes first
    - phase 2 arm 2: day 1 of weeks 1, 4, 10, and either at the time of initial unconfirmed PR, confirmed PD per modified irRC (Appendix D), or at weeks 24 for subjects with SD, whichever comes first
- Blood and urine samples will be collected, stored, and ultimately tested for detection of talimogene laherparepvec DNA using qPCR at the following time points (Refer to Laboratory Manual for blood and urine sample collection procedures):
    - phase 2 arm 1: prior to study drug administration on day 1 of weeks 1, 4, 6, and 8
- Optional tumor biopsy (only for subjects who consent to the tumor biopsy):
    - phase 1b: At least one injected lesion and/or one uninjected lesion will be biopsied according to the following schedule:
        - within 3 days prior to the subject receiving the first dose of study treatment on day 1 week 1
        - within 3 days prior to dose of week 6 (pre-ipilimumab dose 1), week 15 (pre-Ipilimumab dose 4), and week 24.
    - phase 2 arm 1: At least one injected lesion and/or one uninjected lesion will be biopsied according to the following schedule:
        - within 3 days prior to the subject receiving the first dose of study treatment on day 1 week 1 (archival biopsy tissue may be substituted if prior biopsy was performed within 1 month prior to day 1, and no systemic anticancer therapies were given 1 month prior to the biopsy)
        - within 3 days prior to dose of week 6 (pre-ipilimumab dose 1), and either at the time of initial unconfirmed PR, confirmed PD per modified irRC (Appendix E), or at week 24 for subjects with SD, whichever comes first
    - phase 2 arm 2: At least one lesion will be biopsied according to the following schedule:
        - within 3 days prior to the subject receiving the first dose of study treatment on day 1 week 1 (archival biopsy tissue may be substituted if prior biopsy was performed within 1 month prior to day 1, and no systemic anticancer therapies were given 1 month prior to the biopsy)
        - either at the time of initial unconfirmed PR, confirmed PD per modified irRC (Appendix E), or at week 24 for subjects with SD, whichever comes first.
    - Refer to Laboratory Manual for tumor biopsy procedures.

- Swab of cold sore, vesicles and other lesions suspected to be herpetic in origin (if any) for real-time polymerase chain reaction (qPCR) testing:
  - for phase 1b and phase 2 arm 1: subject should return to clinic within 3 days of the occurrence of a reportable lesion suspected to be herpetic in origin such as cold sores or vesicles. The lesion should be evaluated by the investigator and swabbed if HSV infection is suspected. The sample will collected, stored, and ultimately tested using qPCR to evaluate whether the talimogene laherparepvec DNA is detectable in the sample.
- Radiographic tumor imaging assessments must include CT scan, PET/CT, MRI, or US of the chest, abdomen, and pelvis and all other sites of disease. Abdomen and pelvis MRI/CT scans or CT scans performed with PET must be with contrast if they are to be used for radiographic tumor imaging assessments. In addition, CT scan or MRI of the brain with contrast will only be performed if symptoms or signs suggestive of CNS metastasis are present. The imaging modality selected (eg, CT or MRI) should remain constant for any individual subject. Imaging to be performed independent of treatment cycle at day 1 week 12 (± 1 week) and then every 12 weeks (± 1 week) until disease progression per modified irRC (Appendix E) Clinical tumor assessments must include clinical measurement of cutaneous, subcutaneous, or nodal tumor measurement by caliper to be performed independent of treatment cycle at day 1 week 12 (± 1 week) and then every 12 weeks (± 1 week) until disease progression per modified irRC (Appendix E).
- Tumor response will be assessed using the modified irRC (Appendix E) at day 1 week 12 (± 1 week) and then every 12 weeks (± 1 week) until clinically relevant disease progression. Response (CR, or partial response [PR]) or disease progression to be confirmed by second consecutive clinical and radiographic assessments no less than 4 weeks from the date of the first documented response or disease progression. Confirmation of disease progression is required only in the absence of rapid clinical deterioration (rapid decline in performance status or rapid disease progression requiring other therapy).
- Completion of PRO questionnaires: EQ-D5 and EORTC QLQ-C30
  - phase 2 (arm 1): prior to study treatment administration at day 1 of weeks 1, 4, 6, 9, 12, 15, 18, 22, 24 then every 4 weeks until end of study treatment.
  - phase 2 (arm 2): **completion until no longer than 3 years after the last subject is randomized.**
- Talimogene laherparepvec treatment
  - phase 1b and phase 2 arm 1(before ipilimumab administration when co-administered): day 1 of weeks 1, 4, 6, 8, 10, 12, 14, 16, 18, then every 2 weeks until end of study treatment
- Ipilimumab treatment
  - phase 1b and phase 2 arm 1 (after talimogene laherparepvec administration when co-administered): day 1 of weeks 6, 9, 12, 15
  - phase 2 arm 2: day 1 of weeks 1, 4, 7, 10

### 7.2.3 Safety Follow-up

Upon permanent discontinuation from the study treatment for any reason, the following procedures will be performed approximately 30 (+ 7) days after the last dose of

talimogene laherparepvec or 60 (+ 7) days after the last dose of ipilimumab, whichever is later:

- recording of concomitant medication(s)
- physical examination as per standard of care including weight
- vital signs: systolic/diastolic blood pressure, resting pulse, respiration rate, temperature. Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign CRF. Record all measurements on the vital signs CRF. The temperature measurement selected for a subject should be from the same location throughout the study and documented on the vital signs CRF.
- ECOG performance status assessment (Appendix F)
- a 12-lead ECG: Subject must be in supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The ECG must include the following measurements: Heart Rate, PR, QRS, QT, and QTc intervals. The investigator will review all ECGs. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to Amgen.
- recording of AE(s)/SAE(s). SAEs will be reported within 24 hours of discovery of the event
- local laboratory tests:
  - hematology panel: hemoglobin, hematocrit, WBC with 5-part differential (3-part differential if 5-part unable to be performed), RBC, platelets
  - chemistry panel: sodium, potassium, chloride, total protein, albumin, calcium, creatinine, total bilirubin, alkaline phosphatase, AST, ALT
  - thyroid function tests: TSH, free T4
  - serum or urine pregnancy test for female subjects of childbearing potential
- Blood samples will be drawn for biomarker analysis, including HSV-1 antibody serostatus. Refer to Laboratory Manual for biomarker sample procedures.
- Phase 1b and phase 2 arm 1: Blood and urine samples will be collected, stored, and ultimately tested for detection of talimogene laherparepvec DNA using qPCR
- Swab of cold sore, vesicles and other lesions suspected to be herpetic in origin (if any) for qPCR:
  - for phase 1b and phase 2 arm 1: the lesion should be evaluated by the investigator and swabbed if HSV infection is suspected. The lesion should be evaluated by the investigator and swabbed if HSV infection is suspected. The sample will collected, stored, and ultimately tested using qPCR to evaluate whether the talimogene laherparepvec DNA is detectable in the sample.
- Radiographic tumor imaging, clinical tumor assessment and tumor response assessment is to be performed if the subject ended study treatment prior to disease

progression per the modified irRC (Appendix E) and has not had clinical tumor assessment performed within 12 weeks (± 1 week) of the visit.

- Radiographic tumor imaging assessments must include CT scan, PET/CT, MRI, or US of the chest, abdomen, and pelvis and all other sites of disease. Abdomen and pelvis MRI/CT scans or CT scans performed with PET must be with contrast if they are to be used for radiographic tumor imaging assessments. In addition, CT scan or MRI of the brain with contrast will only be performed if symptoms signs suggestive of CNS metastasis are present. The imaging modality selected (eg, CT or MRI) should remain constant for any individual subject.
- Clinical tumor assessments must include clinical measurement of cutaneous, subcutaneous, or nodal tumor measurement by caliper to be performed.
- Tumor response will be assessed using the modified irRC (Appendix E). Response (CR, or PR) or disease progression to be confirmed by second consecutive clinical and radiographic assessments no less than 4 weeks from the date of the first documented response or disease progression. Confirmation of disease progression is required only in the absence of rapid clinical deterioration (rapid decline in performance status or rapid disease progression requiring other therapy).

- Phase 2: Completion of PRO questionnaires: EQ-D5 and EORTC QLQ-C30

### 7.2.4 Long-term Follow-up

All subjects who permanently discontinue study drug for any reason other than withdrawal of full consent will be contacted by clinic visit or telephone to assess survival and initiation of additional melanoma therapy and any talimogene laherparepvec-related adverse events.

Contact for all subjects will be attempted every 12 weeks (± 28 days) following the safety follow-up visit until death, subject withdraws full consent, or up to **60** months after the last subject is randomized in phase 2.

Radiographic imaging, clinical tumor assessment, and tumor response assessment as detailed in Section 7.2.2 will be performed every 12 weeks (± 1 week) until documentation of disease progression per modified irRC (Appendix E), start of new anticancer therapy, or end of study whichever occurs first for subjects discontinuing study treatment for any reason other than PD. Subjects who have reached a confirmed CR may increase their interval of radiographic assessments up to 6 months after the first 2 years beyond confirmed CR and up to 12 months after the first 5 years beyond confirmed CR as **per Principal Investigator (PI) discretion**. **Subjects without CR will be assessed radiographically every 6 months after the first 2 years until the subject is 5 years off of therapy, then as per PI discretion. Patient Reported Outcome completion will be performed until no longer than 3 years after the last subject is randomized.** Subjects who have received talimogene laherparepvec and

completed the long-term follow-up for any reason other than death or withdrawal of full consent and who provide consent will continue follow-up for survival under a separate ongoing registry protocol which is in place for the long-term follow-up of subjects treated with talimogene laherparepvec in clinical trials. The registry protocol will also monitor for late and long-term adverse events thought to be potentially related to talimogene laherparepvec.

#### 7.2.5 Reporting Exposure to Talimogene Laherparepvec in Phase 1b and Phase 2 Arm 1

If a household member, caregiver, or healthcare provider who have had close contact with the subject is suspected to have been exposed to talimogene laherparepvec (eg, who have had signs or symptoms suspected to be herpetic in origin or accidentally exposed to talimogene laherparepvec), report the potential or known unintended exposure to talimogene laherparepvec, suspected related signs or symptoms, and detection of talimogene laherparepvec DNA by qPCR testing in a swab taken from a lesion, if any, in a subject's household member, caregiver, or healthcare provider as specified Section 9.4.

### 7.3 Biomarker Development

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. In oncology, there is particular interest in the molecular changes underlying the oncogenic processes that may identify cancer subtypes, stage of disease, assess the amount of tumor growth, or predict disease progression, metastasis, and responses to investigational product(s) or protocol required therapies.

Amgen may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to talimogene laherparepvec and/or ipilimumab. Refer to the laboratory manual for detailed collection and handling procedures for all biomarker development samples.

#### 7.3.1 Blood Samples

Blood samples are to be collected for biomarker development as described in Sections 7.2.2 and 7.2.3.

#### 7.3.2 Tumor Tissue Samples

**Archived Tumor Tissue Sample:**

A block of formalin-fixed paraffin-embedded tumor tissue collected prior to the study is to be sent to the central laboratory along with the corresponding pathology report as

described in Section 7.2.1. The tumor block is to be carefully selected by a pathologist or a skilled experienced histology associate to include generous tumor tissue using the Pathology Report as a guide. In lieu of a block, approximately 20 unstained sections on charged slides from the same block can be submitted. Refer to Laboratory Manual for tumor specific instructions on slide preparation. [redacted]

**Optional Tumor Biopsy Sample (Only for subjects who consent to the tumor biopsy):**

[redacted] Refer to Laboratory Manual for tumor biopsy procedures.

### 7.4 Pharmacogenetic Studies

If the subject consents to the optional pharmacogenetic portion of this study, DNA analyses on blood samples may be performed. These optional pharmacogenetic analyses focus on inherited genetic variations to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. The goals of the optional studies include the use of genetic markers to help in the investigation of cancer and/or to identify subjects who may have positive or negative response to talimogene laherparepvec and/or ipilimumab. No additional samples are collected for this part of the study. For subjects who consent to this/these analysis/analyses, DNA may be extracted.

### 7.5 Sample Storage and Destruction

Any blood sample collected according to the Schedule of Assessments (Table 2, Table 3 and Table 4) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be single coded prior to being shipped from the site for analysis, or storage. Results are stored in a secure database to ensure confidentiality.

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the cancer, the dose response and/or prediction of response to talimogene laherparepvec and/or ipilimumab, characterize antibody response, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years from the end of the study.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of pharmacogenetic, biomarker development, or other exploratory studies are not placed in the subject's medical record and are not made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). Following the request from the subject, the investigator is to provide the sponsor with the required study and subject numbers so that any remaining samples and any other components from the cells can be located and destroyed. If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See Section 11.3 for subject confidentiality.

### 7.6 Patient Reported Outcomes for Subjects Enrolled in Phase 2

PROs will be assessed using the following questionnaires: the EQ-5D and EORTC QLQ-C30. The two questionnaires are commonly used, uniformly accepted and validated instruments to evaluate health outcomes in subjects with cancer.

#### 7.6.1 EQ-5D

The EQ-5D questionnaire is a 2-page, generic preference-based Quality of Life (QOL) measure comprised of a 5-item health status measure and a visual analogue scale (VAS) (Kind, 1996; Rabin and de Charro, 2001) and is used to generate 2 scores. The EQ-5D utility score is based on answers to 5 questions that evaluate mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D VAS generates a single health status index with an analogue scale that ranges from 0 to 100 in which subjects are asked to rate their current health state by drawing a line from a box marked.

#### 7.6.2 EORTC QLQ-C30

The EORTC QLQ-C30 is a 2-page, self-reporting 30-item generic instrument for use in cancer subjects across tumor types. It assesses 15 domains consisting of 5 functional domains (physical, role, emotional, cognitive, social), 9 symptom domains (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties), and a global health status or QOL scale (Aaronson et al, 1993).

## 8. WITHDRAWAL AND REPLACEMENT OF SUBJECTS

### 8.1 Withdrawal of Subjects

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution.

Subjects (or a legally acceptable representative) can decline to continue receiving talimogene laherparepvec, ipilimumab, and/or other protocol-required procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from talimogene laherparepvec and/or ipilimumab and must discuss with the subject the options for continuation of the Schedule of Assessments (Table 2, Table 3 and Table 4) and collection of data, including endpoints and AEs. The investigator must document the change to the Schedule of Assessments (Table 2, Table 3 and Table 4) and the level of follow-up that is agreed to by the subject (eg, in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records).

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publically available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

Reasons for removal from protocol-required therapies or procedural assessments might include the following:

- subject request to end talimogene laherparepvec or ipilimumab administration
- safety concern (eg, due to an AE, failure to follow contraception, breast feeding, and/or protocol-required therapies requirements)
- disease progression per modified irRC (Appendix E).

Reasons for removal of a subject from the study might include the following:

- decision by sponsor
- withdrawal of consent from study
- death
- lost to follow-up

### 8.2 Replacement of Subjects

Subjects enrolled in the phase 1b part of the study may be replaced if they are not evaluable for DLT (ie, either a subject did not receive study treatment, permanently discontinued talimogene laherparepvec prior to receiving the first dose of ipilimumab for any reason, or ended the study treatment prior to week 12 for reason other than experiencing a DLT) until approximately 6 to 9 DLT evaluable subjects are enrolled (refer to Section 3.1.1). Subjects randomized to the phase 2 part of the study will not be replaced.

## 9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

### 9.1 Adverse Events

#### 9.1.1 Definition of Adverse Events

An AE is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The investigator is responsible for ensuring that any AEs observed by the investigator or reported by the subject are recorded in the subject's medical record.

The definition of AEs includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome. A preexisting condition that has not worsened during the study or involves an intervention such as elective cosmetic surgery or a medical procedure while on study, is not considered an AE.

Disease progression of the primary tumor should not be captured as an AE (including fatal AE). If there are signs and/or symptoms of disease progression (regardless of primary or secondary tumor) that are new or worsened from baseline signs and/or symptoms, these should be reported as AE(s). If a new primary malignancy appears, it will be considered an AE.

### 9.1.2 Reporting Procedures for Adverse Events

The investigator is responsible for ensuring that all AEs observed by the investigator or reported by the subject that occur after enrollment/randomization through 30 (+ 7) days after the last dose of talimogene laherparepvec or 60 (+ 7) days after the last dose of ipilimumab, whichever is later, are reported using the applicable CRF (eg, Medical History or AE Summary CRF). In addition, talimogene laherparepvec-related adverse events that occur during the long-term follow-up period until the end of study should also be captured in the Adverse Event CRF although these events will not be considered treatment-emergent adverse events.



The investigator must assign the following AE attributes:

- adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms)
- dates of onset and resolution
- severity
- assessment of relatedness to talimogene laherparepvec and/or ipilimumab
- action taken.

The AE grading scale used will be the CTCAE version 3.0. The grading scale used in this study is described in Appendix A. The investigator must assess whether the AE is possibly related to the talimogene laherparepvec and/or ipilimumab. This relationship is indicated by a “yes” or “no” response to the question: Is there a reasonable possibility that the event may have been caused by talimogene laherparepvec and/or ipilimumab?

The investigator must assess whether the SAE is possibly related to any study-mandated screening procedure. This relationship is indicated by a “yes” or “no”

response to the question: "Is there a reasonable possibility that the event may be related to screening procedures?"

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as AEs. However, laboratory value changes that require treatment or adjustment in current therapy are considered AEs. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the AE.

The investigator's clinical judgment is used to determine whether a subject it to be removed from treatment due to an AE. A subject, or subject's parent/legal guardian, can also voluntarily withdraw from treatment due to an AE. If the subject withdraws consent, the subject is encouraged to undergo, at a minimum, an end-of-study assessment.



## 9.2 Serious Adverse Events

### 9.2.1 Definition of Serious Adverse Events

A SAE is defined as an AE that meets at least 1 of the following serious criteria:

- fatal
- life threatening (places the subject at immediate risk of death)
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- congenital anomaly/birth defect
- other medically important serious event

An AE would meet the criterion of "requires hospitalization", if the event necessitated an admission to a health care facility (eg, overnight stay).

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a SAE under the criterion of "other medically important serious event". Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

Since the criteria for the CTCAE grading scale differs from the regulatory criteria for SAEs, if AEs correspond to grade 4 "life threatening" CTCAE grading scale criteria (eg, laboratory abnormality reported as grade 4 without manifestation of life threatening status), it will be left to the investigator's judgment to also report these abnormalities as

SAEs. For any AE that applies to this situation, comprehensive documentation of the event's severity status must be recorded in the subject's medical record.

### 9.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all SAEs observed by the investigator or reported by the subject that occur after signing of the informed consent through 30 (+7) days after the last dose of talimogene laherparepvec or 60 (+ 7) days after the last dose of ipilimumab, whichever is later, are recorded in the subject's medical record and are submitted to Amgen. The SAE must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the applicable CRF.

After the protocol-required reporting period defined above, the investigator does not need to actively monitor subjects for serious adverse events. However, if the investigator becomes aware of a serious adverse event after this protocol-required reporting period, the investigator will report the event to Amgen within 24 hours following the investigator's knowledge of the event. Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting.

If the electronic data capture (EDC) system is unavailable to the site staff to report the SAE, the information is to be reported to Amgen via an electronic SAE Contingency Report Form within 24 hours of the investigator's knowledge of the event.
See Appendix B for a sample of the SAE Worksheet/electronic SAE Contingency Report Form. For EDC studies where the first notification of a SAE is reported to Amgen via the electronic SAE Contingency Report Form, the data must be entered into the EDC system when the system is again available.

The investigator must assess whether the serious adverse event is possibly related to any study-mandated activity or procedure. This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by a study activity/procedure"?

The investigator is expected to follow reported serious adverse events until stabilization or reversibility.

New information relating to a previously reported SAE must be submitted to Amgen. All new information for SAEs must be sent to Amgen within 24 hours following knowledge the new information. The investigator may be asked to provide additional follow-up information, which may include a discharge summary or extracts from the medical

record. Information provided about the SAE must be consistent with that recorded on the applicable CRF (eg, AE Summary CRF).

If a subject is permanently withdrawn from protocol-required therapies because of a SAE, this information must be submitted to Amgen.

Amgen reports SAEs and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and IRBs/IECs in compliance with all reporting requirements according to local regulations and good clinical practice.

The investigator is to notify the appropriate IRB/IEC of SAEs occurring at the site and other AE reports received from Amgen, in accordance with local procedures and statutes.

### 9.3 Pregnancy and Lactation Reporting

If a pregnancy occurs in a female subject, or female partner of a male subject, while the subject is taking protocol-specified therapies, report the pregnancy to Amgen as specified below.

In addition to reporting any pregnancies occurring during the study treatment, investigators should monitor for pregnancies that occur after the last dose of protocol-required therapies through 3 months after the end of treatment.

The pregnancy should be reported to **Amgen Global Patient Safety within 24 hours of learning** of a **subject's** pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C). **After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 3 months after the end of treatment. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).**

If a lactation case occurs while the female subject is taking protocol-specified therapies report the lactation case to Amgen as specified below.

In addition to reporting a lactation case during the study treatment, investigators should monitor for lactation cases that occur after the last dose of protocol-required therapies through 3 months after the end of treatment.

Any lactation case should be reported to **Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event**. Report a lactation case on the Lactation Notification Worksheet (Appendix D).

**With the female subject's signed authorization for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 3 months after discontinuing protocol-required therapies.**

### 9.4 Reporting of Exposure to Talimogene Laherparepvec in Phase 1b and Phase 2 Arm 1

If a household member, caregiver, or healthcare provider who has had close contact with the subject is suspected to have been exposed to talimogene laherparepvec (eg, have or who have had signs or symptoms suspected to be herpetic in origin or who have been accidentally exposed to talimogene laherparepvec), while the subject is taking talimogene laherparepvec, report the exposure to Amgen as specified below. In addition to reporting an unintended exposure case during the study treatment, investigators should monitor for potential exposure cases that occur after the last dose of talimogene laherparepvec through 30 (+ 7) days after the last dose of talimogene laherparepvec.

Any potential or known unintended exposure should be reported to Amgen within 24 hours of the investigator's knowledge of the event of exposure. Amgen will seek to follow-up with the exposed individual, if necessary, to collect more information about the exposed individual contact with clinical trial subject, signs and/or symptoms related to the exposure, medical history, and/or outcome of the exposure. If the exposed individual is reporting sign or symptoms suspected to be related to talimogene laherparepvec exposure, the exposed individual may be asked to have a swab taken to evaluate for the presence of talimogene laherparepvec DNA in the lesion by qPCR testing.

## 10. STATISTICAL CONSIDERATIONS

### 10.1 Study Endpoints, Analysis Sets, and Covariates

#### 10.1.1 Study Endpoints

##### 10.1.1.1 Primary Endpoint

Phase 1b: The primary endpoint is the incidence of AEs and clinical laboratory abnormalities defined as dose limiting toxicity (DLT).

Phase 2: Objective Response Rate (ORR): Incidence rate of subjects with confirmed response (CR or PR) (response evaluation by an investigator using modified irRC).

#### 10.1.1.2 Secondary Endpoints

Efficacy Endpoints: For the phase 1b part, objective response rate. For the phase 2 part, best overall response, disease control rate, durable response rate, time to response, duration of response, progression-free survival, resection rate**,** overall survival (OS), landmark OS by year.

- Best overall response (BOR): The best overall response in descending order a subject can achieve is CR, PR, SD and PD per the modified irRC (Appendix E), where the SD must be no earlier than 77 days after the date of enrollment/randomization.
- Disease control rate (DCR): A confirmed CR/PR or a SD, per the modified irRC (Appendix E), is considered disease control.
- Durable response rate (DRR): The incidence rate of subjects with a duration of response of at least 6 months
- Time to response (TTR): Time from randomization date to the date of the first confirmed objective response (CR/PR) per the modified irRC (Appendix E).
- Duration of response (DOR): (calculated only for those subjects with an objective response) time from first confirmed objective response to confirmed disease progression per the modified irRC (Appendix E) or death, whichever occurs earlier.
- Progression-free survival (PFS): Time from randomization to the date of first of confirmed disease progression per modified irRC criteria (Appendix E), or death, whichever occurs earlier.
- Resection rate: Incidence rate of surgical procedures for melanoma that resulted in partial reduction or complete eradication of all previously unresectable cutaneous or visceral metastatic disease. Subjects who received surgical procedures for melanoma with palliative intent (eg, for pain control) in the presence of disease progression will be excluded from the denominator.
- Overall Survival (OS): time from randomization date to the date of death from any cause.
- Landmark OS by year: The Kaplan-Meier (K-M) estimate for OS of the proportion of subjects alive at yearly intervals.

**Safety Endpoints:**

- For phase 2: Incidence of all AEs, grade ≥ 3 AEs, SAEs, and events requiring the discontinuation of study drug, local effects on the tumor (ie, pain, inflammation and ulceration), clinically significant laboratory changes and clinically significant changes in vital signs.
- For phase 1b: The same safety endpoints will be evaluated as phase 2 but not including AEs and clinical laboratory abnormalities defined as DLT.

#### 10.1.1.3 Exploratory Endpoints

The following are the exploratory endpoints:

- Summary scores at each assessment and changes from baseline of PROs in phase 2 as assessed by EQ-5D and the EORTC QLQ-C30

### 10.1.2 Analysis Sets

**DLT Analysis Set**

The DLT analysis set will include the first 6 to 9 DLT evaluable subjects enrolled in the phase 1b who must have had the opportunity to be on treatment for at least 6 weeks from the initial dosing of ipilimumab and received at least 1 dose of talimogene laherparepvec and 1 dose of ipilimumab.

**Intent-to-Treat Analysis Set**

The Intent-to-Treat (ITT) Analysis Set is defined as all randomized subjects regardless of whether they received study treatment. Subjects will be analyzed according to their randomized treatment group. The ITT analysis set is used for the primary analysis of all efficacy endpoints for the phase 2 part of the study.

**Safety Analysis Set**

The Safety Analysis Set will include all subjects who received at least 1 dose of talimogene laherparepvec or ipilimumab. The Safety Analysis Set will be defined separately for phase 1b and phase 2 parts of the study. For phase 2 all subjects will be analyzed according to the treatment they received (ie, ipilimumab alone versus talimogene laherparepvec + ipilimumab or talimogene laherparepvec alone). Analyses of efficacy and safety endpoints for phase 1b will utilize the Safety Analysis Set.

**PRO Analysis Set**

The PRO Analysis Set will include all subjects in the ITT analysis set in the phase 2 that have a baseline and at least one post-baseline value for at least one PRO score assessed by EQ-5D and/or the EORTC QLQ-C30.

### 10.1.3 Covariates and Subgroups

Besides the stratification factors the following covariates may be used to examine efficacy and safety in subgroups or in multivariate analyses:

- region, if applicable (USA or non-USA)
- age at baseline: < 50, ≥ 50; < 65, ≥ 65; < 75, ≥ 75 years
- disease stage at baseline: IIIB vs IIIC vs IVM1a vs IVM1b vs IVM1c
- the sum of the products of the two largest perpendicular diameters (SPD) of the index lesions at baseline
- baseline absolute lymphocyte count: ≤ 1000 vs > 1000 at week 6
- baseline LDH: ≤ ULN vs > ULN
- Prior therapy: chemotherapy (yes vs no), immunotherapy (yes vs no), ipilimumab (yes vs no), PD-1 inhibitors (yes vs no), PD-L1 inhibitors (yes vs no), *BRAF* inhibitors (yes vs no), MEK inhibitors (yes vs no)
- Lines of prior therapy: 0 vs 1 vs 2; 0 vs ≥ 1
- Disease state at enrollment: newly diagnosed vs recurrent
- *BRAF* V600 mutation: yes vs no
- Positive HSV-1 baseline and post-baseline serostatus: yes vs no

Tumor tissue or serum biomarkers - the analyses of these data may be performed after collection of all samples during the conduct of the study and therefore may be reported after the primary analysis of efficacy endpoint.

### 10.2 Sample Size Considerations

**Phase 1b:**

Approximately 18 subjects are believed to be sufficient to provide enough evaluable subjects to assess the DLT profile for the combination of the talimogene laherparepvec in combination with ipilimumab for the phase 1b part.

**Phase 2:**

Approximately 200 subjects will be randomized in a ratio of 1:1 to the two treatment arms in the phase 2 part of the study. This sample size was based on comparing the treatment arms with respect to the ORR as primary efficacy endpoint in the ITT Analysis Set with an overall 2-sided 5% significance level for testing the null hypothesis of no treatment effect (see Table 6). Superiority of ORR will not be declared at the interim analysis, therefore the significance levels will not be adjusted for the interim analysis.

**Table 6. ORR Effect Size Scenarios With 90% Power in the ITT Analysis Set**

| | | Effect Size with 90% Power | | | Min. Stat. Sign.* Effect Size | | |
|---|---|---|---|---|---|---|---|
| Ipi ORR | N | Ipi + T-VEC ORR | Absolute Δ | Odds Ratio | Ipi + T-VEC ORR | Absolute Δ | Odds Ratio |
| **5.0%** | 200 | 21.3% | 16.3% | 5.15 | 14.2% | 9.2% | 3.14 |
| | 190 | 21.9% | 16.9% | 5.33 | 14.5% | 9.5% | 3.22 |
| | 180 | 22.6% | 17.6% | 5.54 | 14.9% | 9.9% | 3.32 |
| **10.0%** | 200 | 29.0% | 19.0% | 3.67 | 21.1% | 11.1% | 2.40 |
| | 190 | 29.6% | 19.6% | 3.78 | 21.5% | 11.5% | 2.46 |
| | 180 | 30.3% | 20.3% | 3.91 | 21.8% | 11.8% | 2.51 |
| **15.0%** | 200 | 35.7% | 20.7% | 3.15 | 27.4% | 12.4% | 2.14 |
| | 190 | 36.4% | 21.4% | 3.24 | 27.8% | 12.8% | 2.18 |
| | 180 | 37.1% | 22.1% | 3.34 | 28.1% | 13.1% | 2.22 |
| **20.0%** | 200 | 42.0% | 22.0% | 2.90 | 33.3% | 13.3% | 2.00 |
| | 190 | 42.7% | 22.7% | 2.98 | 33.7% | 13.7% | 2.03 |
| | 180 | 43.3% | 23.3% | 3.06 | 34.1% | 14.1% | 2.07 |

Note: hypothesis tested at α = 0.05; min stat. significance assumes 50% power.

### 10.3 Access to Individual Subject Treatment Assignments by Amgen or Designees

As this is an open-label study, the investigators/site personnel and the trial participating subjects will know the treatment assignments.

To guard against actual or perceived bias due to subjective decisions made by Amgen or Designee in light of the treatment knowledge and data captured during the phase 2 part of the study, Amgen will restrict aggregated treatment results for the phase 2 part of the study prior to screening closure for the study.

### 10.4 Planned Analyses

#### 10.4.1 Interim Analyses

An interim analysis of efficacy and safety in the phase 2 part of the study was planned to be conducted that included the first 60 subjects in the ITT Analysis Set when they had had the opportunity to be followed for at least 24 weeks after randomization. An updated analysis will be conducted once there has been an additional minimum 24 weeks of follow-up for the patients that were included in the prior interim analysis. This includes approximately 80 subjects who were ultimately evaluable for inclusion in the previous interim analysis at the time the data was analyzed.

These interim analyses will allow for a risk-benefit assessment and will provide data to guide prioritization of future talimogene laherparepvec studies. This study will not be discontinued or modified due to the results of the efficacy interim analyses. The analyses will be conducted by an Amgen independent statistical team. The aggregate unblinded efficacy results may be shared with limited key members of Amgen Senior Management and their designees. The interim aggregate results will not be shared with the investigators or the study team members involved in the management of the study until the study has closed to screening.

Descriptive interim analyses for OS will be performed at the time of primary analysis for ORR and at 2 years**, 3 years, and 4 years** after the last subject is randomized in phase 2.

### 10.4.2 Dose Level Review Team (DLRT) for Phase 1b

The phase 1b part of the study data will be monitored by a Dose Level Review Team (DLRT) on an ongoing basis to ensure subject safety. The DLRT consisting of the Amgen study team, including least one clinician, safety representative, and study biostatistician, and at least one participating investigator who has recruited subjects into the phase 1b part of the study, will be responsible for reviewing all available safety data and DLT and will make the corresponding decisions in accordance with the rules set out in (see Section 3.1.1).

### 10.4.3 Data Review Team (DRT) for Phase 2

For the phase 2 part of the study, a Data Review Team (DRT) internal to Amgen but independent of the talimogene laherparepvec product team will be formed (see Section 3.1.2). This team will review unblinded safety data after approximately 16 subjects have been randomized and have had the opportunity to be on treatment for at least 6 weeks from the initial dosing of ipilimumab and received at least 1 dose of talimogene laherparepvec and/or 1 dose of ipilimumab. In addition, this team will review unblinded safety data after approximately 16 subjects who received prior therapy for stage IIIB to IV melanoma before enrollment into the study and have had the opportunity to be on study treatment for at least 6 weeks from the initial dosing of ipilimumab and received at least 1 dose of talimogene laherparepvec and/or 1 dose of ipilimumab. The DRT may recommend additional reviews of the safety data based on the outcome of the planned reviews. This independent DRT will be governed by a study-specific DRT charter.

### 10.4.4 Primary Analysis

The clinical study report (CSR) will be written based on the results of the primary analysis of phase 2 and also include the results from phase 1b.

**Phase 1b**

The goal of the primary analysis is to determine the safety and tolerability of talimogene laherparepvec in combination with ipilimumab as assessed by incidence of DLT.
The primary analysis will occur when the last subject enrolled in the phase 1b has had the opportunity to be on treatment for at least 6 weeks from the initial dosing of ipilimumab.

**Phase 2**

The primary goal of the primary analysis is to evaluate the efficacy as assessed by the ORR, per investigator assessment according to the modified irRC, of treatment with talimogene laherparepvec in combination with ipilimumab versus ipilimumab alone in subjects with unresected, stages IIIB to IV melanoma. The primary analysis of ORR will be conducted on the ITT Analysis Set approximately 6 months after the last subject is randomized in the phase 2.

### 10.4.5 Final Analysis

The final analysis will occur approximately **5** years after the last subject is randomized in phase 2. The analysis of OS will be conducted at this final analysis and will use all events at the time. The CSR will be amended with the updated results from the final analysis at the completion of the study.

## 10.5 Planned Methods of Analysis

### 10.5.1 General Considerations

The DLT analysis set will be used to summarize the subject incidence of DLT for phase 1b part of the study and the safety analysis set will be used for all other analyses of safety. Besides the summary of subject incidence of DLT for the phase 1b part, the safety analysis in phase 1b part and phase 2 part of the study will include, but is not be limited to, the following:

- all AEs, grade ≥ 3 AEs, SAEs, and events requiring the discontinuation of study drug, local effects on the tumor (ie, pain, inflammation and ulceration)
- clinically significant laboratory changes and clinically significant changes in vital signs.

The safety analysis will be conducted separately for the phase 1b part and the phase 2 part as well as the efficacy analysis. For the phase 1b part, the efficacy analysis will be conducted on the Safety Analysis Set. Exact binomial 2-sided 95%

confidence interval (CI) (Clopper and Pearson, 1934) will be provided for the ORR and summary statistics will be provided for other efficacy endpoints, if appropriate. For the phase 2, the efficacy analysis will be conducted on the ITT Analysis Set by randomized treatment and on the Safety Analysis Set by actual treatment received for the safety analysis.

The primary analysis of response variant endpoints will be based on investigator assessments per modified irRC. Sensitivity analyses of selected response variants, eg, BOR and PFS, will be based on RECIST 1.1 (Eisenhauer et al, 2009) and modified RECIST 1.1.

Modified RECIST 1.1: A modification from the RECIST 1.1 where, in the absence of rapid clinical deterioration, a response of PD will require a subsequent confirmation at least 4 weeks apart.

In the event Amgen elects to have tumor response evaluated by an independent centralized EAC (see Section 7.2), additional sensitivity analyses of some of the response variant endpoints will be provided based on the evaluation of response by the EAC using modified irRC, RECIST 1.1, and/or modified RECIST 1.1.



### 10.5.2 Primary Endpoint

**Phase 1b**

The subject incidence of DLT will be summarized using DLT analysis set.

**Phase 2**

A Chi-square test with continuity correction (Fleiss, et al 1980) will be used to test whether there is difference in the ORR between treatments with talimogene laherparepvec in combination with ipilimumab relative to ipilimumab alone. An overall 2-sided 5% significance level will be used for the Chi-square test. For each treatment arm, exact binomial 2-sided 95% CI (Clopper and Pearson, 1934) will be generated for the ORR. Wilson's score method with continuity correction will be used to calculate a 95% CI for the between-arm difference in rates (Newcombe, 1998).

### 10.5.3 Secondary Efficacy Endpoint(s)

For phase 2, the following statistical approaches will be applied.

For disease control rate, durable response rate and resection rate, exact binomial 2 sided 95% CI (Clopper and Pearson, 1934) will be generated by treatment. Wilson's score method with continuity correction will be used to calculate a 95% CI for the between-arm difference in rates (Newcombe, 1998).

Best overall response (BOR) of CR, PR, SD, PD and UE, per modified irRC, will be tabulated by treatment group. An unconfirmed CR/PR and PD will be classified as SD and UE, respectively. A BOR of SD, not due to unconfirmed CR or PR, will require a minimum duration of 77 days from the date of enrollment/randomization.

If, at the primary analysis of ORR, the null hypothesis of no treatment effect in comparing ORR between the 2 treatment arms is rejected, OS will be compared with an un-stratified log-rank test at the study's Final Analysis **with type I error** 0.05. The OS treatment hazard ratio and its 2-sided 95% CI will be estimated using an un-stratified Cox proportional hazards model. Kaplan-Meier (KM) curves for OS will be generated by treatment arm in the ITT analysis set. KM estimates and the 95% CIs for within each treatment and between treatment differences of annual OS rates will be provided. The CI for treatment annual rate differences will be based on variance estimates using Greenwood's formula (Kalbfleisch and Prentice, 1980). CIs for the KM quartiles will be provided by treatment arm (Brookmeyer and Crowley, 1982). Interim analyses of OS will be performed at the time of the ORR primary analysis and at 2 years**, 3 years, and 4 years** after the last subject has been randomized. **All** interim analyses will be descriptive.

Analyses of time-to-event endpoints such as TTR, PFS and DOR will follow the ones described for OS, except that all p-values will be descriptive.

Sensitivity analyses of best overall response and PFS will be re-derived based on a modified RECIST 1.1 (see SAP for details).



### 10.5.4 Safety Endpoints

Subject incidence rates of treatment-emergent AEs (including all AEs, grade ≥ 3 AEs, SAEs, AEs of interest and events requiring the discontinuation of study drug, local effects on the tumor [ie, pain, inflammation and ulceration]) through either the 30 days after the last dose of talimogene laherparepvec or 60 days after the last dose of ipilimumab, whichever is later will be summarized. Medical Dictionary for Regulatory Activities (MedDRA) will be used to code AEs to a system organ class (SOC) and a preferred term within the SOC. The CTCAE version 3.0 will be used to grade severity of AEs. In addition clinically significant laboratory changes and clinically significant changes in vital signs will be summarized with descriptive statistics. Summary statistics will also be provided for concomitant medications, study drug delay and discontinuation, overall exposure, and changes in ECOG performance status.

Tables and/or narratives of deaths through either the 30 days after the last dose of talimogene laherparepvec or 60 days after the last dose of ipilimumab, whichever is later will be provided as treatment-emergent AEs. Talimogene laherparepvec-related AEs reported during the long-term follow-up will be listed separately.

The ECG measurements from this clinical study will be performed as per standard of care for routine safety monitoring, rather than for purposes of assessment of potential QTc effect. Therefore, they will not be summarized.

The qPCR analysis result of talimogene laherparepvec DNA in swab samples taken from cold sore, vesicles and other lesions suspected to be herpetic in origin (if any) will be summarized.

Potential or known unintended exposure to talimogene laherparepvec, related suspected signs or symptoms, and detection of talimogene laherparepvec DNA in a subject's household member, caregiver, or healthcare provider will be reported.



### 10.5.5 PRO Endpoints

The PRO analyses will be conducted on the PRO Analysis Set. Summary scores by EQ-5D and the EORTC QLQ-C30 questionnaires at each assessment and changes from baseline in phase 2 will be reported. For the EQ-5D questionnaire, two scores will be estimated; the utility score calculated from the 5 domains using a scoring algorithm and the VAS score based on the 0-100 feeling thermometer. Changes from baseline will be summarized at specified time points of interest, and differences between treatment groups for each defined score will be analyzed. For the EORTC QLQ- C30 questionnaire, each of the 30 scores, as well as the 5 functional scales, 9 symptom scales, and a global health status or QOL scale will be summarized similarly. The calculation of scores and methods for handling missing data will be based on the questionnaire's standard scoring guidelines. Details of all the PRO analyses will be provided in the statistical analysis plan.

## 11. REGULATORY OBLIGATIONS

### 11.1 Informed Consent

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Amgen clinical study manager to the investigator. The written informed consent document is to be prepared in the language(s) of the potential patient population.

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational product or other protocol-specified therapy are administered.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record. The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject.

If a potential subject is illiterate or visually impaired the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood.



### 11.2 Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IRB/IEC for written approval. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The investigator is to notify the IRB/IEC of deviations from the protocol or SAEs occurring at the site and other AE reports received from Amgen, in accordance with local procedures.

The investigator is responsible for obtaining annual IRB/IEC approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen.

### 11.3 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the CRF demographics page, in addition to the unique subject identification number, include the age at time of enrollment.
- For SAEs reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

In compliance with Federal regulations/International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.



### 11.4 Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multicenter studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will be any or all of the following:

- a recognized expert in the therapeutic area
- an investigator who provided significant contributions to either the design or interpretation of the study
- an investigator contributing a high number of eligible subjects

## 12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

### 12.1 Protocol Amendments and Study Termination

If Amgen amends the protocol, agreement from the investigator must be obtained. The IRB/IEC must be informed of all amendments and give approval. The investigator must send a copy of the approval letter from the IRB/IEC to Amgen.

Amgen reserves the right to terminate the study at any time. Both Amgen and the investigator reserve the right to terminate the investigator's participation in the study according to the study contract. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen investigational product by an extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen investigational product, and by what mechanism, after termination of the trial and before it is available commercially.

### 12.2 Study Documentation and Archive

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Amgen Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

In this study, the ETO System captures the following data points and these are considered source data: subject identification number and randomization number.

CRF entries may be considered source data if the CRF is the site of the original recording (ie, there is no other written or electronic record of data).

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Elements to include the following:

- subject files containing completed CRF, informed consent forms, and subject identification list
- study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen
- investigational product-related correspondence including, Proof of Receipts (POR), Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable.
- noninvestigational product(s) and or medical device(s) documentation, as applicable.

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

Retention of study documents will be governed by the Clinical Trial Agreement.

### 12.3 Study Monitoring and Data Collection

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that subject confidentiality is respected.

The Amgen clinical monitor is responsible for verifying the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The clinical monitor is to have access to subject medical records and other study-related records needed to verify the entries on the CRFs.

The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Compliance Auditing function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the CRFs must be maintained and readily available.
- Updates to CRFs will be automatically documented through the software's "audit trail".
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review is performed on subject data received at Amgen. During this review, subject data is checked for consistency, omissions, and any apparent discrepancies. In addition, the data is reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications are created in the EDC system database for site resolution and closed by Amgen reviewer.
- The investigator signs only the Investigator Verification Form for this electronic data capture study. This signature indicates that investigator inspected or reviewed the data on the CRF, the data queries, and the site notifications, and agrees with the content.

Amgen (or designee) will perform self-evident corrections to obvious data errors in the clinical trial database, as documented in the Study Specific Self Evident Corrections Plan. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (eg, same results sent twice with the same date with different visit-week 4 and early termination) and clarifying "other, specify" if data are provided (eg, race, physical examination). Each investigative site will be provided a list of the types of corrections applied to study data at the initiation of the trial and at study closeout.



### 12.4 Investigator Responsibilities for Data Collection

The investigator is responsible to comply with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (Table 2, Table 3, and Table 4), the investigator can search publically available records [where permitted]) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

### 12.5 Language

Case report forms must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

### 12.6 Publication Policy

To coordinate dissemination of data from this study, Amgen encourages the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff as appropriate as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship – the criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors, 2006), which states the following:

- Authorship credit is to be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published. Authors are to meet conditions 1, 2, and 3.
- When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals are to fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors are to qualify for authorship, and all those who qualify are to be listed.
- Each author is to have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

### 12.7 Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

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## 14. APPENDICES

## Appendix A. Additional Safety Assessment Information

**Adverse Event Grading Scale**

The Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be used for AE grading. The CTCAE version 3.0 is available at the following location: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

## Appendix B. Sample Serious Adverse Event Form

| AMGEN<br>Study # 20110264<br>Talimogene<br>Laherparepvec | **Electronic Adverse Event Contingency Report Form**<br>**For Restricted Use** |
|---|---|

**Reason for reporting this event via fax**

**The Clinical Trial Database (eg. Rave):**

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

**[If the protocol provides instructions to submit certain types of events ONLY to Amgen Safety and not to the Clinical Trial Database, state that reason below and remove these instructions. If no protocol-specific reasons, remove these instructions and the following bullet.]**

Protocol specific reason(s):

☐ *<<Note protocol instruction/reason here and change text from italics to standard.>>*

***<<For completion by Amgen prior to providing to sites: SELECT OR TYPE IN A FAX#>>***

**1. SITE INFORMATION**

| Site Number | Investigator | Country |
|---|---|---|
| | | |

| Reporter | Phone Number | Fax Number |
|---|---|---|
| | ( ) | ( ) |

**2. SUBJECT INFORMATION**

| Subject ID Number | Age at event onset | Sex | Race | If applicable, provide End of Study date |
|---|---|---|---|---|
| | | ☐F ☐M | | |

**If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term:** _____
**and start date:** Day ____ Month _____ Year _____

**3. ADVERSE EVENT**

**Provide the date the Investigator became aware of this information:** Day____ Month____ Year____

| Adverse Event diagnosis or syndrome<br>If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report<br>*List one event per line. If event is fatal, enter the cause of eeath. Entry of "death" is not acceptable, as this is an outcome.* | Date Started<br>Day Month Year | Date Ended<br>Day Month Year | Check only if event occurred before first dose of IP/drug under study | Is event serious? | If serious, enter Serious Criteria code (see codes below) | Relationship<br>Is there a reasonable possibility that theEvent may have been caused by IP/drug under study or an Amgen device used to administer the IP/drug under study?<br>T-vec No✓ Yes✓ <Pldevice> No✓ Yes✓ <Pldevice> No✓ Yes✓ <Pldevice> No✓ Yes✓ | Outcome of Event<br>-Resolved<br>-Not resolved<br>-Fatal<br>-Unknown | Check only if event is related to study procedure<br>eg, biopsy |
|---|---|---|---|---|---|---|---|---|
| | | | | ☐ Yes ☐ No | | | | |
| | | | | ☐ Yes ☐ No | | | | |
| | | | | ☐ Yes ☐ No | | | | |

**Serious Criteria:**
01 Fatal
02 Immediately life-threatening
03 Required/prolonged hospitalization
04 Persistent or significant disability /incapacity
05 Congenital anomaly / birth defect
06 Other medically important serious event

**4. Was subject hospitalized or was a hospitalization prolonged due this event?** ☐No ☐Yes If yes, please complete all of Section 4

| Date Admitted<br>Day Month Year | Date Discharged<br>Day Month Year |
|---|---|
| | |

| AMGEN<br>Study # 20110264<br>Talimogene<br>Laherparepvec | **Electronic Adverse Event Contingency Report Form**<br>**For Restricted Use** |
|---|---|

| Site Number | Subject ID Number |
|---|---|
| | |

**5. Was IP/drug under study administered/taken prior to this event?** ☐No ☐Yes If yes, please complete all of Section 5

| IP/Drug/Amgen Device: | | Date of Initial Dose<br>Day Month Year | Prior to, or at time of Event<br>Date of Dose<br>Day Month Year | Dose | Route | Frequency | Action Taken with Product<br>01 Still being Administered<br>02 Permanently discontinued<br>03 Withheld | Lot # and Serial # |
|---|---|---|---|---|---|---|---|---|
| Talimogene Laherparepvec | ☐blinded ☐open label | | | | | | | Lot # _____ ☐ Unknown<br>Serial # _____ ☐ Unavailable / Unknown |
| <<IP/Drug/Device>> | ☐blinded ☐open label | | | | | | | Lot # _____ ☐ Unknown<br>Serial # _____ ☐ Unavailable / Unknown |

**6. CONCOMITANT MEDICATIONS (eg, chemotherapy)** Any Medications? ☐ No ☐ Yes If yes, please complete:

| Medication Name(s) | Start Date<br>Day Month Year | Stop Date<br>Day Month Year | Co-suspect<br>No✓ | <br>Yes✓ | Continuing<br>No✓ | <br>Yes✓ | Dose | Route | Freq. | Treatment Med<br>No✓ | <br>Yes✓ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |
| | | | | | | | | | | | |

**7. RELEVANT MEDICAL HISTORY** ***(include dates, allergies and any relevant prior therapy)***

**8. RELEVANT LABORATORY VALUES** ***(include baseline values)*** Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete:

| Date<br>Day Month Year | Test<br>Unit | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |
| | | | | | | | | | | | | |

**9. OTHER RELEVANT TESTS** ***(diagnostics and procedures)*** Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

| Date<br>Day Month Year | Additional Tests | Results | Units |
|---|---|---|---|
| | | | |
| | | | |

*FORM-056006* *Version 6.0 Effective Date 07 JUL 2014*

Page 2 of 3

| AMGEN<br>Study # 20110264<br>Talimogene<br>Laherparepvec | **Electronic Adverse Event Contingency Report Form**<br>**For Restricted Use** |
|---|---|

| | | | |
|---|---|---|---|
| | Site Number | Subject ID Number | |

**10. CASE DESCRIPTION** ***(Provide narrative details of events listed in section 3)*** Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

| Signature of Investigator or Designee -<br>*I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.* | Title | Date |
|---|---|---|

## Appendix C. Pregnancy Notification Worksheet

AMGEN Pregnancy Notification Worksheet

*Fax Completed Form to the Country-respective Safety Fax Line*

US: +888 814 8653

**1. Case Administrative Information**

Protocol/Study Number: 20110264

Study Design: ■ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

**2. Contact Information**

Investigator Name _____ Site # _____

Phone (____)_____ Fax (____)_____ Email _____

Institution _____

Address _____

**3. Subject Information**

Subject ID # _____ Subject Gender: ☐ Female ☐ Male Subject DOB: mm___/ dd___/ yyyy____

**4. Amgen Product Exposure**

| Amgen Product | Dose at time of conception | Frequency | Route | Start Date |
|---|---|---|---|---|
| | | | | mm___/dd___/yyyy____ |

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm___/dd___/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

**5. Pregnancy Information**

Pregnant female's LMP mm___/ dd___/ yyyy____ ☐ Unknown

Estimated date of delivery mm___/ dd___/ yyyy____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm___/ dd___/ yyyy____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm___/ dd___/ yyyy____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

Amgen maintains a Pregnancy Surveillance Program that collects data about pregnancy of women who have been exposed to an Amgen product directly or via male sexual partner. Information from this program and from other sources of information, will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during pregnancy.

Effective Date: March 27, 2011 Page 1 of 1

## Appendix D. Lactation Notification Worksheet

**AMGEN® Lactation Notification Worksheet**

*Fax Completed Form to the Country-respective Safety Fax Line*
SELECT OR TYPE IN A FAX# enter fax number

**1. Case Administrative Information**

Protocol/Study Number: 20110264

Study Design: ☑ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

**2. Contact Information**

Investigator Name _____ Site # _____

Phone (____)_____ Fax (____)_____ Email _____

Institution _____

Address _____

**3. Subject Information**

Subject ID # _____ Subject Date of Birth: mm____/ dd____/ yyyy____

**4. Amgen Product Exposure**

| Amgen Product | Dose at time of breast feeding | Frequency | Route | Start Date |
|---|---|---|---|---|
| | | | | mm____/dd____/yyyy____ |

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm____/dd____/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

**5. Breast Feeding Information**

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

Amgen maintains a Lactation Surveillance Program that collects data about women who have been exposed to an Amgen product while breastfeeding. Information from this program and from other sources of information will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during lactation.

Effective Date: 03 April 2012, version 2. Page 1 of 1

## Appendix E. Modified Immune-related Response Criteria (irRC) for Review of Disease Response

A systematic tumor response criteria designated immune-related response criteria (irRC) was defined by Wolchok et al, 2009, in an attempt to capture additional tumor response patterns observed with immunotherapy in advanced melanoma beyond those described by the Response Evaluation Criteria in Solid Tumors (RECIST) or the World Health Organization (WHO) criteria. A modified version of the irRC will be employed in this study.

### Method of Measurement of Melanoma Tumor Lesions

**Clinical Examination Using Caliper**: All measurements will be determined using a ruler or calipers and reported in metric notation (mm) and will be recorded bi-dimensionally. Clinical lesions will only be considered measurable when they are superficial and can be accurately and serially measured in at least 2 dimensions ≥ 5 x 5 mm as assessed using calipers (eg, superficial cutaneous melanoma lesion). [Note: When a lesion can be evaluated by both, clinical examination and imaging, radiographic imaging evaluations should be undertaken since it is more objective]

**CT scans (or MRI):** Computed tomography (CT) scans by contrast-enhanced or spiral scan (or magnetic resonance imaging [MRI] scan) will be performed to evaluate tumor response for visceral or nodal/soft tissue disease (including lymph nodes). Measurability of lesions on CT scan is based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be the greater of either at least 10 mm or twice the slice thickness. MRI is acceptable to assess disease extent if used consistently throughout the study.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. A switch from contrast enhanced CT to non-contrast CT or to MRI (or vice versa) should not preclude response assessment if, in the judgment of the site radiologist, there is no significant difference in the assessment by changing modalities. This may occur if a subject has developed a medical contraindication to IV contrast for CT scans while on trial. For example, a non-contrast CT of the chest with MRI of the abdomen/pelvis with contrast could be used assess disease extent in the event of an iodinated CT contrast dye allergy. This change would require the preapproval of the sponsor medical monitor.

**Positron Emission Tomography (PET)/CT Scans:** If a combined PET/CT scan is performed at the discretion of the investigator, the CT portion of that exam should not be substituted for the dedicated CT exams required by this protocol. The PET portion of the CT may introduce additional data which may bias the investigator assessment of response if it is not routinely or serially performed. However, if the investigator or the site radiologist can document that the CT performed as part of a PET/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET/CT can be used for tumor measurements.

**Ultrasound:** Ultrasound (US) may be used to assess superficial palpable lymph nodes and subcutaneous lesions where US provides a more accurate measure than clinical measurement or CT. In addition, US can be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination. However, if US is not useful in assessment of lesion size it must not be used to as a method of measurement. If new lesions are identified by US in the course of the study, confirmation by CT or MRI is advised.

**Measurement of Lesions**

Measurability is defined by the ability to measure a lesion bi-dimensionally with surface area determined by multiplying the longest diameter by the diameter perpendicular to the longest diameter as defined below. An individual lesion measure is therefore provided by the product of a tumors longest diameter and the diameter perpendicular to that.

All measurements will be determined using a ruler or calipers and reported in metric notation (mm) and will be recorded bi-dimensionally.

**Definitions of Measurable and Nonmeasurable Lesions**

At baseline, lesions are categorized as measurable or nonmeasurable according to the following definitions:

**Measurable Lesions:**

Measurable lesions are defined at baseline as lesions that can be accurately and serially measured in at least 2 dimensions and:

- for which the longest diameter is ≥ 10 mm and the perpendicular diameter is ≥ 5mm as measured by CT scan (CT scan slice thickness no greater than 5 mm) or MRI for visceral or soft tissue disease. Lymph nodes must measure > 15 mm in their short axis to be considered measurable lesions when assessed by CT scan
- for which the short axis is ≥ 5 mm caliper measurement by clinical exam for superficial cutaneous or subcutaneous melanoma lesion as measured by caliper

**Nonmeasurable:**

All other lesions, including small lesions (longest diameter < 10 mm by CT/MRI for visceral or soft tissue disease [lymph nodes with short axis ≤ 15 mm to 10 mm] or < 5 x 5 mm caliper measurement by clinical exam for superficial cutaneous melanoma lesion) and other truly nonmeasurable lesions are considered non-measurable and characterized as nonindex lesions. This will include any measurable lesions beyond the maximum number of 5 cutaneous lesions and 10 visceral lesions (maximum 5 lesions per organ) that were not chosen as index lesions. Other examples of nonmeasurable lesions include some bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of the skin or (lymphangitis cutis/pulmonis), and groups of lesions that are small and numerous. Baseline lymph nodes that have a short axis < 10 mm are considered nonpathological and should not be recorded or followed.

**Bone Lesions:**

- Bone scans, PET scans or plain films are not considered adequate imaging techniques to measures bone lesions. However, these techniques can be used to confirm the presence or absence of bone lesions.
- Lytic bone lesions or mixed Lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging technique such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above
- Blastic bone lesions are not nonmeasurable.

**Cystic Lesions:**

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same subject, these are preferred for selection as index lesions.

**Lesions with Prior Local Treatment:**

- Tumor lesions situated in a previously irradiate area, or an area subject to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

**Measureable Tumor Assessment/Burden:**

**Baseline Documentation of "Index Lesions":**

All baseline evaluations should be performed as close as to the enrollment or randomization and never more than 4 weeks (ie, 28 days) prior to enrollment/randomization.

At baseline up to 5 cutaneous lesions and 10 visceral lesions, a maximum of 5 per organ, will be chosen to measure over the course of therapy. The distribution of these index lesions should be representative of the subject's overall disease status. Index lesions should be selected on the basis of their size (lesions with longest bi-dimensionally perpendicular diameters) and suitability for accurate repeated measurements by imaging techniques (CT, MRI or US) and/or other method such as clinical exam.

The sum of the products of the two largest of perpendicular diameters (SPD) of all index lesions will be calculated and reported.

**Baseline Documentation of "Non-index Lesions":** All other lesions (or sites of disease), including any measurable lesions that were not chosen as index lesions will be identified as nonindex lesions. Measurable nonindex lesions should also be recorded and assessed qualitatively over the course of therapy.

**Follow-up:**

At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (accurately and serially measured in at least 2 dimensions ≥ 5 x 5 mm (lymph node with short axis > 15 mm); up to 5 new cutaneous lesions and 10 visceral lesions [maximum 5 new lesions per organ]) are added together to provide the total tumor burden.

Tumor Burden = SPDindex lesions + SPDnew, measurable lesions.

Non-measurable nonindex disease measurements are not required and these lesions should be followed as "present", "absent", or in rare cases "unequivocal progression".

If residual tumor cannot be distinguished from the effects of therapy or is too small to measure, the residual tumor should be assigned a default code of present (for non-index and non-measurable lesions) or a default value of 5x5 mm (for radiographically assessed lesions) or 3x3 mm (for clinically assessed lesions) as the bi-dimensionally perpendicular diameters (for index lesions and new measurable lesions). Otherwise, the

actual measurements should be recorded. Lymph nodes measuring below 10 mm in the short axis should be recorded as 0x0 mm.

**Response Criteria**

**Evaluation of Objective Response Rate:**

The subject response will be assessed based on the response of the index lesions and the presence or absence of new measurable lesions, and, in the case of CR, the presence or absence of nonindex lesions. The overall response is derived from time-point response assessments (based on tumor burden) as described in Table 1 and Table 2:

**Table 1. Definition of Measurable Tumor Response**

| | |
|---|---|
| Complete Response (CR): | Complete disappearance of all lesions (whether measurable or not, and no new lesions) confirmation by a repeat, consecutive assessment no less than 4 weeks (28 days) from the date first documented. Any pathological lymph nodes (whether measurable or not) must have reduction in short axis to <10 mm. |
| Partial Response (PR): | Decrease in tumor burden ≥ 50% relative to baseline confirmed by a consecutive assessment at least 4 weeks (28 days) after first documentation. |
| Progressive Disease (PD): | Increase in tumor burden ≥ 25% relative to nadir (minimum recorded tumor burden) confirmation by a repeat, consecutive assessment no less than 4 weeks (28 days) from the date first documented disease progression. |
| Stable Disease (SD): | Not meeting criteria for CR or PR, in absence of PD. |
| Unable to Evaluate (UE): | Any lesion present at baseline which was not assessed or was unable to be evaluated leading to an inability to determine the status of that particular tumor for that time point. |
| Not Applicable (NA) | No index lesions were identified at baseline |
| Not Done (ND) | Radiographic image or clinical measurement were not performed at this time point to evaluate the index lesions |

**Table 2. Matrix for Determining the Overall Response at Each Assessment Point**

| Measurable Response | Non-measurable Response | | Overall Response |
|---|---|---|---|
| **Index and new, measurable lesions (tumor burden)[a], %** | **Non-index** | **New, nonmeasurable lesions** | **Using irRC** |
| ↓100 | Absent/NA[d] | Absent | CR[b] |
| ↓100 | Stable | Any | PR[b] |
| ↓100 | Unequivocal progression | Any | PR[b] |
| **↓100** | **Unevaluable** | **Any** | **PR[b]** |
| ↓≥ 50 | Absent/Stable/NA[d] | Any | PR[b] |
| ↓≥ 50 | Unequivocal progression | Any | PR[b] |
| ↓< 50 to < 25↑ | Absent/Stable/NA[d] | Any | SD |
| ↓< 50 to < 25↑ | Unequivocal progression | Any | SD |
| ≥ 25 | Any | Any | PD[b] |
| UE | Any | Any | UE |
| ND | Any | Any | UE |
| NA[c] | Any | Any | UE |

[a] Decrease disease relative to baseline, including new measurable lesions only (> 5x5mm).
[b] Assuming response (CR or PR) or progression are confirmed by a second, consecutive assessment at least 4 weeks (28 days) apart.
[c] No index lesions identified at baseline. When a patient has only nonmeasurable disease (ie, no index lesions identified at baseline) the response will be unevaluable.
[d] No non-index lesions identified at baseline.
CR = CR; PR = partial response; SD = stable disease; PD = disease progression; UE = unable to evaluable; ND = not Done; NA = not applicable.



Determination of irRC best overall response is based on changes in total tumor burden from the baseline (nadir, for PD) tumor assessment, regardless of any initial increase in baseline lesions or the appearance of new lesions.

Subjects are considered to have PR or SD even if new lesions were present, as long as they met the respective thresholds of response as described in Table 2.

Subjects with SD, particularly those with slow-declining tumor burden ≥ 25% from baseline at the last tumor assessment, are considered clinically meaningful because they show an objectively measurable reduction in tumor burden without reaching the 50% threshold that defines PR (it represented an objectively measured reduction not commonly observed in the natural history of advanced melanoma patients).

**Response Confirmation**

To be assigned a status of CR or PR changes in tumor measurements must be confirmed by consecutive repeat assessments performed no less than 4 weeks (28 days) after the criteria for response are first met.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR status.

If a subject is classified as having PD at a postbaseline tumor assessment, then confirmation of PD by a second consecutive assessment in the absence of rapid clinical deterioration is required. The definition of confirmation of progression represents an increase in tumor burden ≥ 25% compared with the nadir at two consecutive time points at least 4 weeks (28 days) apart. It is recommended that this be done at the discretion of the investigator because follow-up with observation alone may not be appropriate for subjects with a rapid decline in performance status. Confirmation of PD allows for the capture of all observed responses using the irRC as most of these late responding subjects have a trend toward response within 4 weeks (28 days) after initial PD.

For subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression**,** PD cannot be assigned at the time as the overall objective tumor response. Every effort should be made to document the objective progression even after discontinuation of treatment.

A best overall response of SD requires a visit response of SD or better no earlier than 77 days after the date of enrollment/randomization; otherwise the overall response will be UE.

**Subjects who have had a procedure to completely/partially resect a lesion will be evaluated as follows:**

The procedure itself and all post-procedure lesion assessments should always be recorded in the CRF. A completely resected lesion should be assigned a default code of 0 x 0 mm (for index and new measurable lesions) or “absent” (for non-index and new non-measurable lesions). A partially resected lesion should be assigned its measurement post-procedure (for index or new measurable lesions) or “present” (for non-index or new non-measurable lesions). If the resected lesion contained no melanoma under pathology evaluation, subsequent tumor assessments post-procedure may be used for tumor burden calculations and/or determination of response. If the

resected lesion contained melanoma or pathology results were unknown, the recorded tumor assessments post-procedure may be used for tumor burden calculations, but determination of response will be considered unevaluable (UE) for response except in the case of PD.

If the new tumor burden post-procedure is lower than the nadir before the procedure, then the new nadir will be set to the post-procedure tumor burden. Otherwise, the previous pre-procedure nadir will be retained as the nadir. Subsequent assessments for PD will be determined from the nadir.

**Merging lesions**

When two or more index/new measurable lesions merge, the smaller lesion should have 0 x 0 mm recorded for the current and all future assessments, and the larger lesion should have the size of the merged lesion recorded for the current assessment and be followed for future assessments. When two or more non-index/new non-measurable lesions merge, the smaller lesion should be recorded as absent for the current and all future assessments, and the larger lesion should be recorded as present for the current assessment and followed for future assessments. If an index/new measurable lesion and a non-index/new non-measurable lesion merge, the non-index/new non-measurable lesion should be absent for the current and all future assessments while the index lesion/new measurable lesion should include both merged lesions for recording measurements.

**Separating lesions**

When an index/new measurable lesion splits into 2 or more lesions. The largest measurable part of the split lesion should be considered to be the previously recorded index/new measurable lesion with measurements provided for the current assessment and followed for future assessments. The remaining lesions would be new measurable lesions or new non-measurable lesions depending on measurability.

## Appendix F. Eastern Cooperative Oncology Group Performance Status Scale

| Grade | Description |
|---|---|
| 0 | Fully active, able to carry on all pre-disease performance without restriction. |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, ie, light housework or office work. |
| 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. Cannot carry on any self-care. Totally confined to bed or chair. |
| 5 | Dead |

**Amendment 5**

**Protocol Title: 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**

Amgen Protocol Number TVEC 20110264

EudraCT number 2012-000307-32

Amendment Date: 07 November 2018

**Rationale:**

This protocol is being amended to:

- Add 4-year and 5-year overall survival status to the stastical analysis plan
- Update End of Study and Pregnancy Language to align with new protocol template
- Make administrative and editiorial updates

**Description of Changes:**

Section: Global

Change: Date updated throughout from 02 March 2016 to **07 November 2018**.

Section: Title Page

Replace:

[redacted], MD
Clinical Research Medical Scientist
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
Telephone: [redacted]
Email: [redacted]

[redacted]
Clinical Research Study Manager
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
Telephone: [redacted]
Email address: [redacted]

With:

[redacted], MD
Clinical Research Medical Scientist
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
Telephone: [redacted]
Email: [redacted]

[redacted]
**Global Clinical Trial Manager**
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
Telephone: [redacted]
Email address: [redacted]

Section: Title Page

Add:

**Amendment 5 Date** **07 November 2018**

Section: Synopsis, Phase 1b Study Design, paragraph 4; Phase 2 Study Design, paragraph 5

Replace:

Subjects will be followed for safety approximately 30 (+ 7) days after the last dose of talimogene laherparepvec or 60 (+ 7) days after the last dose of ipilimumab, whichever is later, and survival for approximately 36 months after the last subject is randomized in phase 2.

With:

Subjects will be followed for safety approximately 30 (+ 7) days after the last dose of talimogene laherparepvec or 60 (+ 7) days after the last dose of ipilimumab, whichever is later, and survival for approximately **60** months after the last subject is randomized in phase 2.

Section: Synopsis, Treatment

Add:

For phase 2: completion of patient reported outcome (PRO) questionnaires: EuroQoL-5D (EQ-5D) and the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) **until no longer than 3 years after the last subject is randomized.**

Section: Synopsis, Long-term follow-up, paragraph 1

Replace:

All subjects who permanently discontinue study drug for any reason other than withdrawal of full consent will be contacted by clinic visit or telephone every 12 weeks (± 28 days) following the safety follow-up to assess survival, initiation of additional melanoma therapy, and whether any talimogene laherparepvec-related AEs have occurred until death, subject withdraws full consent, or up to 36 months after the last subject is randomized in phase 2.

With:

All subjects who permanently discontinue study drug for any reason other than withdrawal of full consent will be contacted by clinic visit or telephone every 12 weeks (± 28 days) following the safety follow-up to assess survival, initiation of additional melanoma therapy, and whether any talimogene laherparepvec-related AEs have occurred until death, subject withdraws full consent, or up to **60** months after the last subject is randomized in phase 2.

Section: Synopsis, Long-term follow-up, paragraph 2

Replace:

Radiographic imaging, clinical tumor assessment, and tumor response assessment as detailed in Section 7.2.2 and completion of PRO questionnaires (EQ-5D and EORTC QLQ-C30 for only subjects enrolled in phase 2) will be performed every 12 weeks (± 1 week) until documentation of confirmed disease progression per modified irRC (Appendix E) for subjects discontinuing study treatment for any reason other than progressive disease (PD).

With:

Radiographic imaging, clinical tumor assessment, and tumor response assessment as detailed in Section 7.2.2 will be performed every 12 weeks (± 1 week) until documentation of confirmed disease progression per modified irRC (Appendix E) for subjects discontinuing study treatment for any reason other than progressive disease (PD). Completion of PRO questionnaires (EQ-5D and EORTC QLQ-C30) **will be performed until no longer than 3 years after the last subject is randomized.**

Section: Synopsis, Statistical Considerations, paragraph 2

Replace:

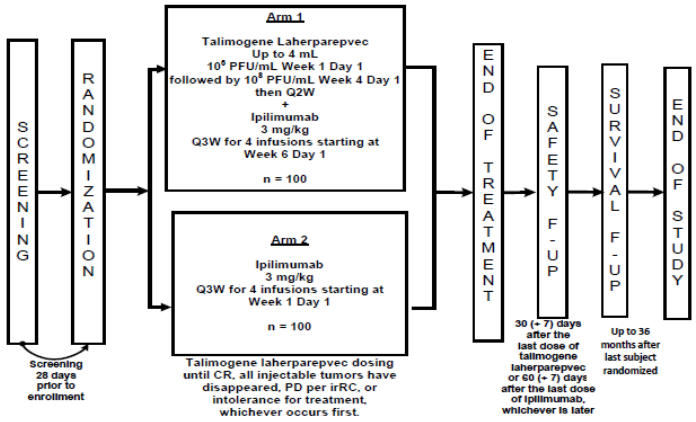
Two descriptive interim analyses of OS will be performed, one at the time of the ORR primary analysis and another at 2 years after the last subject is randomized. Analysis of TTR, PFS and DOR will follow the same method as described for OS, but all p-values will be descriptive.

With:

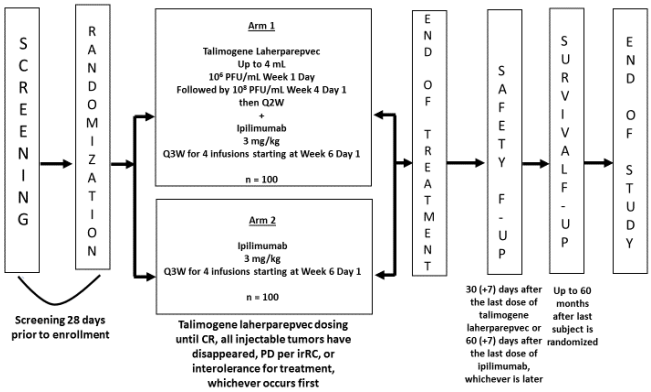
**D**escriptive interim analyses **for** OS will be performed at the time of **primary analysis for** ORR and at 2 years**, 3 years, and 4 years** after the last subject is randomized **in phase 2.** Analysis of TTR, PFS and DOR will follow the same method as described for OS, but all p-values will be descriptive.

Section: Synopsis, Study Design and Treatment Schema for Phase 2

Replace:




With:



Section: Study Glossary

Replace:

| | |
|---|---|
| end of study (primary completion) | defined as when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary analysis of the phase 2. |
| end of study (end of trial) | defined as when the last subject is assessed or receives an intervention for evaluation in the study. |

With:

| | |
|---|---|
| end of study (primary completion) | defined as **the date** when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary analysis of phase 2**, whether the study concluded as planned in the protocol or was terminated early**. |
| end of study (end of trial) | defined as when the last subject **across all sites** is assessed or receives an intervention for evaluation in the study **(ie, last subject last visit), following any additional parts in the study (ie, long-term follow-up), as applicable**. |

Section: Study Glossary

Add:

| | |
|---|---|
| **PI** | **Principal Investigator** |

Section: Study Glossary

Delete:

| | |
|---|---|
| ~~PSP~~ | ~~Pregnancy Surveillance Program~~ |

Section 3.1.1: Study Design of Phase 1b, paragraph 4; 3.1.2: Study Design of Phase 2, paragraph 5

Replace:

Subjects will be followed for safety approximately 30 (+ 7) days after the last dose of talimogene laherparepvec or 60 (+ 7) days after the last dose of ipilimumab, whichever is later, and survival for approximately 36 months after the last subject is randomized in phase 2.

With:

Subjects will be followed for safety approximately 30 (+ 7) days after the last dose of talimogene laherparepvec or 60 (+ 7) days after the last dose of ipilimumab, whichever is later, and survival for approximately **60** months after the last subject is randomized in phase 2.

Section 3.4.1.1: Phase 1b Study Duration for Participants, paragraph 1

Replace:

Subjects will be followed for safety approximately 30 (+ 7) days after the last dose of talimogene laherparepvec or 60 (+ 7) days after the last dose of ipilimumab, whichever is later, and survival for approximately 36 months after the last subject is randomized in phase 2.

With:

Subjects will be followed for safety approximately 30 (+ 7) days after the last dose of talimogene laherparepvec or 60 (+ 7) days after the last dose of ipilimumab, whichever is later, and survival for approximately **60** months after the last subject is randomized in phase 2.

Section 3.4.1.2: Phase 2 Study Duration for Participants, paragraph 2

Replace:

The duration for the phase 2 is approximately 55 months. The duration of screening for each subject will be approximately 28 days. The subject accrual period is planned for approximately 18 months. The duration of treatment will vary for each subject. Subjects randomized to arm 1 will be treated until CR, all injectable tumors have disappeared, confirmed disease progression per the modified irRC (Appendix E), or intolerance of study treatment, whichever occurs first. Subjects randomized to arm 2 will be treated for approximately 4 months. Subjects will be followed for safety approximately 30 (+ 7) days after the last dose of talimogene laherparepvec or 60 (+ 7) days after the last dose of ipilimumab, whichever is later, and survival for approximately 36 months after the last subject is randomized in phase 2.

With:

The duration for the phase 2 is approximately **60** months. The duration of screening for each subject will be approximately 28 days. The subject accrual period is planned for

approximately 18 months. The duration of treatment will vary for each subject. Subjects randomized to arm 1 will be treated until CR, all injectable tumors have disappeared, confirmed disease progression per the modified irRC (Appendix E), or intolerance of study treatment, whichever occurs first. Subjects randomized to arm 2 will be treated for approximately 4 months. Subjects will be followed for safety approximately 30 (+ 7) days after the last dose of talimogene laherparepvec or 60 (+ 7) days after the last dose of ipilimumab, whichever is later, and survival for approximately **60** months after the last subject is

Section 3.4.2: End of Study

Replace:

Primary Completion: The time when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary analysis of the phase 2. The primary completion is anticipated to occur approximately 6 months after the date the last subject is randomized in the phase 2.

End of Trial: The time when the last subject is assessed or receives an intervention for evaluation in the study. The end of study will occur when the last subject discontinues the study treatment and has had the opportunity to complete the long-term survival follow-up.

With:

Primary Completion: The time when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary analysis of phase 2**, whether the study concluded as planned in the protocol or was terminated early**. The primary completion is anticipated to occur approximately 6 months after the date the last subject is randomized in the phase 2.

**End of Study: The end of study date is defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up) as applicable.**

Section 7.1: Schedule of Assessments, Table 2 Schedule of Assessments for Phase 1b, footnote f; Table 3 Schedule of Assessments for Phase 2 – Arm 1, footnote f; Table 4, Schedule of Assessments for Phase 2 – Arm 2, footnote f

Replace:

Subjects will be followed for survival by clinic visit or telephone contact every 12 weeks ± 28 days from the date of the safety follow-up visit until up to 36 months after the last subject is randomized in phase 2. Subsequent cancer treatments for melanoma and whether any talimogene laherparepvec-related AEs have occurred will be collected as part of the long-term follow-up survival assessment.

With:

Subjects will be followed for survival by clinic visit or telephone contact every 12 weeks ± 28 days from the date of the safety follow-up visit until up to **60** months after the last subject is randomized in phase 2. Subsequent cancer treatments for melanoma and whether any talimogene laherparepvec-related AEs have occurred will be collected as part of the long-term follow-up survival assessment.

Section 7.1: Schedule of Assessments, Table 2 Schedule of Assessments for Phase 1b, footnote r; Table 3 Schedule of Assessments for Phase 2 – Arm 1, footnote r; Table 4, Schedule of Assessments for Phase 2 – Arm 2, footnote r

Replace:

Subjects who have reached a confirmed CR may increase their interval of radiographic assessments up to 6 months after the first 2 years beyond confirmed CR and up to 12 months after the first 5 years beyond confirmed CR as long as CR is maintained.

With:

Subjects who have reached a confirmed CR may increase their interval of radiographic assessments up to 6 months after the first 2 years beyond confirmed CR and up to 12 months after the first 5 years beyond confirmed **complete response (**CR**)** as long as **per Principal Investigator (PI) discretion**. **Subjects without CR will be assessed radiographically every 6 months after the first 2 years until the subject is 5 years off of therapy, then as per PI discretion.**

Section 7.1: Schedule of Assessments, Table 3 Schedule of Assessments for Phase 2 – Arm 1, footnote bb; Table 4 Schedule of Assessments for Phase 2 – Arm 2, footnote w

Replace:

Completion of PRO (EQ-D5 and EORTC QLQ-C30) questionnaires prior to study treatment administration at day 1 of weeks 1, 4, 6, 9, 12, 15, 18, 22, 24, then every 4 weeks until end of study treatment, and at the safety follow-up visit. For subjects who have discontinued treatment for any reason other than confirmed PD, every effort should be made to complete PRO (EQ-D5 and EORTC QLQ-C30) questionnaires every 12 weeks (+1 week) during the long-term follow-up until documentation of confirmed PD per modified irRC (Appendix E), start of new anticancer therapy, or end of study whichever occurs first.

With:

Completion of PRO (EQ-D5 and EORTC QLQ-C30) questionnaires prior to study treatment administration at day 1 of weeks 1, 4, 6, 9, 12, 15, 18, 22, 24, then every 4 weeks until end of study treatment, and at the safety follow-up visit. For subjects who have discontinued treatment for any reason other than confirmed PD, every effort should be made to complete PRO (EQ-D5 and EORTC QLQ-C30) questionnaires every 12 weeks (+1 week) during the long-term follow-up until **no longer than 3 years after the last subject is randomized.**



Section 7.2.2: Treatment, completion of PRO questionnaires: EQ-D5 and EORTC QLQ-C30

Replace:

- phase 2 (arm 2): prior to study treatment administration at day 1 of weeks 1, 4, 7, 10, and during weeks 12 and 24 for subjects who have discontinued treatment for any reason other than confirmed PD.

With:

- phase 2 (arm 2): **completion until no longer than 3 years after the last subject is randomized.**

Section 7.2.4: Long-term Follow-up, paragraph 2

Replace:

Contact for all subjects will be attempted every 12 weeks (± 28 days) following the safety follow-up visit until death, subject withdraws full consent, or up to 36 months after the last subject is randomized in phase 2.

With:

Contact for all subjects will be attempted every 12 weeks (± 28 days) following the safety follow-up visit until death, subject withdraws full consent, or up to **60** months after the last subject is randomized in phase 2.

Section 7.2.4: Long-term Follow-up, paragraph 3

Replace:

Radiographic imaging, clinical tumor assessment, and tumor response assessment as detailed in Section 7.2.2 and PRO questionnaires (EQ-D5 and EORTC QLQ-C30 only for subjects enrolled in phase 2) will be performed every 12 weeks (± 1 week) until documentation of disease progression per modified irRC (Appendix E), start of new anticancer therapy, or end of study whichever occurs first for subjects discontinuing study treatment for any reason other than PD. Subjects who have reached a confirmed CR may increase their interval of radiographic assessments up to 6 months after the first 2 years beyond confirmed CR and up to 12 months after the first 5 years beyond confirmed CR as long as CR is maintained.

With:

Radiographic imaging, clinical tumor assessment, and tumor response assessment as detailed in Section 7.2.2 will be performed every 12 weeks (± 1 week) until documentation of disease progression per modified irRC (Appendix E), start of new anticancer therapy, or end of study whichever occurs first for subjects discontinuing study treatment for any reason other than PD. Subjects who have reached a confirmed CR may increase their interval of radiographic assessments up to 6 months after the first 2 years beyond confirmed CR and up to 12 months after the first 5 years beyond confirmed CR as **per PI discretion**. **Subjects without CR will be assessed radiographically every 6 months after the first 2 years until the subject is 5 years off of therapy, then as per Principal Investigator (PI) discretion. Patient Reported**

**Outcome completion will be performed until no longer than 3 years after the last subject is randomized.**

Section 9.3: Pregnancy and Lactation Reporting

Replace:

If a pregnancy occurs in a female subject, or female partner of a male subject, while the subject is taking protocol-specified therapies, report the pregnancy to Amgen as specified below.

In addition to reporting any pregnancies occurring during the study treatment, investigators should monitor for pregnancies that occur after the last dose of protocol-required therapies through 3 months after the end of treatment.

The pregnancy should be reported to Amgen's global Pregnancy Surveillance Program within 7 business days of the site receiving notification of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C). The Pregnancy Surveillance Program (PSP) will seek to follow the pregnant woman throughout her pregnancy and her baby up to 12 months after birth.

If a lactation case occurs while the female subject is taking protocol-specified therapies report the lactation case to Amgen as specified below.

In addition to reporting a lactation case during the study treatment, investigators should monitor for lactation cases that occur after the last dose of protocol-required therapies through 3 months after the end of treatment.

Any lactation case should be reported to Amgen's global Lactation Surveillance Program within 7 days of the site receiving notification of a lactation case. Report a lactation case on the Lactation Notification Worksheet (Appendix D).

With:

If a pregnancy occurs in a female subject, or female partner of a male subject, while the subject is taking protocol-specified therapies, report the pregnancy to Amgen as specified below.

In addition to reporting any pregnancies occurring during the study treatment, investigators should monitor for pregnancies that occur after the last dose of protocol-required therapies through 3 months after the end of treatment.

The pregnancy should be reported to **Amgen Global Patient Safety within 24 hours of learning** of a **subject's** pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C). **After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 3 months after the end of treatment. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).**

If a lactation case occurs while the female subject is taking protocol-specified therapies report the lactation case to Amgen as specified below.

In addition to reporting a lactation case during the study treatment, investigators should monitor for lactation cases that occur after the last dose of protocol-required therapies through 3 months after the end of treatment.

Any lactation case should be reported to **Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event**. Report a lactation case on the Lactation Notification Worksheet (Appendix D).

**With the female subject's signed authorization for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 3 months after discontinuing protocol-required therapies.**

Section 10.4.1: Interim Analyses, Paragraph 3

Add:

Descriptive interim analyses for OS will be performed at the time of primary analysis for ORR and at 2 years**, 3 years, and 4 years** after the last subject is randomized in phase 2.

Section 10.4.5: Final Analysis

Replace:

The final analysis will occur approximately 3 years after the last subject is randomized in phase 2. The primary analysis of OS will be conducted at this final analysis and will use

all events at the time. The CSR will be amended with the updated results from the final analysis at the completion of the study.

With:

The final analysis will occur approximately **5** years after the last subject is randomized in phase 2. The analysis of OS will be conducted at this final analysis and will use all events at the time. The CSR will be amended with the updated results from the final analysis at the completion of the study.

Section 10.5.3: Secondary Efficacy Endpoint(s), paragraph 4

Replace:

If, at the primary analysis of ORR, the null hypothesis of no treatment effect in comparing ORR between the 2 treatment arms is rejected, OS will be compared with an un-stratified log-rank test at the study's Final Analysis (using 2 sided 0.05). The OS treatment hazard ratio and its 2-sided 95% CI will be estimated using an un-stratified Cox proportional hazards model. Kaplan-Meier (KM) curves for OS will be generated by treatment arm in the ITT analysis set. KM estimates and the 95% CIs for within each treatment and between treatment differences of annual OS rates will be provided. The CI for treatment annual rate differences will be based on variance estimates using Greenwood's formula (Kalbfleisch and Prentice, 1980). CIs for the KM quartiles will be provided by treatment arm (Brookmeyer and Crowley, 1982). Interim analyses of OS will be performed at the time of the ORR primary analysis and at 2 years after the last subject has been randomized. Both interim analyses will be descriptive.



With:

If, at the primary analysis of ORR, the null hypothesis of no treatment effect in comparing ORR between the 2 treatment arms is rejected, OS will be compared with an un-stratified log-rank test at the study's Final Analysis **with type I error** 0.05. The OS treatment hazard ratio and its 2-sided 95% CI will be estimated using an un-stratified Cox proportional hazards model. Kaplan-Meier (KM) curves for OS will be generated by treatment arm in the ITT analysis set. KM estimates and the 95% CIs for within each treatment and between treatment differences of annual OS rates will be provided. The CI for treatment annual rate differences will be based on variance estimates using Greenwood's formula (Kalbfleisch and Prentice, 1980). CIs for the KM quartiles will be provided by treatment arm (Brookmeyer and Crowley, 1982). Interim analyses of OS will be performed at the time of the ORR primary analysis and at 2 years**, 3 years, and**

**4 years** after the last subject has been randomized. **All** interim analyses will be descriptive.

Section 14: Appendices, Table 2 Matrix for Determining the Overall Response at Each Assessment Point

Add:

| | | | |
|---|---|---|---|
| **↓100** | **Unevaluable** | **Any** | **PR[b]** |

**Amendment 4**

**Protocol Title: 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**

Amgen Protocol Number TVEC [AMG678] 20110264

EudraCT Number 2012-000307-32

Amendment Date: 02 March 2016

**Rationale:**

This protocol is being amended for the following reasons:

- In Amendment 3, Appendix E had been amended to provide clearer text regarding how to assess response in complete or partially resected lesions. However, in Section 6.6, there were instructions on how to record responses after a tumor resection that are inconsistent with Appendix E. The text in Section 6.6 has been edited to ensure consistency with Appendix E.
- The aggregate unblinded results on the approximately 80 subjects that were included in both interim analyses that previously had only been shared with limited key members of Amgen Senior Management and their designees may now be shared with investigators and study team members on an as-needed basis after the study has closed screening to inform decision making for this program.
- Minor administrative changes and clarifications.

**Amendment 3**

**Protocol Title: 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**

Talimogene Laherparepvec

Amgen Protocol Number (Talimogene Laherparepvec) 20110264

| | |
|---|---|
| Date: | 18 June 2012 |
| Amendment 1 Date: | 07 August 2013 |
| Amendment 2 Date: | 08 October 2014 |
| **Amendment 3 Date:** | **30 November 2015** |

**Rationale:**

- Given low number of subjects receiving 2nd or later line of treatment who are enrolled in the study, which had been assumed to be 50% in Amendment 2, the testing of ORR in the First-line Analysis Set is removed and the overall nominal level of 0.05 will be used in the Intent-to-treat (ITT) Analysis Set.
- In order to increase the probability that the number of events needed to test overall survival (OS) can be reached, the study duration is extended to a maximum of 3 years follow-up after the last subject was randomized.
    - OS will be formally tested, if the statistical significance in comparing objective response rate (ORR) using ITT Analysis Set is met, at the study's final analysis. Two interim analyses of OS will be performed at the time of the ORR primary analysis and at 2 years since last subject has been randomized in phase 2.
- Updated the background section to include the latest results from the phase 1b portion of this study.
- Removed Canada from list of potential site locations because no sites will be opened there.
- Removed exclusion criterion for subjects who received any nononcology vaccine therapies used for the prevention of infectious disease as it is unlikely this would have an adverse effect on therapy.
- Updated language to clarify definition of autoimmune disease in exclusion criterion.
- Added exclusion criteria for sexually active subjects who are unwilling to use a barrier and for subjects unwilling to minimize exposure with his/her blood or other body fluids to individuals who are at higher risks for herpes simplex type-1 virus (HSV-1) induced complications in order to further safeguard against potential transmission of talimogene laherparepvec to close contacts of subjects.
- Removed nononcology vaccine therapies used for the prevention of infectious disease as prohibited concomitant medications as it is unlikely these would have an adverse effect on therapy.
- Talimogene laherparepvec-related adverse events during the long-term follow-up period will be collected. Although there is a talimogene laherparepvec registry

protocol capturing reporting of any long-term talimogene laherparepvec-related adverse events, the subjects would not be eligible to enroll in this registry protocol until after they have ended their participation in this study. Subjects may be in long-term follow-up for many years prior to participation in the registry, and this change will allow for reporting of long-term talimogene laherparepvec-related adverse events during the long-term follow-up period between the safety follow-up period and the time that the subjects can enroll in the registry protocol.

- Specified that progression should be confirmed in otherwise clinically stable subjects before switching to alternative therapies as subjects may experience response after initial progression on either arm of the study.
- Allowed for more flexibility in frequency of radiographic follow-up for subjects who have reached a complete response (CR) in long-term follow-up. Subjects who have reached a confirmed CR may need less radiographic imaging per investigator discretion after prolonged periods of CR.
- Added a second updated analysis that will be conducted 24 weeks after the first interim analysis of efficacy and safety.
- Removed the talimogene laherparepvec product team from list of groups who will not view the interim analysis results. However, all study team members and investigators will continue to be blinded to the interim aggregate results to protect data integrity.
- Clarified language regarding partial or complete removal of lesions in appendix for modified immune-related response criteria.
- Made minor edits for grammatical and formatting errors.

**Amendment 2**

**Protocol Title: 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**

Talimogene Laherparepvec

Amgen Protocol Number 20110264

Amendment Date: 08 October 2014

**Rationale:**

Ipilimumab is approved for use in untreated and previously treated advanced melanoma patients (Yervoy®, 2013). Results with another checkpoint inhibitor, pembrolizumab, have shown that similar response rates in subjects with advanced or unresectable melanoma whether or not the subjects were previously treated with ipilimumab (Hamid et al, 2013). Therefore, the study will now allow subjects previously treated with other systemic therapies to enroll in order to adapt to the changing landscape of melanoma treatment and to study the combination therapy in a second line or greater setting.

The following changes have been incorporated into protocol amendment 2:

- Change the primary objective/endpoint of phase 2 from assessment of overall survival (OS) to confirmed objective response rate (ORR) (CR+PR) (response evaluation by an investigator using modified immune-related response criteria [irRC]). Assessment of OS has been changed to a secondary objective/endpoint.
- Increase sample size of phase 2 from 140 to 200 to formally test for ORR (rather than estimating OS)
- Update the inclusion criteria to allow subjects who received prior treatment for melanoma to enroll into phase 2 as defined below:
  - Either treatment naïve or received only one line of systemic anticancer therapy if BRAF wild-type or up to two lines of systemic anticancer therapy including one BRAF inhibitor-containing regimen if BRAF mutant. Treatments given in an adjuvant setting (eg, interferon, radiotherapy, isolated limb perfusion, or investigational agents) are not considered as prior lines of therapy. No prior talimogene laherparepvec, other oncolytic virus therapies, or tumor vaccines is allowed, even if given in the adjuvant setting.
  - Subjects treated with prior ipilimumab must have had PR, CR, or at least 6 months of stable disease followed by disease progression

## Amendment 1

**Protocol Title: 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 Previously Untreated, Unresected, Stage IIIb-IV Melanoma**

Talimogene Laherparepvec

Amgen Protocol Number 20110264

Amendment Date: 07 August 2013

**Rationale:**

The protocol has been amended to incorporate the following changes:

- Change the term “unresectable” to “unresected” at all instances in the protocol when referring to the subject population for this trial since the term “unresectable” implies an objective method of determining resectability which is not defined in this protocol
- Update the background section to include results of the primary analysis the talimogene laherparepvec phase 3 trial in unresected stage IIIb to VIM1c melanoma (OPTiM; Study 005-05)
- Exclude adult subjects who lack capacity to consent and for whom consent must be provide by a legally authorized representative since adult subjects who are enrolled by an legally authorized representative are not appropriate for this research
- Exclude subject with a history of complicated herpes infection (eg, herpetic keratitis or meningoencephalitis).
- Include collection of swab from cold sores, vesicles, and other lesions suspected to be herpetic in origin, if any, during treatment and safety follow-up. The swab samples will be stored and ultimately tested for detection of talimogene laherparepvec DNA using real-time polymerase chain reaction (qPCR)
- Include collection of blood and urine from subjects enrolled in phase 1 at the safety follow-up visit and from subjects enrolled in phase 1 arm 1 prior to study drug administration on day 1 of week 1, 4, 6, and 8, and at the safety follow-up visit. The blood and urine samples will be stored and ultimately tested for detection of talimogene laherparepvec DNA using qPCR
- Include reporting potential or unknown intended exposure to talimogene laherparepvec, suspected signs or symptoms, and detection of talimogene laherparepvec in a subject’s household member, caregiver, or healthcare provider as specified in Section 9.4 of the protocol
- Add PR to electrocardiogram (ECG) assessment data points as it is a required data element per Amgen Data Element Standards
- Update the optional tumor biopsy procedure for biomarker analyses to include biopsy of at least one injected lesion and/or one uninjected lesion
- Allow subjects who have ended the protocol-specified long-term follow-up period for reasons other than death or full withdrawal of consent to enroll into a separate ongoing registry study which is in place for long-term follow-up of subjects treated with talimogene laherparepvec in clinical trials

- Update serious adverse event (SAE) reporting procedures to instruct the investigators to report SAEs that occur outside of the protocol-specified SAE reporting period per EU CT-3 guidance
- Update the statistical analysis to include descriptive analyses of the qPCR results of talimogene laherparepvec DNA in swab samples obtained from lesions suspected to be herpetic in origin, if any, and in the blood and urine
- Update the modified Immune-related Response Criteria in Appendix E to correct contradictory information regarding the baseline tumor measurement requirements and correct errors in Table 2.
- Other administrative changes and corrections were made through the protocol

  - Subjects previously treated with anti-PD1 or anti-CTLA-4 antibodies must not have discontinued therapy due to any treatment-related adverse events, including immune-related adverse event. Prior treatment-related adverse events should also be fully resolved and not requiring treatment for at least 28 days prior to randomization.

- Add ordinal best overall response, disease control rate (DCR), categorical response score, deep response rate, and durable response rate (DDR) as secondary endpoints in phase 2
- Remove the exploratory biomarker objective to investigate association between human leukocyte antigen (HLA) type and other genetic variations in drug metabolism genes, cancer genes, and drug target genes, and clinical outcomes since clinical outcome are not likely to be associated with HLA type and other genetic variations
- Add PRO exploratory objectives/endpoints and assessments (EQ-5D and EORTC QLQ-C30) in phase 2
- Update the background section to include the results of the primary analysis of the OPTiM phase 3 trial and the results of the primary analysis of the phase 1b part of the 20110264 study
- Clarify the statement about immune-related response criteria (irRC) progressive disease during the first 6 months of study treatment. Treatment should not be continued if progressive disease is confirmed per irRC within first 6 months of treatment.
- Update the stratification factors. Randomization will be stratified by stage of disease (stage IIIB/C and IVM1a vs stage IVM1b and IVM1c) and prior therapy (treatment naïve vs previously treated with systemic anticancer immunotherapy vs previously treated with systemic anticancer treatment other than immunotherapy).
- Updated definition of measurable disease in the inclusion criteria and the modified irRC (Appendix E)
- Revise the coagulation function requirements at baseline to align with anticoagulation requirement in other ongoing talimogene laherparepvec studies
- Update the exclusion criteria to allow enrollment of subjects who have treated central nervous system (CNS) metastasis provided that subjects are stable by imaging for 2 months
- Update the exclusion criteria to allow enrollment of subjects with type I DM and prior splenectomy or splenic irradiation
- Update the exclusion criteria to clarify that subjects with any other symptomatic autoimmune disease are not eligible for the study
- Update the exclusion criteria to clarify that subjects with evidence of clinically significant immunosuppression such as any severe congenital or acquired cellular and/or humoral immune deficiency, or concurrent opportunistic infection are not eligible for the study
- Update the exclusion criteria to add excluded prior anticancer therapies separately by study phase (phase 1b and phase 2)
- Update the exclusion criteria and prohibited therapies to restrict the use of “Non-oncology" vaccine for the prevention of infectious disease to within 28 days prior to enrollment and during the first 24 weeks of the treatment period

- Update the exclusion criteria and prohibited therapies to allow use of concomitants therapeutic anticoagulants
- Define dexamethasone dosing threshold for restarting talimogene laherparepvec
- Add instruction that copies of all imaging studies performed during the phase 2, including those performed before the implementation of amendment 2, will be collected and held at an independent centralized radiology vendor for potential retrospective evaluation of response by an independent centralized endpoint assessment committee (EAC)
- Update the schedule of assessments and study procedures for phase 2 to instruct the investigator to collect biopsy either at the time of initial unconfirmed partial response, confirmed progressive disease per modified irRC, or at week 24 for subjects with stable disease, whichever comes first
- Update the schedule of assessments and study procedures to clarify that abdomen, pelvis, and brain MRI/CT scans or CT scans performed with PET must be with contrast if they are to be used for radiographic tumor imaging assessments
- Update schedule of assessments and procedures for phase 2 to inform the investigator that archival biopsy tissue may be substituted for fresh tumor biopsy if prior biopsy was performed within 1 month prior to day 1, and no systemic anticancer therapies were given 1 month prior to the biopsy)
- Updates were made to the statistical consideration section of the protocol including the definition of study endpoints, sample size assumptions, and analysis methods to align with the changes made to the primary and secondary objectives of the study. In addition, sensitivity analyses of objective response by RECIST 1.1 (conventional and modified) were added to the planned method of analyses.
- Add interim analysis of efficacy and safety for phase 2 part of the study for purpose of sharing the data with Amgen senior management for internal decision making.
  - Timing of interim analysis of efficacy and safety: When at least 60 subjects randomized in the phase 2 have received at least 1 dose of talimogene laherparepvec or ipilimumab and have had the opportunity to be followed for at least 24 weeks after randomization.
- Add interim analysis of safety for phase 2 part of the study for purpose of Data Review Team (DRT) evaluation to assess the safety of talimogene laherparepvec in combination with ipilimumab in subjects who received prior treatment for melanoma.
  - Timing of the interim analysis of safety: After approximately 16 subjects who received prior therapy for stage IIIB to IV melanoma before enrollment into the study and have had the opportunity to be on treatment for at least 6 weeks from the initial dosing of ipilimumab and received at least 1 dose of talimogene laherparepvec and/or 1 dose of ipilimumab.
- Update the modified irRC (Appendix E) to include instructions to handle lesion that are too small to measure and lesions that are merging or separating

Other changes and administrative corrections were made throughout the protocol. Refer to the subsequent sections of this document for detailed description of the changes incorporated into protocol amendment 2.

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# Approval Signatures

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| Document Approvals | |
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