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

Amgen Protocol Number (Talimogene Laherparepvec) 20120325
EudraCT number: 2013-005552-15

Clinical Study Sponsor: Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
Telephone: +1-805-447-1000

Key Sponsor Contact(s):
PPD, PhD, MD
Clinical Research Senior Medical Scientist
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

PPD
Clinical Research Study Manager

Date: 18 March 2014
Superseding Date 05 December 2014
Amendment 1 31 August 2015
Superseding Date 21 September 2015

Confidentiality Notice
This document contains confidential information of Amgen Inc.

This document must not be disclosed to anyone other than the site study staff and members of the institutional review board/independent ethics committee/institutional scientific review board or equivalent.

The information in this document cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

If you have questions regarding how this document may be used or shared, call the Amgen Medical Information number: US sites, 1- 800-77-AMGEN, Canadian sites, 1-866-50-AMGEN; for all other countries, 1-805-447-1000.

NCT number 02366195
This NCT number has been applied to the document for purposes of posting on clinicaltrials.gov

CONFIDENTIAL
Investigator’s Agreement

I have read the attached protocol entitled A Phase 2, Multicenter, Open-label, Single-arm Trial to Evaluate the Correlation Between Objective Response Rate and Baseline Intratumoral CD8+ Cell Density in Subjects With Unresected Stage IIIB to IVM1c Melanoma Treated with Talimogene Laherparepvec, dated 21 September 2015, and agree to abide by all provisions set forth therein.

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

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

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

**Study Phase:** 2

**Indication:** Unresected stage IIIB to IVM1c melanoma

**Primary Objective:** The primary objective is to explore the correlation between baseline intratumoral CD8+ cell density and objective response rate (ORR) in subjects with unresected stage IIIB to IVM1c melanoma treated with talimogene laherparepvec.

**Secondary Objective(s):**
- to explore the correlation between baseline intratumoral CD8+ cell density and durable response rate (DRR), duration of response (DOR), and changes in tumor burden
- to explore the correlation between changes in intratumoral CD8+ cell density during treatment and ORR, DRR, DOR, and changes in tumor burden
- to evaluate ORR, DOR, time to treatment failure (TTF), DRR, OS, and change in tumor burden during treatment
- to evaluate the safety and tolerability of talimogene laherparepvec

**Exploratory Objective(s):**
- to investigate the correlation between the changes in the population of tumor specific cytotoxic T cells and immunoscore during treatment and clinical response
- to identify other potential blood and tissue biomarkers which correlate with or predict clinical outcome to talimogene laherparepvec

**Hypotheses:**
No formal statistical hypothesis will be tested in this trial. The study will explore the hypothesis that intratumoral CD8+ cell density at baseline correlates with objective response rate in subjects with unresected stage IIIB to IVM1c melanoma treated with talimogene laherparepvec.

**Primary Endpoint:**
Correlation between baseline intratumoral CD8+ cell density and objective response rate

**Secondary Endpoint(s):**
- correlation between baseline intratumoral CD8+ cell density and DRR, DOR, and changes in tumor burden
- correlation between changes in intratumoral CD8+ cell density during treatment and ORR, DRR, DOR, and changes in tumor burden
- efficacy endpoints: ORR, DOR, TTF, DRR, OS, and change in tumor burden during treatment
- safety endpoints: subject incidence of treatment-emergent and treatment-related adverse events (including all adverse events, grade ≥ 3 adverse events, serious adverse events, fatal adverse events, events of interest, adverse events requiring the discontinuation of study drug), clinically significant laboratory changes, and incidence of symptomatic herpetic lesions that are positive for talimogene laherparepvec

**Exploratory Endpoint(s):**
- correlation between the changes in the population of tumor specific cytotoxic T cells and immunoscore during treatment and clinical response
- identification of other potential blood and tumor biomarkers which correlate with or predict clinical outcomes to talimogene laherparepvec
Study Design:
This is a phase 2, multicenter, open-label, single-arm study to evaluate biomarkers in subjects with unresected stage IIIB to IVM1c melanoma who are treated with talimogene laherparepvec.

Subjects will be treated with talimogene laherparepvec until the subject has achieved a complete response, all injectable tumors have disappeared, clinically significant (resulting in clinical deterioration or requiring change of therapy) disease progression beyond 6 months of treatment, per modified World Health Organization (WHO) response criteria (WHO handbook for reporting results of cancer treatment, 1979; refer to Appendix D), or intolerance of study treatment, whichever occurs first.

Subjects will be followed for safety 30 (+ 7) days after the last dose of talimogene laherparepvec and for survival every 12 weeks (± 28 days) for up to approximately 24 months after the last subject is enrolled in the study. Thereafter, subjects will be followed under an ongoing separate registry protocol (Study 20120139) for the long-term survival follow-up of subjects treated with talimogene laherparepvec. The registry protocol will also monitor for late and long-term adverse events thought to be potentially related to talimogene laherparepvec and use of anti-cancer therapy for melanoma.

Blood and tumor tissue samples will be collected at timepoints outlined in the Schedule of Assessments (Table 2). Tumor biopsies (taken from accessible cutaneous, subcutaneous or nodal lesions) will be performed on an uninjected lesion on day 1 of week 1, on a different uninjected lesion at week 6 (if available), and at disease progression that results in treatment discontinuation from the lesion responsible for progression as outlined in Section 7.2.2. Samples will be analyzed to explore if intratumoral CD8+ cell density at baseline and its change during treatment is correlated with the objective response rate in subjects with unresected stage IIIB-IVM1c melanoma treated with talimogene laherparepvec.

For a full description of the study design, please refer to Section 3.1.

Sample Size: Approximately 110 subjects will be enrolled in the study.

Summary of Subject Eligibility Criteria:

Key Inclusion Criteria:
Male or female ≥ 18 years of age with histologically confirmed diagnosis of stage IIIB to IVM1c melanoma for whom surgery is not recommended. Subject who is treatment naïve or had received prior treatment for melanoma. Subject must have measurable disease and must be a candidate for intralesional therapy with at least 1 injectable cutaneous, subcutaneous, or nodal melanoma lesion (≥ 10 mm in longest diameter) or with multiple injectable lesions that in aggregate have a longest diameter of ≥ 10 mm. Also, subject must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and must have a serum lactate dehydrogenase (LDH) ≤ 1.5 X upper limit of normal and adequate hematologic, hepatic, and renal organ function.

Key Exclusion Criteria:
Subject must not have clinically active cerebral metastases, greater than 3 visceral metastases (this does not include lung or nodal metastases associated with visceral organs), or any bone metastases, primary ocular or mucosal melanoma, history or evidence of symptomatic autoimmune disease (such as pneumonitis, glomerulonephritis, vasculitis, 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. Subject must not have evidence of clinically significant immunosuppression or active herpetic skin lesions or prior complications of HSV-1 infection (eg, herpetic keratitis or encephalitis) and must not require intermittent or chronic systemic treatment with an antiherpetic drug (eg, acyclovir), other than intermittent topical use. Subjects known to have acute or chronic active hepatitis B, hepatitis C, or human immunodeficiency virus
infection will also be excluded. Subjects must not have been treated previously with talimogene laherparepvec.

For a full list of eligibility criteria, please refer to Section 4.

Investigational Product Dosage and Administration:
Talimogene laherparepvec will be administered by intralesional injection into injectable cutaneous, subcutaneous, and nodal lesions with or without image ultrasound 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. The second dose up to 4.0 mL of $10^8$ PFU/mL should be administered 21 (+5) days after the initial dose (ie, no sooner than day 22, but should not be delayed more than 5 days after the day 21 time point). Subsequent doses up to 4.0 mL of $10^8$ PFU/mL should be given every 14 (± 3) days.

Procedures:

Screening:
The following will be performed during the screening period:
- confirmation that the informed consent form has been signed
- review of inclusion and exclusion criteria
- review of medication and medical/surgical history
- physical examination
- vital signs and ECOG Performance Status assessment
- local laboratory tests:
  - hematology panel
  - chemistry panel
  - serum lactate dehydrogenase (LDH)
  - prothrombin time (PT) (or international normalization ratio [INR]) and partial thromboplastin time (PTT)
  - serum or urine pregnancy test for female subjects of childbearing potential
- radiographic tumor imaging and clinical tumor assessment
- recording of concomitant medications
- recording/reporting of any serious adverse events that occur after subject signs informed consent

Treatment:
The following will be performed during the treatment period:
- vital signs
- physical examination
- ECOG Performance Status assessment
- local laboratory tests
  - hematology panel
  - chemistry panel
- archived tumor tissue for $BRAF^{V600E/K}$ mutation testing and biomarker analyses
- central laboratory tests
  - swabs of cold sore, vesicles and other lesions suspected to be herpetic origin (if any) for qPCR analysis of talimogene laherparepvec DNA
  - blood samples for herpes simplex virus (HSV) serostatus
- blood samples for biomarker analysis
- tumor biopsies for biomarker analyses
- radiographic tumor imaging, clinical tumor assessment, and tumor response assessment
- photographs of all visible cutaneous and subcutaneous tumor lesions (select sites only) always within 3 days of the treatment visit starting from the first treatment visit
- recording of concomitant medications, adverse events, and serious adverse events at each visit
- administration of talimogene laherparepvec at day 1 of each treatment cycle

Safety Follow-Up Visit:
The following will be performed during the safety follow-up visit:
- physical examination
- vital signs and ECOG Performance Status assessment
- local laboratory tests:
  - hematology panel
  - chemistry panel
  - serum or urine pregnancy test for female subjects of childbearing potential
- central laboratory tests:
  - swabs of cold sores, vesicles, and other lesions suspected to be herpetic in origin (if any) for qPCR analysis of talimogene laherparepvec DNA
- radiographic tumor imaging, clinical tumor assessment, and tumor response only if subject has discontinued study treatment for reason other than disease progression or death and if not performed within 4 weeks (+1 week) of the safety follow-up visit
- recording of concomitant medications, adverse events, and serious adverse events

Long-term Follow-up/End of Study:
All subjects who permanently discontinue talimogene laherparepvec for any reason other than withdrawal of full consent or death will be contacted by telephone or clinic visit to assess survival, adverse events thought to be potentially related to talimogene laherparepvec, and use of anti-cancer therapies for melanoma every 12 weeks (± 28 days) following the safety follow-up visit until death, subject withdraws full consent, or up to 24 months after the last subject is enrolled in the study.

If subject has discontinued talimogene laherparepvec for reason other than disease progression or death, radiographic tumor imaging, clinical tumor assessments, ECOG Performance Status assessment, assessment of swabs of lesions of suspected herpetic origin by qPCR for talimogene laherparepvec DNA, and tumor response assessments will be performed until documented disease progression beyond 6 months of treatment, per modified WHO response criteria (Appendix D), or until the start of a new anticancer therapy or end of study, whichever the earliest.

After the long term follow-up period of this study has ended, subjects who end the study for any reason other than death or withdrawal of full consent will be followed for survival under an ongoing separate registry protocol (Study 20120139) that is in place for the long-term follow-up of all 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 and use of anti-cancer therapies for melanoma.

Reporting Exposure to Talimogene Laherparepvec:
Reporting potential or known unintended exposure to talimogene laherparepvec, suspected related signs or symptoms, and detection of talimogene laherparepvec in a subject’s household member, caregiver, or healthcare provider as specified in Section 9.4.
For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedule of Assessments (Table 2).

**Statistical Considerations:**

All analyses will be descriptive with no formal hypothesis testing. The primary objective of the study is to explore the correlation between baseline intratumoral CD8+ cell density and objective response rate (ORR). The sample size was selected based on practical considerations. The adequacy of the sample size is discussed in Section 10.2.

The main goals of the primary analysis are to evaluate the correlation between baseline intratumoral CD8+ cell density and ORR, DRR, DOR, and changes in tumor burden, in addition to the correlation between changes in intratumoral CD8+ cell density during treatment and ORR, DRR, DOR, and changes in tumor burden. The timing of the primary analysis will be when all subjects have had the opportunity to complete 12 months of treatment with talimogene laherparepvec.

**An interim analysis to evaluate the study objectives will be conducted on approximately the first 50 subjects who received at least 1 dose of talimogene laherparepvec, with the biomarker recorded at baseline, and have had the opportunity to be in the study (treatment or follow-up) for 6 months.**

The final analysis will occur **either 24 months after the last subject has been enrolled or when the last subject discontinues the study treatment and has had the opportunity to complete the safety follow-up, whichever is later.**

Descriptive statistics will be provided for demographic, safety, efficacy, and biomarkers as appropriate. In general, the safety analysis set will be used for all safety analyses. The safety analyses include incidence of treatment-emergent and treatment-related adverse events (all adverse events, ≥ grade 3 adverse events, serious adverse events, fatal adverse events and adverse events defined as events of interest).

The efficacy analysis will be conducted using the safety analysis set as well, unless otherwise specified. The ORR will be estimated with the associated 95% CI. Descriptive statistics for DRR, time to treatment failure, changes in tumor burden, and OS will be provided. In addition, DOR and changes in tumor burden for responders will also be summarized.

The correlation between a baseline biomarker and response rate will be evaluated. The functional manner in which the response rate may vary with the biomarker is unknown; therefore multiple functional relationships may be examined. Pearson’s correlation coefficient (r) will be estimated between the biomarker change and the maximum decrease in index lesions to evaluate the correlation between changes in a biomarker post-treatment and the effect of treatment on measurable lesions, in addition to correlating biomarker changes with objective response using logistic regression.

For further details on the statistical analysis, please refer to Section 10.

**Sponsor:** Amgen Inc.

Data Element Standards Version(s)/Date(s): Version 4.0, 31 October 2013
Talimogene Laherparepvec

Up to 4 mL

$10^6$ PFU/mL at Day 1
followed by
$10^8$ PFU/mL 21 (+5) days later, then every 14 (±3) days

N=110

Talimogene laherparepvec
dosing until CR, all injectable lesions have disappeared, PD per modified WHO criteria, or intolerance for treatment, whichever occurs first.
# Study Glossary

<table>
<thead>
<tr>
<th>Abbreviation or Term</th>
<th>Definition/Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>alanine aminotransferase</td>
</tr>
<tr>
<td>AST</td>
<td>aspartate aminotransferase</td>
</tr>
<tr>
<td>BRAF, BRAF&lt;sup&gt;V600&lt;/sup&gt;, BRAF&lt;sup&gt;V600E/K&lt;/sup&gt;</td>
<td>v-raf murine sarcoma viral oncogene homolog B1, BRAF V600 mutation, BRAF V600E/K mutations</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>CR</td>
<td>complete response</td>
</tr>
<tr>
<td>CRF</td>
<td>case report form</td>
</tr>
<tr>
<td>CSR</td>
<td>Clinical Study Report</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>CTCAE</td>
<td>Common Terminology Criteria for Adverse Events</td>
</tr>
<tr>
<td>CZ</td>
<td>Crystal Zenith</td>
</tr>
<tr>
<td>DOR</td>
<td>duration of response</td>
</tr>
<tr>
<td>DRR</td>
<td>durable response rate</td>
</tr>
<tr>
<td>ECOG</td>
<td>Eastern Cooperative Oncology Group</td>
</tr>
<tr>
<td>eCRF</td>
<td>electronic case report form</td>
</tr>
<tr>
<td>EDC</td>
<td>electronic data capture</td>
</tr>
<tr>
<td>End of Study for Individual Subject</td>
<td>defined as the date the subject withdraws full consent from the study, completes the long-term follow-up, or dies, whichever is earlier</td>
</tr>
<tr>
<td>End of Study (end of trial)</td>
<td>defined as 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 talimogene laherparepvec and has had the opportunity to complete the safety follow-up visit or the long term follow-up visit, whichever occurs later</td>
</tr>
<tr>
<td>End of Treatment</td>
<td>defined as the last dose of the protocol-specified treatment plus 30 days after the last dose</td>
</tr>
<tr>
<td>ETO system</td>
<td>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.</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FSH</td>
<td>follicle stimulating hormone</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>granulocyte macrophage colony-stimulating factor</td>
</tr>
<tr>
<td>HLA</td>
<td>human leukocyte antigen</td>
</tr>
<tr>
<td>HR</td>
<td>hazard ratio</td>
</tr>
<tr>
<td>HSV, HSV-1, HSV-2</td>
<td>herpes simplex virus, herpes simplex virus type 1, herpes simplex virus type 2</td>
</tr>
<tr>
<td>Abbreviation or Term</td>
<td>Definition/Explanation</td>
</tr>
<tr>
<td>----------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonisation</td>
</tr>
<tr>
<td>IEC</td>
<td>independent ethics committee</td>
</tr>
<tr>
<td>IgG</td>
<td>immunoglobulin G</td>
</tr>
<tr>
<td>IgM</td>
<td>immunoglobulin M</td>
</tr>
<tr>
<td>INR</td>
<td>international normalization ratio</td>
</tr>
<tr>
<td>IPIM</td>
<td>Investigational Product Instruction Manual</td>
</tr>
<tr>
<td>IRB</td>
<td>institutional review board</td>
</tr>
<tr>
<td>LDH</td>
<td>lactate dehydrogenase</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>NA</td>
<td>not applicable</td>
</tr>
<tr>
<td>ND</td>
<td>not done</td>
</tr>
<tr>
<td>NPV</td>
<td>negative predictive value</td>
</tr>
<tr>
<td>ORR</td>
<td>objective response rate</td>
</tr>
<tr>
<td>OS</td>
<td>overall survival</td>
</tr>
<tr>
<td>PD</td>
<td>disease progression</td>
</tr>
<tr>
<td>PDn</td>
<td>nonclinically relevant disease progression</td>
</tr>
<tr>
<td>PDr</td>
<td>clinically relevant disease progression</td>
</tr>
<tr>
<td>PET</td>
<td>positron emission tomography</td>
</tr>
<tr>
<td>PFU</td>
<td>plaque-forming unit</td>
</tr>
<tr>
<td>PPV</td>
<td>positive predictive value</td>
</tr>
<tr>
<td>PR</td>
<td>partial response</td>
</tr>
<tr>
<td>PSP</td>
<td>Pregnancy Surveillance Program</td>
</tr>
<tr>
<td>PT</td>
<td>prothrombin time</td>
</tr>
<tr>
<td>PTT</td>
<td>partial thromboplastin time</td>
</tr>
<tr>
<td>QC</td>
<td>every cycle</td>
</tr>
<tr>
<td>qPCR</td>
<td>real-time polymerase chain reaction</td>
</tr>
<tr>
<td>Q4C</td>
<td>every fourth cycle</td>
</tr>
<tr>
<td>RBC</td>
<td>red blood cells</td>
</tr>
<tr>
<td>ROC</td>
<td>receiver operating characteristic</td>
</tr>
<tr>
<td>SAE(s)</td>
<td>serious adverse event(s)</td>
</tr>
<tr>
<td>SOC</td>
<td>system organ class</td>
</tr>
<tr>
<td>Abbreviation or Term</td>
<td>Definition/Explanation</td>
</tr>
<tr>
<td>---------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Source Data</td>
<td>Information from an original record or certified 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]). Example of source data include: subject identification.</td>
</tr>
<tr>
<td>Study Day 1</td>
<td>Defined as the first day that protocol-specified investigational product is administered to the subject.</td>
</tr>
<tr>
<td>TTF</td>
<td>Time to treatment failure</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper limit of normal</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
</tr>
<tr>
<td>WBC</td>
<td>White blood cells</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
TABLE OF CONTENTS

Protocol Synopsis ............................................................................................................. 3

Study Design and Treatment Schema .............................................................................. 8

Study Glossary .................................................................................................................. 9

1. OBJECTIVES ......................................................................................................... 16
   1.1 Primary ....................................................................................................... 16
   1.2 Secondary .................................................................................................. 16
   1.3 Exploratory ................................................................................................. 16

2. BACKGROUND AND RATIONALE ........................................................................ 16
   2.1 Melanoma ................................................................................................... 16
   2.2 Talimogene Laherparepvec Investigational Product Background .......... 21
   2.3 Rationale .................................................................................................... 23
   2.4 Clinical Hypotheses .................................................................................... 23

3. EXPERIMENTAL PLAN ......................................................................................... 23
   3.1 Study Design .............................................................................................. 23
   3.2 Number of Sites .......................................................................................... 25
   3.3 Number of Subjects .................................................................................... 25
   3.4 Replacement of Subjects ............................................................................ 25
   3.5 Estimated Study Duration ........................................................................... 25
      3.5.1 Study Duration for Subjects ........................................................ 25
      3.5.2 End of Study ............................................................................... 26

4. SUBJECT ELIGIBILITY .......................................................................................... 26
   4.1 Inclusion and Exclusion Criteria ................................................................. 26
      4.1.1 Inclusion Criteria ......................................................................... 26
      4.1.2 Exclusion Criteria ........................................................................ 28

5. SUBJECT ENROLLMENT ..................................................................................... 29

6. TREATMENT PROCEDURES ............................................................................... 30
   6.1 Classification of Product ............................................................................... 30
   6.2 Investigational Product ................................................................................. 30
      6.2.1 Amgen Investigational Product Talimogene Laherparepvec .......... 30
         6.2.1.1 Dosage, Administration, and Schedule .................................... 31
         6.2.1.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation ........................................................ 33
   6.3 Other Protocol-required Therapies ............................................................ 35
   6.4 Concomitant Therapy ................................................................................. 35
   6.5 Other Treatment Procedures ...................................................................... 36
6.6 Medical Devices
6.7 Product Complaints
6.8 Excluded Treatments and/or Procedures During Study Period

7. STUDY PROCEDURES

7.1 Schedule of Assessments
7.2 General Study Procedures
  7.2.1 Screening and Enrollment
  7.2.2 Treatment
  7.2.3 Safety Follow-up Visit
  7.2.4 Long-term Follow-up/End of Study
  7.2.5 Reporting Exposure to Talimogene Laherparepvec
  7.2.6 Optional Photography Substudy (Select Sites Only)

7.3 Biomarker Development
  7.3.1 Blood Samples
  7.3.2 Tumor Tissue Samples

7.4 Pharmacogenetic Studies

7.5 Sample Storage and Destruction

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw
8.2 Investigator or Sponsor Decision to Withdraw or Terminate Subjects' Participation Prior to Study Completion
8.3 Reasons for Removal From Treatment or Study
  8.3.1 Reasons for Removal From Treatment
  8.3.2 Reasons for Removal From Study

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Adverse Events
  9.1.1 Definition of Adverse Events
  9.1.2 Definition of Serious Adverse Events

9.2 Reporting of Adverse Events
  9.2.1 Reporting Procedures for Adverse Events That do not Meet Serious Criteria
  9.2.2 Reporting Procedures for Serious Adverse Events

9.3 Pregnancy and Lactation Reporting

9.4 Reporting of Exposure to Talimogene Laherparepvec

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates
  10.1.1 Study Endpoints
    10.1.1.1 Primary Endpoint
    10.1.1.2 Secondary Endpoints
    10.1.1.3 Exploratory Endpoints
  10.1.2 Analysis Sets
10.1.3 Covariates and Subgroups ................................................................. 61
10.2 Sample Size Considerations ............................................................... 61
10.3 Planned Analyses .................................................................................. 62
  10.3.1 Interim Analyses ............................................................................ 62
  10.3.2 Primary Analysis .......................................................................... 63
  10.3.3 Final Analysis ................................................................................ 63
10.4 Planned Methods of Analysis ............................................................... 63
  10.4.1 Primary Endpoint ......................................................................... 63
  10.4.2 Secondary Endpoint (s) ................................................................. 64
  10.4.3 Safety Endpoints .......................................................................... 64
  10.4.4 Exploratory Endpoints ................................................................. 65
10.5 Handling of Missing and Incomplete Data ......................................... 65

11. REGULATORY OBLIGATIONS .................................................................... 65
  11.1 Informed Consent ............................................................................. 65
  11.2 Institutional Review Board/Independent Ethics Committee ............... 66
  11.3 Subject Confidentiality ....................................................................... 67
  11.4 Investigator Signatory Obligations ..................................................... 67

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS ................................................. 68
  12.1 Protocol Amendments and Study Termination .................................... 68
  12.2 Study Documentation and Archive ................................................... 68
  12.3 Study Monitoring and Data Collection ............................................. 69
  12.4 Investigator Responsibilities for Data Collection .............................. 70
  12.5 Language ......................................................................................... 70
  12.6 Publication Policy ............................................................................ 71
  12.7 Compensation .................................................................................. 71

13. REFERENCES .......................................................................................... 72

14. APPENDICES ........................................................................................ 76

List of Tables

Table 1. Talimogene Laherparepvec Injection Volume Guideline Based on Tumor Size ................................................................. 32
Table 2. Schedule of Assessments ................................................................ 39
Table 3. Laboratory Analytes ........................................................................ 43
Table 4. Expected 95% Confidence Intervals by Various True ORRs .............. 62
Table 5. Definition of Index Lesion Tumor Response Including New Lesions .......... 87
Table 6. Definition of Nonindex Lesion Tumor Response .................................. 88
Table 7. Matrix for Determining the Overall Response at Each Assessment Point ................................................................. 89
List of Appendices

Appendix A. Additional Safety Assessment Information .............................................. 77
Appendix B. Sample Serious Adverse Event Report Form ........................................... 78
Appendix C. Pregnancy and Lactation Notification Worksheets ................................... 81
Appendix D. Modified World Health Organization (WHO) Response Criteria ............. 83
Appendix E. Eastern Cooperative Oncology Group Performance Status
Scale ........................................................................................................ 90
1. OBJECTIVES

1.1 Primary

The primary objective is to explore the correlation between baseline intratumoral CD8+ cell density and objective response rate (ORR) in subjects with unresected stage IIIB to IVM1c melanoma treated with talimogene laherparepvec.

1.2 Secondary

The secondary objectives are as follows:

- to explore the correlation between baseline intratumoral CD8+ cell density and durable response rate (DRR), duration of response (DOR), and changes in tumor burden
- to explore the correlation between changes in intratumoral CD8+ cell density during treatment and ORR, DRR, DOR, and changes in tumor burden
- to evaluate ORR, DOR, time to treatment failure (TTF), DRR, OS, and change in tumor burden during treatment
- to evaluate the safety and tolerability of talimogene laherparepvec

1.3 Exploratory

The exploratory objectives are as follows:

- to investigate the correlation between the changes in the population of tumor specific cytotoxic T cells and immunoscore during treatment and clinical response
- to identify other potential blood and tissue biomarkers which correlate with or predict clinical outcome to talimogene laherparepvec

2. BACKGROUND AND RATIONALE

2.1 Melanoma

Cutaneous melanoma is the fifth most common cancer in men and the seventh most common cancer in women in the United States of America (USA), with an estimated 73,870 new cases and 9,940 deaths expected in 2015 (Siegel et al, 2015). In Europe, the annual incidence of melanoma is somewhat lower than that in the USA, with a crude rate of approximately 14 per 100,000 as compared to 20 per 100,000 in the USA, but is the sixth most common cancer among women (Ferlay et al, 2013; Siegel et al, 2014). In Europe as a whole, approximately 100,442 new cases were diagnosed in 2012 (Ferlay et al, 2013). 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 spread to multiple regional nodal sites (stage III) is infrequently curable with standard therapy. For those with multiple or clinically detectable nodal metastases or in-transit/satellite lesions (stages III B and III C), the 5-year survival rate ranges between 40% (for stage III C disease) to 59% (for stage III B disease) (Balch et al, 2009). For patients with distant spread to skin, nodes, or visceral organs (stage IV disease), the 5-year survival rates are generally low, ranging from 20% for stage M1a disease (skin, subcutaneous or nodes only), 5% to 10% for stage M1b disease (lung only), and < 5% for stage M1c disease (other visceral lesions or high serum lactate dehydrogenase [LDH]); median survival is 12 months for stages M1a and M1b disease and 4 to 6 months for stage M1c disease (O’Day and Boasberg, 2006; Tannous et al, 2005).

Until recently, 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 (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 close patient monitoring in specialized facilities with well-trained staff based on the notable toxicity profile associated with its administration.

Recently, the Food and Drug Administration (FDA), European Commission, and other regulatory agencies have approved 6 novel therapies for advanced melanoma: an immune stimulatory agent, ipilimumab (Yervoy®, 2015), pembrolizumab (Keytruda®, 2015) and nivolumab (Opdivo®, 2015) and 3 agents for use in patients with BRAF mutant melanoma, a v-raf murine sarcoma viral oncogene homolog B1 (BRAF) inhibitor, vemurafenib (Zelboraf®, 2015), the BRAF inhibitor dabrafenib (Tafinlar™, 2013) and the MEK inhibitor trametinib (Mekinist™, 2014). The studies upon which approvals for ipilimumab and vemurafenib were based demonstrated improved survival compared to control treatments. The pivotal study of ipilimumab showed an overall survival (OS) improvement in subjects with human leukocyte antigen (HLA)-A2*0201 genotype previously treated metastatic melanoma as compared with a gp100 peptide vaccine (Hodi et al, 2010; Yervoy® 2015). The median overall survival (OS) was 10.0 months in the group that received ipilimumab in combination with the gp100 peptide vaccine and 6.4 months in the group that received gp100 peptide vaccine alone (hazard ratio
(HR] = 0.68, p < 0.001) (Hodi et al, 2010). Approximately 8% more patients survived 2 years in the ipilimumab arm than in the control arm (21.6% vs 13.7%). The objective response rate was 5.7% vs 1.5%, respectively (p = 0.04). Similar results were reported for another study conducted in previously untreated subjects with metastatic melanoma who received ipilimumab and dacarbazine vs placebo and dacarbazine (Robert et al, 2011).

The pivotal vemurafenib study showed improved OS and objective response rates in a substantial proportion of subjects with previously untreated metastatic melanoma with the \textit{BRAF}^{V600E} mutation who received vemurafenib vs standard dacarbazine (Chapman et al, 2011). The median OS was 13.6 months in the vemurafenib group and 9.4 months in the dacarbazine group (OS data for dacarbazine patients who crossed over to vemurafenib treatment were censored at the time of crossover) (Chapman et al, 2012). The hazard ratio for death was 0.62 (95% Confidence interval [CI]: 0.49, 0.77). The objective response rate was 48% vs 5%, respectively (p < 0.001) (Chapman et al, 2011).

In 2013, regulatory agencies also approved the \textit{BRAF} inhibitor dabrafenib (Tafinlar™, 2013) and the \textit{MEK} inhibitor trametinib (Mekinist™, 2014), both in \textit{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). Additionally, dabrafenib and trametinib were approved recently as a combination therapy for \textit{BRAF}-mutant (\textbf{V600 E/K}) unresectable or metastatic melanoma. (Flaherty et al, 2012b; Long et al, 2015; Robert et al, 2015).

Nivolumab, an anti-PD-1 monoclonal antibody, demonstrated improvement in 1-year OS in treatment naïve subjects with wild-type BRAF advanced melanoma compared to dacarbazine (73% versus 42%; HR 0.42, 99.8% CI 0.25-0.73) (Robert et al, 2015); improved ORR in subjects previously treated with either ipilimumab or \textit{BRAF} inhibitor versus dacarbazine or carboplatin with paclitaxel (32% vs 10%) (Weber et al, 2015), and improved PFS and ORR (either alone or in combination with ipilimumab) compared to ipilimumab alone in treatment naïve subjects (Larkin et al, 2015).

Pembrolizumab, is a monoclonal antibody that targets PD-1 protein, improved PFS and OS versus ipilimumab in subjects with advanced melanoma. Six-month progression-free rates were 47% and 46%, for pembrolizumab administered every 2 and 3 weeks, versus 27% for ipilimumab (HR 0.58; P<0.001 for both
pembrolizumab regimens versus ipilimumab). Twelve-months OS rates were 74%, 68%, and 58%, respectively (HR 0.63, P=0.0005 for pembrolizumab every 2 weeks and 0.69, P=0.004 for pembrolizumab every 3 weeks) (Robert et al, 2015)

While the approval of these newer agents represents a clear milestone in the treatment of advanced melanoma, limitations still exist. The two-year overall survival following ipilimumab remains only approximately 20%, and the drug is associated with severe and potentially fatal immunological adverse effects (Hodi et al, 2010). Although not as common and severe as with ipilimumab, a wide range of immune related toxicities has been reported with pembrolizumab and nivolumab, which include pneumonitis, hepatitis, colitis, nephritis, thyroid dysfunction and others (Larkin et al, 2015; Robert et al, 2015; Weber et al, 2015).

Vemurafenib, dabrafenib, and trametinib are indicated only in patients with BRAFV600 mutations, and are associated with early development of resistance in most cases, leading to short durations of response. The safety profiles of vemurafenib and dabrafenib include increased incidence of cutaneous squamous cell carcinoma or high grade keratoacanthoma in almost 20% of patients treated with vemurafenib and > 5% of patients treated with dabrafenib (Zelboraf®, 2015; Tafinlar™, 2013). Additionally, grade 2 or higher dermatologic reactions including rash, pruritus, and hyperkeratosis are common with both agents. Trametinib is associated with cuneiform dermatitis, peripheral edema, hypertension, decreased cardiac ejection fraction, and ocular events (Mekinist™, 2014). Thus, the need remains for additional treatment options for patients with advanced melanoma (including those with regional and/or distant metastases).

Biomarkers of melanoma prognosis and treatment effect and toxicity have been increasingly well studied in the past few years. BRAF mutations have been identified that predict for response to BRAF inhibitors (Hoeflich et al, 2009). Immunologic-based biomarkers are likely to be important for immunotherapies, including talimogene laherparepvec. Many tumors, including melanoma, are heavily infiltrated by inflammatory and lymphoid cells which can be used as prognostic and predictive biomarkers and a variety of “immunoscores” have been employed in attempts to capture the maximal prognostic value of intratumoral immune cells (Galon et al, 2012). These immunoscores are generally algorithms that combine the number of one or more types of immune cells observed in the tumor with information on the localization of the immune cells within the tumor (eg, proximity to blood vessels, invasive margin). The most commonly used immunoscore is based on the density of cytotoxic CD8+ T-lymphocytes.
in the center and in the invasive margins of tumor (Mlecnik et al, 2011). The prognostic value of immunoscores composed of a combination of immunohistochemical staining densities for both intratumoral CD3+ / CD8+ T cells, combined with the location of the cells either in the invasive margin or central tumor, has been well documented in colon cancer and was shown to have a prognostic significance superior to that of the AJCC TNM classification system (Galon et al, 2006, Galon et al, 2012). An international effort is underway to qualify an immunoscore as a predictive and prognostic biomarker for other cancers (Galon et al, 2014).

Infiltrating T cells have also been shown to be prognostic for melanoma (Erdag et al, 2012). The authors’ primary analysis was performed using an immunoscore that counted CD45+ cells (lymphocytes) and combined the number of cells with the pattern of localization near blood vessels as detected by CD34+ staining. They further showed that the single cell type most strongly correlated with survival was CD8+ cells which is why we have chosen to focus on CD8+ cells as the primary biomarker analysis in the current study. Since talimogene laherparepvec is assumed to work via activation of tumor specific T cells, it is important to understand whether the number of infiltrating T cells at baseline impacts drug efficacy, especially since approximately one-third of melanomas have few or no infiltrating T cells (Erdag et al, 2012).

The postulated dual mechanism of action of talimogene laherparepvec comprises a direct oncolytic effect achieved by infection and replication of the virus in tumor tissue resulting in tumor cell lysis and local release of tumor antigens, and enhancement of a systemic immune response by expression of GM-CSF in the tumor microenvironment to recruit and activate antigen presenting cells. Activated antigen presenting cells initiate an adaptive antitumor immune response, ultimately leading to a persistent immunity. In the current study we will measure tumor antigen-specific T cell responses induced by talimogene laherparepvec treatment in order to further explore mechanisms of action.

Furthermore, baseline tumor mutational load and corresponding neoantigen signatures have been shown to correlate with responsiveness to immunotherapy (Rizvi et al, 2015; Snyder et al, 2014). It will be important to understand if tumor mutational load can be predictive for response to talimogene laherparepvec as well.

In addition, we will also explore the possibility that altered viral replication might affect response. Deletion of the ICP34.5 gene is one of the means by which talimogene laherparepvec was engineered to limit replication to tumor cells. ICP34.5 normally
interferes with the PKR (double-stranded RNA activated protein kinase) pathway which cells activate to protect themselves from viral infection. This PKR pathway is typically inactivated in tumors, but the degree of residual PKR signaling in tumor cells may influence replication of talimogene laherparepvec. Analysis of mutations in the PKR pathway and possibly other tumor cell pathways will be performed in this study in order to explore whether these mutations may affect response to treatment.

2.2 Talimogene Laherparepvec Investigational Product Background

Talimogene laherparepvec is an intralesionally delivered oncolytic immunotherapy comprised of a genetically engineered HSV-1 (herpes simplex virus type 1) that selectively replicates in tumor tissue (Talimogene Laherparepvec Investigator’s Brochure). The neurovirulence factor ICP34.5 and the ICP47-encoding gene are functionally deleted in the virus, while the gene for human granulocyte macrophage colony-stimulating factor (GM-CSF) is inserted. The role of ICP47 is to block antigen presentation to major histocompatibility complex class I molecules by blocking the transporter associated with antigen processing 1 and 2. This deletion also allows the increased expression of the US11 gene. This promotes virus growth in cancer cells without decreasing tumor selectivity.

Additionally, the virus contains the coding sequence for human GM-CSF, a pleiotropic cytokine involved in the stimulation of cellular immune responses by 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). These 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).

Clinical data currently available has provided evidence of talimogene laherparepvec’s efficacy in patients with regionally and distantly metastatic melanoma (Talimogene Laherparepvec Investigator’s Brochure). In particular, a high rate of complete response (CR) was achieved (16% in the phase 2 study with talimogene laherparepvec in stage III C to IV melanoma) (Senzer et al, 2009; Talimogene Laherparepvec Investigator’s Brochure). Moreover, responses were observed in both injected and uninjected sites, including visceral sites. Responses were seen most often in earlier stage disease, including stage III B/C and stage IVM1a, and in disease with lower visceral burden.
In the open-label, randomized, phase 3 study of talimogene laherparepvec versus subcutaneously administered GM-CSF in stages IIIB, IIIC, and IV unresectable melanoma, talimogene laherparepvec or GM-CSF was administered until CR, clinically significant disease progression, intolerable side effects, 12 months of therapy without an objective response, or withdrawal of consent (Study 20110263; OPTiM). The primary endpoint of the study is durable response rate, defined as the rate of subjects with an objective response by central review (CR or partial response [PR]) lasting continuously for 6 months and starting any time within 12 months of initiating therapy.

Primary analysis of the OPTiM Study 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). **Overall response rate was also improved from 6% with GM-CSF to 26% with talimogene laherparepvec (P < 0.0001, descriptive).** Similarly, 11% of patients had a CR in the talimogene laherparepvec arm vs. < 1% in the GM-CSF arm. In the event-driven primary OS analysis (secondary end point), median OS with talimogene laherparepvec treatment was 23.3 months compared with 18.9 months with GM-CSF treatment (HR, 0.79 [95% CI, 0.62–1.00]; P = 0.051) (Andtbacka et al, 2015). At the final planned analysis of OS which happened when last enrolled subject completed 3 years of follow-up, median OS was 23.3 months in the talimogene laherparepvec arm and 18.9 months in the GM-CSF arm (HR, 0.79; 95% CI, 0.62–1.00; P=0.049), (descriptive) (Andtbacka et al, 2015).

The most common side effects were fatigue, chills, and pyrexia. Serious adverse events occurred in 36% of the talimogene laherparepvec subjects and 21% of the GM-CSF subjects. **The only grade 3/4 adverse event occurring in ≥ 2% of patients was cellulitis (talimogene laherparepvec, n=6 [2.1%]; GM-CSF, n=1 [< 1%]).** Of 10 fatal events in the talimogene laherparepvec arm, none were considered treatment-related per investigator and most (80%) were associated with disease progression with the exception of sepsis in the setting of salmonella infection and myocardial infarction (Andtbacka et al, 2015).

Refer to the latest version of the Talimogene Laherparepvec Investigator's Brochure, for additional information.
2.3 Rationale
The purpose of the study is to explore the correlation between baseline intratumoral CD8+ cell density and objective response rate (ORR) in subjects with unresected stage IIIB to IVM1c melanoma. In addition, the study is planned to inform on the mechanism(s) of systemic action of talimogene laherparepvec on distant metastatic tumors and to identify candidate biomarkers which may predict treatment outcome. Biopsy samples will be used to investigate the relationship between intratumoral CD8+ cell density and response to treatment. Leaving one lesion uninjected during the treatment for biopsy at week 6 is critical for defining the proposed locally-initiated systemic anti-tumor immune response of talimogene laherparepvec. One hypothesis is that tumors with significant number of infiltrating CD8+ T cells will be more likely to respond to an immunotherapy with talimogene laherparepvec. Additionally, we hypothesize that talimogene laherparepvec treatment increases the number of tumor antigen specific T cells and further that subjects with higher levels of tumor antigen specific T cells will have greater response to treatment. In addition to examining the association, if any, between tumor infiltrating T cells prior to treatment and clinical response to treatment, a number of other biomarkers will be assessed to determine any association with response.

2.4 Clinical Hypotheses
No formal statistical hypothesis will be tested in this trial. The study will explore the hypothesis that intratumoral CD8+ cell density at baseline correlates with objective response rate in subjects with unresected stage IIIB to IVM1c melanoma treated with talimogene laherparepvec.

3. EXPERIMENTAL PLAN
3.1 Study Design
This is a phase 2, multicenter, open-label, single-arm study to evaluate biomarkers in subjects with unresected stage IIIB to IVM1c melanoma who are treated with talimogene
laherparepvec. Subjects with unresected stage IIIB to IVM1c melanoma who meet the eligibility criteria outlined in Section 4 will be considered for participation in this study.

Talimogene laherparepvec will be administered by intralesional injection into injectable cutaneous, subcutaneous, and nodal tumors initially at a dose of 10^6 Plaque-Forming Unit (PFU)/mL at study day 1 followed by a dose of 10^8 PFU/mL 21 (± 5) days after the initial dose and every 14 (± 3) days thereafter. Subjects will be treated with talimogene laherparepvec until the subject has achieved a CR, all injectable tumors have disappeared, clinically significant (resulting in clinical deterioration or requiring change of therapy) disease progression beyond 6 months of treatment, per modified World Health Organization (WHO) response criteria (WHO handbook for reporting results of cancer treatment, 1979; refer to Appendix D), or intolerance of study treatment, whichever occurs first. Due to the mechanism of action, subjects may experience transient growth of existing tumors or the appearance of new tumors prior to achieving maximal clinical benefit of talimogene laherparepvec. Therefore, dosing should be continued for at least 6 months from the time of initial dose regardless of progression provided that the subject is able to tolerate the treatment and does not develop deterioration of health status requiring other treatment.

Subjects will be followed for safety 30 (± 7) days after the last dose of talimogene laherparepvec for survival, adverse events thought by the investigator to be potentially related to talimogene laherparepvec, and use of anticancer therapies for melanoma every 12 weeks (± 28 days) for up to approximately 24 months after the last subject is enrolled in the study. Thereafter, subjects will be followed under an ongoing separate registry protocol (Study 20120139) for the long-term survival follow-up of subjects treated with talimogene laherparepvec. The registry protocol will also monitor for late and long-term adverse events thought by the investigator to be potentially related to talimogene laherparepvec and use of anti-cancer therapies for melanoma.

Blood and tumor tissue samples will be collected at timepoints outlined in the Schedule of Assessments (Table 2). Tumor biopsies will be performed from an uninjected lesion on day 1 of week 1, from a different uninjected lesion at week 6 (if available), and from the lesion responsible for progression at the time of disease progression that results in treatment discontinuation as outlined in Section 7.2.2. Samples will be analyzed to explore if intratumoral CD8+ cell density at baseline and its change during
treatment is correlated with the objective response rate in subjects with unresected stage IIIB-IVM1c melanoma treated with talimogene laherparepvec.

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

The study endpoints are defined in Section 10.1.1.

### 3.2 Number of Sites
Approximately 50 sites in Europe and the USA will participate in the study. Additional sites and regions may be added to the study as necessary. Sites that do not enroll subjects within 6 months of site initiation may be closed.

### 3.3 Number of Subjects
Participants in this clinical investigation shall be referred to as “subjects”. Approximately 110 subjects will be enrolled in the study. Refer to Section 10.2 for sample size considerations.

### 3.4 Replacement of Subjects
Subjects who are withdrawn or removed from treatment or from the study will not be replaced.

### 3.5 Estimated Study Duration
#### 3.5.1 Study Duration for Subjects
The subject enrollment period is planned for approximately 17 months.

The duration of the screening period for each subject will be up to 28 days. The duration of treatment will vary for each subject. Subjects will be treated with talimogene laherparepvec until the subject has achieved a CR, all injectable tumors have disappeared, clinically relevant (resulting in clinical deterioration or requiring change in therapy) disease progression beyond 6 months of treatment, per modified WHO response criteria (Appendix D), or intolerance of study treatment, whichever occurs first. Subjects will be followed for safety 30 (+ 7) days after the last dose of talimogene laherparepvec and for survival, adverse events thought by the investigator to be potentially related to talimogene laherparepvec, and use of anti-cancer therapy for melanoma every 12 weeks (± 28 days) for up to approximately 24 months after the last subject is enrolled in the study. The estimated average per-subject study duration is approximately 32 months.
After the end of the long term follow up subjects who end the study for any reason other than death or withdrawal of full consent will continue to be followed for survival under an ongoing separate registry protocol (Study 20120139). The registry protocol will also monitor for adverse events thought by the investigator to be potentially related to talimogene laherparepvec and use of anti-cancer therapies for melanoma.

3.5.2 End of Study

Primary Completion: the time when the last subject is assessed or receives an intervention for the purpose of final collection of data for the primary analysis. The primary completion is anticipated to occur when all subjects have had the opportunity to complete 12 months of treatment.

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 **24 months after the last subject has been enrolled** or when the last subject discontinues talimogene laherparepvec and has had the opportunity to complete the safety follow-up visit, whichever occurs later.

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 activities/procedures, the appropriate written informed consent must be obtained (see Section 11.1).

4.1 Inclusion and Exclusion Criteria

4.1.1 Inclusion Criteria

101 Subject has provided informed consent prior to initiation of any study-specific activities/procedures

102 Male or female age ≥ 18 years at the time of informed consent

103 Histologically confirmed diagnosis of melanoma

104 Subject with stage IIIB to IVM1c melanoma for whom surgery is not recommended

105 Subject who is treatment naïve or **had received prior treatment** for melanoma. Any systemic treatment for melanoma must have been completed at least 28 days prior to enrollment
106 Candidate for intralesional therapy (ie, disease is appropriate for direct injection or through the use of ultrasound guidance) defined as one of the following:

- at least 1 injectable cutaneous, subcutaneous, or nodal melanoma lesion ≥ 10 mm in longest diameter, or
- multiple injectable melanoma lesions that in aggregate have a longest diameter of ≥ 10 mm

107 Measurable disease defined as one or more of the following:

- at least 1 melanoma lesion that can be accurately and serially measured in at least 2 dimensions and for which the greatest diameter is ≥ 10 mm as measured by contrast-enhanced or spiral computed tomography (CT) scan, magnetic resonance imaging (MRI), or ultrasound for nodal/soft tissue disease (including lymph nodes)
- at least 1 ≥ 10 mm superficial cutaneous or subcutaneous melanoma lesion as measured by calipers
- multiple superficial melanoma lesions which in aggregate have a total diameter of ≥ 10 mm

108 Serum lactate dehydrogenase (LDH) levels ≤ 1.5 X upper limit of normal (ULN) within 28 days prior to enrollment

109 Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (see Appendix E)

110 Adequate organ function determined within 28 days prior to enrollment, defined as follows:

- absolute neutrophil count ≥ 1500/mm³
- platelet count ≥ 75,000/mm³
- hemoglobin ≥ 8 g/dL without need for hematopoietic growth factor or transfusion support
- serum creatinine ≤ 1.5 x ULN
- serum bilirubin ≤ 1.5 x ULN
- aspartate amino transferase (AST) ≤ 2.5 x ULN
- alanine amino transferase (ALT) ≤ 2.5 x ULN
- alkaline phosphatase ≤ 2.5 x ULN
- serum albumin ≥ 2.5 g/dL
- prothrombin time (PT) ≤ 1.5 x ULN (or international normalization ratio [INR] ≤ 1.3)*
- partial thromboplastin time (PTT) ≤ 1.5 x ULN*

* Prolongation in INR, PT, and PTT when the result is from therapeutic anticoagulation treatment are permitted for subjects whose injectable lesions are cutaneous and/or subcutaneous such that direct pressure could be applied in the event of excessive bleeding.
4.1.2 Exclusion Criteria

201 Clinically active cerebral metastases. Subjects with up to 3 cerebral metastases may be enrolled, provided that all lesions have been adequately treated with stereotactic radiation therapy (including Gamma Knife) or resection, with no evidence of progression and have not required steroids for at least two months prior to enrollment.

202 Greater than 3 visceral metastases (this does not include lung metastases or nodal metastases associated with visceral organs). For subjects with ≤ 3 visceral metastases, no lesion > 3 cm and liver lesions must be stable for at least 1 month prior to enrollment.

203 Bone metastases

204 Primary ocular or mucosal melanoma

205 History or evidence of symptomatic autoimmune disease (such as pneumonitis, glomerulonephritis, vasculitis, 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.

206 Evidence of clinically significant immunosuppression such as the following:

- primary immunodeficiency state such as Severe Combined Immunodeficiency Disease
- concurrent opportunistic infection
- receiving systemic immunosuppressive therapy (> 2 weeks), including oral steroid doses > 10 mg/day of prednisone or equivalent during the 2 months prior to enrollment

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

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

209 Previous treatment with talimogene laherparepvec

211 Currently receiving treatment with another investigational device or drug study, or less than 28 days since ending treatment with another investigational device or drug study(s)

212 Other investigational procedures while participating in this study are excluded

213 Known to have acute or chronic active hepatitis B infection

214 Known to have acute or chronic active hepatitis C infection

215 Known to have human immunodeficiency virus infection

216 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 for ≥ 3 years before enrollment and felt to be at low risk for recurrence by the treating physician
- adequately treated non-melanoma skin cancer without evidence of disease
• adequately treated cervical carcinoma in situ without evidence of disease
• adequately treated breast ductal carcinoma in situ without evidence of disease
• prostatic intraepithelial neoplasia without evidence of prostate cancer
• adequately treated urothelial papillary noninvasive carcinoma or carcinoma in situ

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

218 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’s and investigator’s knowledge

219 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 medical monitor, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion

220 Subject previously has entered this study

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

222 Female subject of childbearing potential who is unwilling to use acceptable method(s) of effective contraception during study treatment and through 3 months after the last dose of talimogene laherparepvec

Note: Women not of childbearing potential are defined as: Any female who is post-menopausal (age > 55 years with cessation of menses for 12 or more months or < 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.

Note: Acceptable methods of effective contraception are defined in the informed consent form. Where required by local laws and regulations, additional country-specific requirements are outlined in a country-specific protocol supplement at the end of the Appendix Section of the protocol.

223 Sexually active subjects and their partners unwilling to use male or female latex condom to avoid potential viral transmission during sexual contact while on treatment and within 30 days after treatment with 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, if applicable (see Section 11). All subjects must personally sign and date the informed consent form before commencement of study-specific activities/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 must remain
constant throughout the entire clinical study; it must not be changed at the time of
rescreening or enrollment.

Subjects who 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. Subjects who are determined not eligible after rescreen must be
screen-failed in the ETO system and the reason for the screen-failure provided.
Subjects may be enrolled only once into this study.

Upon confirmation of eligibility, the site staff will use the ETO system to enroll a subject.
A subject will be considered enrolled when the investigator confirms that the subject has
met all eligibility criteria and the subject is registered as enrolled in the ETO system.
The investigator is to document confirmation of eligibility in the subject’s medical record
and in the case report form (CRF).

6. TREATMENT PROCEDURES

6.1 Classification of Product

The Amgen Investigational Product used in this study is talimogene laherparepvec.

The Investigational Product Instruction Manual (IPIM), a document external to this
protocol, contains detailed information regarding the description, storage, preparation,
and administration of talimogene laherparepvec.

6.2 Investigational Product

6.2.1 Amgen Investigational Product Talimogene Laherparepvec

Talimogene laherparepvec will be manufactured and packaged by Amgen Inc. and
distributed using Amgen clinical study drug distribution procedures. Talimogene
laherparepvec is supplied as a sterile frozen liquid in a single-use 2-cc Crystal Zenith
(CZ resin) vial with a gray Fluorotec®-coated chlorobutyl elastomer stopper, aluminum
seal, and polypropylene cap. Each vial contains a minimum of 1.0 mL talimogene laherparepvec at either 10⁶ PFU/mL or 10⁸ PFU/mL concentrations. The supply for 10⁶ PFU/mL concentration will be packaged separately from the supply for 10⁸ PFU/mL concentration. Additional details on talimogene laherparepvec packaging and formulation are provided in the Investigational Product Instruction Manual.

### 6.2.1.1 Dosage, Administration, and Schedule

Talimogene laherparepvec must be prepared and administered by a qualified healthcare professional. Subjects should be assessed clinically for adverse events/toxicity prior to each dose using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (Appendix A). Complete blood count with differential and chemistry panels including liver function laboratory tests (such as ALT, AST, and total bilirubin) should be obtained according to the Schedule of Assessments (see Table 2) and the results should be checked before scheduled doses as per the requirements described in the Schedule of Assessments. Dosing will occur only if these test values are acceptable, per Section 6.2.1.2.

Talimogene laherparepvec will be administered by intralesional injection only into injectable cutaneous, subcutaneous, and nodal tumors, with or without image ultrasound guidance. Talimogene laherparepvec must not be administered into visceral organ metastases. The initial dose of talimogene laherparepvec is up to 4.0 mL of 10⁶ PFU/mL. Subsequent doses of talimogene laherparepvec are up to 4.0 mL of 10⁸ PFU/mL.

The first cycle of talimogene laherparepvec will be 21 (+ 5) days. Subsequent cycles of talimogene laherparepvec will be 14 (± 3) days. On day 1 of cycle 1 the first dose of talimogene laherparepvec will be up to 4.0 mL of 10⁶ PFU/mL. The second injection up to 4.0 mL of 10⁸ PFU/mL, should be administered 21 (+ 5) days after the initial injection (ie, no sooner than day 22 but should not be delayed more than 5 days after the 21-day time point). Subsequent injections up to 4.0 mL of 10⁸ PFU/mL should be given every 14 (± 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 treatment is 4.0 mL. Investigators are encouraged to use the maximum amount whenever lesions allow. Dose reduction for adverse events 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 adverse event such as pain, the total volume given should be recorded, and the reason for intolerance should be documented as an adverse event.

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. The tumor size assessment should be done by clinical exam using ruler or caliper for cutaneous and palpable and protruding subcutaneous and nodal lesions, or by measurements under ultrasound of deep-seated subcutaneous and nodal lesions.

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

<table>
<thead>
<tr>
<th>Tumor Size (longest dimension)</th>
<th>Maximum Injection Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 5.0 cm</td>
<td>4.0 mL</td>
</tr>
<tr>
<td>&gt; 2.5 cm to 5.0 cm</td>
<td>2.0 mL</td>
</tr>
<tr>
<td>&gt; 1.5 cm to 2.5 cm</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>&gt; 0.5 cm to 1.5 cm</td>
<td>0.5 mL</td>
</tr>
<tr>
<td>≤ 0.5 cm</td>
<td>0.1 mL</td>
</tr>
</tbody>
</table>

At baseline, if there are ≥ 2 lesions, one cutaneous, subcutaneous or nodal lesion (i.e., the lesion considered lowest priority for injection) should be left uninjected at least until it is biopsied at week 6 (see Section 7.2.2). **(No biopsy will be taken at week 6 for subjects with 1 lesion present at baseline).** All other reasonably injectable lesions (cutaneous, subcutaneous, and nodal disease that can be injected with or without ultrasound guidance) should be injected with the maximum dosing volume available on an individual dosing occasion (Table 1). On each treatment day, prioritization of injections is recommended as follows (aside from leaving one lesion uninjected until it is biopsied at week 6):

- 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, including the previously uninjected lesion(s) after the biopsy at week 6 if 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.
A subject will be treated with talimogene laherparepvec until the subject has achieved a CR, all injectable tumors have disappeared, clinically significant (resulting in clinical deterioration or requiring change of therapy) disease progression beyond 6 months of treatment, per modified World Health Organization (WHO) response criteria (Appendix D), 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 clinically significant deterioration of health status requiring discontinuation of treatment with talimogene laherparepvec and is able to tolerate the treatment.

The dose, start date, and lot number of talimogene laherparepvec are to be recorded on the electronic case report form (eCRF).

6.2.1.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

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 any of the following treatment-related toxicities, talimogene laherparepvec administration should be delayed until the toxicity has resolved to at least CTCAE grade 1 or has returned to 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 antiviral drugs (eg, acyclovir, valacyclovir, famciclovir), but may receive a topically administered antiviral drug more than 20 cm from a talimogene laherparepvec injection site. If a subject requires treatment with systemic antiviral drugs (eg, acyclovir, valacyclovir, famciclovir) talimogene laherparepvec should be withheld and the investigator or designee should notify the Amgen medical monitor as soon as possible. Subject may be allowed to continue treatment after discussion between the Amgen medical monitor and the investigator to determine the appropriateness of treatment resumption.
Dosing 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 the subject requires corticosteroid dosing of > 10 mg prednisone daily (or equivalent) for related toxicities, talimogene laherparepvec dosing must be withheld until the corticosteroid dose has decreased to ≤ 10 mg prednisone daily (or equivalent).

All necessary supportive care shall be available to subjects except for those listed in Section 6.8. Talimogene laherparepvec treatment should be continued based on the potential benefit/risk assessment of the subject.

If talimogene laherparepvec treatment is 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 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 an adverse event that is considered related to talimogene laherparepvec, the subject must be permanently withdrawn from talimogene laherparepvec treatment.

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.

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 6.5). In this case, discontinuation from the treatment occurs immediately upon introduction of the new agent.

- Clinically relevant disease progression beyond 6 months of treatment occurs as defined per the modified WHO response criteria (Appendix D).

- 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) including but not limited to male or female latex condom to avoid potential viral transmission during sexual contact.

- 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.

6.3 Other Protocol-required Therapies
All other protocol-required therapies including topical anesthetic or an injectable local anesthetic medications used for pretreatment of the talimogene laherparepvec injection site 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 6.8.

All prescription and nonprescription concomitant medication administered up to 28 days prior to enrollment, on an ongoing basis after enrollment, 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 case report form (CRF) until 30 days (+ 7 days) after the last dose of talimogene laherparepvec. 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 Other Treatment Procedures
Treatment with talimogene laherparepvec may result in the reduction of tumor burden such that surgical resection of previously unresected lesion becomes possible. Investigators may choose to resect lesions which become suitable for resection to render the subject free of macroscopic disease. Additionally, biopsies will be taken of cutaneous, subcutaneous or nodal lesions for tumor analysis during study. In the event of a complete response, residual visible cutaneous or subcutaneous index lesions must be documented by representative biopsy to not contain viable tumor. If a subject undergoes resection of the lesion in the event other than CR, the investigator or designee should notify the sponsor medical monitor as soon as possible and the procedure should be recorded in the source document and eCRF. In these instances, if the response of other lesions is at least PR (if other lesions remain), the response should be designated PR with the date of surgery as the date of response. If no residual disease remains following surgery, this should also be noted in the eCRF, the response definition again being PR with the date of surgery as the date of response. If no viable melanoma was found in the surgical specimen and all other tumor lesions resolved completely (if were present), the response definition will be CR with the date of surgery as the date of response.

Local palliative radiation treatment for relief of various symptoms including, but not limited to, bleeding or pain associated with the underlying disease will be permitted at any time during the study. Subjects with local symptoms suggestive of disease progression should be evaluated for tumor response per modified WHO response criteria (see Appendix D) prior to the administration of palliative radiotherapy. 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 eCRF.

If a subject demonstrates evidence of recurrent or new central nervous system (CNS) metastases, talimogene laherparepvec should be withheld and the investigator or designee should notify the Amgen medical monitor as soon as possible. Subjects may be allowed to remain on protocol after discussion between the Amgen medical monitor and the investigator to determine the appropriateness of treatment resumption provided
CNS lesions can be treated with stereotactic radiotherapy (including GammaKnife) or resection and if there is no change in the baseline ECOG performance status. Subjects may be allowed to reinitiate talimogene laherparepvec following treatment of CNS metastases while receiving dexamethasone or a similar corticosteroid at no more than 1.5 mg dexamethasone (or 10 mg prednisone or equivalent) per day. If higher doses of a steroid are used, talimogene laherparepvec must be held until that dose level is reached during the period of steroid tapering.

6.6 Medical Devices
Medical devices (eg, syringes, sterile needles, alcohol prep pads), that are commercially available are not usually provided or reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

6.7 Product Complaints
A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of any investigational or non-investigational product(s) or device(s).

Any product complaint(s) associated with an investigational product(s) or non-investigational product(s) or device(s) supplied by Amgen are to be reported according to the instructions provided in the IPIM.

6.8 Excluded Treatments and/or Procedures 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 drug and radiation therapy required for palliation (as noted in Section 6.5)
- chronic oral or systemic steroid medication use at a dose of >10 mg/day of prednisone or equivalent (with the exception of treatment for adverse events [see Section 6.2.1.2] and CNS metastases [see Section 6.5]). Steroids with low systemic absorption [eg, triamcinolone hexacetonide] injected into a joint space is allowed
- antitherpetic drugs (eg, acyclovir), other than if topically administered > 20 cm from a talimogene laherparepvec injection site. If a subject requires treatment with a systemic antitherpetic drugs (eg, acyclovir, valacyclovir, famciclovir) talimogene laherparepvec should be withheld and the investigator or designee should notify the Amgen medical monitor as soon as possible. Subject may be allowed to continue treatment after discussion between the Amgen medical monitor and the investigator to determine the appropriateness of treatment resumption.
• Subjects must not schedule any elective surgeries during the treatment period and for at least 30 days after the last administration of study drug. If a subject undergoes any unexpected surgery during the course of the study, study treatment 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 drug if both the investigator and sponsor medical monitor agree to restart study therapy.

The exclusion criteria describe other medications and procedures which are prohibited in this study (refer to Sections 4.1.2).

There are no prohibited therapies and procedures during the post treatment long-term follow-up period.

7. STUDY PROCEDURES
7.1 Schedule of Assessments

The schedule of assessments for the study is summarized in Table 2.
## Table 2. Schedule of Assessments

<table>
<thead>
<tr>
<th>Cycle&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Screening&lt;sup&gt;*&lt;sup&gt;</th>
<th>Treatment Period&lt;sup&gt;b&lt;sup&gt;</th>
<th>Follow-up Period&lt;sup&gt;c&lt;sup&gt;</th>
<th>Cycle 8 and Beyond&lt;sup&gt;d&lt;sup&gt;</th>
<th>Safety&lt;sup&gt;e&lt;sup&gt;</th>
<th>Survival&lt;sup&gt;f&lt;sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day</td>
<td>≤ 28 days</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>30 (+7) Days</td>
<td>Every 12 (≤ 28 days) Weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### GENERAL & SAFETY ASSESSMENTS

- Informed Consent
- Review of Medical/Surgical History
- Review of Eligibility Criteria
- Concomitant Medications<sup>g</sup>
- Adverse and Serious Adverse Events<sup>h</sup>
- Adverse Events Thought to Be Related to Talimogene Laherparepvec<sup>i</sup>
- Physical Exam<sup>j</sup>
- Vital Signs<sup>k</sup>
- ECOG Performance Status<sup>l</sup>
- Survival Assessment
- Anti-cancer therapy for melanoma<sup>m</sup>

### LOCAL LABORATORY ASSESSMENTS

- Urine or Serum Pregnancy Test<sup>n</sup>
- Hematology<sup>o</sup>
- Chemistry<sup>p</sup>
- Serum LDH
- PT (or INR) and PTT

### CENTRAL LABORATORY ASSESSMENTS

- Archived Tumor Tissue for Biomarker Analysis and BRAF<sup>q</sup>/V600E<sup>r</sup>
- Swab of Herpetic Lesion for qPCR<sup>s</sup>
- Blood for HSV Serostatus<sup>t</sup>

Footnotes defined on next page.
### Table 2. Schedule of Assessments

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Cycle 8 and Beyond</th>
<th>Follow-up Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day</td>
<td>Safety</td>
<td>Survival</td>
</tr>
<tr>
<td>1</td>
<td>30 (+7) Days</td>
<td>12 (±288 days)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>Weeks</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Tumor/Response Assessments

**Clinical Tumor Assessments**
- Day 1 of week 12 and then every 12 weeks until PD or start of new anticancer therapy

**Radiological Tumor Assessments**
- Day 1 of week 12 and then every 12 weeks until PD or start of new anticancer therapy

**Photographs of all Visible Tumor Lesions**
- X X X X X Q2C

**Dosing**
- Talimogene Laherparepvec Administration

**Reporting Exposure to Talimogene Laherparepvec**
- Exposure of Household member, Healthcare provider, or close contact

**Reporting Pregnancy/Lactation**
- Reporting of Pregnancy or Lactation

---

- Screening assessments to be performed within 28 days prior to enrollment, unless otherwise indicated.
- During the treatment period assessments and procedures can be performed within 3 days of the planned visit unless otherwise specified.
- Safety follow-up will be performed 30 (+7) days after the last dose of talimogene lahreperepvec.
- All subjects who permanently discontinue talimogene lahreperepvec for any reason other than withdraw of full consent or death will be contacted by telephone, or clinic visit, to assess survival. Adverse events deemed by the investigator to be potentially related to talimogene lahreperepvec will also be recorded. Follow-up will occur every 12 weeks (± 28 days) following the safety follow-up visit until death, subject withdraws full consent, or up to 24 months after the last subject is enrolled in the study. After the long term follow-up period has ended, subjects who end the study for any reason other than death or withdrawal of full consent will be followed for survival under an ongoing separate registry protocol (Study 20120139) that is in place for the long-term follow-up of subjects treated with talimogene lahreperepvec in clinical trials.
- All concomitant medications that are administered after the subject has signed informed consent through 30 (+7) days after the last administration of talimogene lahreperepvec will be recorded in the case report form. Concomitant medications should be assessed on an ongoing basis and recorded at each subject visit. Only subsequent anticancer therapy for melanoma will be recorded during the long term follow-up survival assessment period.
All nonserious adverse events (related or not related to talimogene laherparepvec) that occur after the first dose through 30 (+7) days after the last administration of talimogene laherparepvec will be recorded in the case report form. In addition, all adverse events deemed by the investigator to be potentially related to talimogene laherparepvec will be recorded in the case report form through the survival follow-up. Adverse events should be assessed on an ongoing basis and recorded at each subject visit. All serious adverse events that occur after the subject has signed the informed consent through 30 (+7) days after the last administration of talimogene laherparepvec will be reported to Amgen and recorded in the case report form. Serious adverse events must be reported to Amgen within 24 hours of discovery.

Physical examination as per standard of care.

Vital signs (blood pressure, heart rate, and temperature) must be performed at screening, prior to talimogene laherparepvec administration on day 1 of cycle 1, 2, and 4, then every other cycle (Q2C) until end of treatment, and at the safety follow-up visit.

Urine or serum pregnancy test must be performed on females of childbearing potential within 3 days prior to enrollment and at the safety follow-up visit. Note: Additional on-treatment pregnancy testing may be performed at the investigator’s discretion or as defined in a country-specific protocol supplement at the end of the Appendix Section of the protocol as required per local laws and regulations.

Blood samples for hematology will be collected at screening, within 3 days prior to talimogene laherparepvec administration on day 1 of cycles 1, 2, and 3, then every 4th cycle (Q4C) until end of treatment, and at the safety follow-up visit. Results must be reviewed prior to scheduled dose of study treatment.

Blood samples for chemistry will be collected at screening, within 3 days prior to talimogene laherparepvec administration on day 1 of cycles 1, 2, and 3, then every 4th cycle (Q4C) until end of treatment, and at the safety follow-up visit. Results must be reviewed prior to scheduled dose of study treatment.

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 should be submitted to the central laboratory within 28 days after enrollment for biomarker analyses. BRAF\(^{V600E/K}\) mutation status may be obtained in a number of ways. For previously Known BRAF\(^{V600E/K}\) Tumor Status, BRAF\(^{V600E/K}\) tumor status result, obtained from a local laboratory prior to screening for this study will be acceptable. For previously Unknown BRAF\(^{V600E/K}\) 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.

Swabs of any lesion suspected to be herpetic in origin will be collected as follows: 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 herpetic infection is suspected. A qPCR analysis will be performed at a central lab on the swab to evaluate whether the talimogene laherparepvec DNA is detectable in the sample.

Blood sample for HSV serostatus will be collected (within 3 days prior to talimogene laherparepvec administration) at day 1 of week 1 [Cycle 1], week 6 [Cycle 3], and week 12 [Cycle 6].

Blood sample for biomarker analysis will be collected (within 3 days prior to talimogene laherparepvec administration) at day 1 of week 1 [Cycle 1], week 6 [Cycle 3], week 12 [Cycle 6], and week 24 [Cycle 12].

Tumor biopsy from cutaneous, subcutaneous or nodal lesions for biomarker analysis should not be collected prior to the subject being enrolled. Tumor biopsy should be collected (within 5 days prior to first talimogene laherparepvec administration) from one lesion at day 1 of week 1 [Cycle 1] and, if there are ≥ 2 lesions at baseline and one is left uninjected as described in Section 6.2.1.1, from an uninjected lesion within 7 days prior to dose at day 1 of week 6 [Cycle 3]. Also within 7 days after documentation of disease progression followed by treatment discontinuation from the available cutaneous, subcutaneous or nodal lesion responsible for PD and easily accessible for biopsy with or without untrasound guidance. Note: uninjected lesion biopsied at day 1 of week 6 [Cycle 3] must be different lesion from the lesion biopsied at day 1 of week 1 [Cycle 1].

Investigator’s clinical measurement of cutaneous, subcutaneous, or nodal tumor by caliper at screening, day 1 of week 12 (± 1 week) [Cycle 6] and then every 12 weeks (± 1 week), or more frequently if clinically indicated, until clinically relevant disease progression beyond 6 months of treatment (per modified WHO response criteria, Appendix D) or until the start of a new anticancer therapy. The screening measurement must be done within 28 days prior to enrollment and will be used as baseline. If subject discontinues talimogene laherparepvec for reason other than disease progression or death, clinical tumor measurements are to be performed at safety follow-up visit (if not performed within previous 4 weeks [± 1 week]) and every 12 weeks (± 1 week) during the long term follow-up period until clinically relevant disease progression beyond 6 months of treatment (per modified WHO response criteria, Appendix D) or until the start of a new anticancer therapy.
Radiographic imaging (CT, PET/CT, MRI, or US) of the chest, abdomen, and pelvis, and all other sites of disease, and CT scan or MRI of brain (only if symptoms or signs suggestive of CNS metastasis are present) at screening, day 1 of week 12 (± 1 week) [Cycle 6] and then every 12 weeks (± 1 week), or more frequently if clinically indicated, until clinically relevant disease progression beyond 6 months of treatment (per modified WHO response criteria, Appendix D or until the start of a new anticancer therapy. The screening assessment must be done within 28 days prior to enrollment and will be used as baseline. If subject discontinues talimogene laherparepvec for reason other than disease progression or death, radiographic imaging is to be performed at safety follow-up visit (if not performed within previous 4 weeks (+ 1 week)) and every 12 weeks (±1 week) during the long term follow-up period until clinically relevant disease progression beyond 6 months of treatment (per modified WHO response criteria, Appendix D) or until the start of a new anticancer therapy.

At select sites only, photographs of all visible cutaneous and subcutaneous tumor lesions at Cycle 1, Cycle 2, and every second subsequent cycle until end of treatment (always within 3 days prior to investigational product administration). See Section 7.2.6

The first cycle of talimogene laherparepvec will be 21 (+ 5) days. Subsequent cycles of talimogene laherparepvec will be 14 (± 3) days (QC). On day 1 of cycle 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 21 (+ 5) days after the initial injection (ie, no sooner than day 22 but should not be delayed more than 5 days after the 21-day time point). Subsequent injections up to 4.0 mL of $10^8$ PFU/mL should be given every 14 (± 3) days. Subjects will be treated with talimogene laherparepvec until the subject has achieved a complete response, all injectable tumors have disappeared, clinically significant (resulting in clinical deterioration or requiring change of therapy) disease progression beyond 6 months of treatment, per modified WHO response criteria (Appendix D), or intolerance of study treatment, whichever occurs first.

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 in a subject’s household member, caregiver, or healthcare provider as specified in Section 9.4

Reporting of pregnancy or lactation: If a pregnancy occurs in a female subject, or female partner of a male subject, or a lactation case occurs while the subject is taking talimogene laherparepvec, the case must be reported to Amgen Global Patient Safety through 3 months after the last dose of talimogene laherparepvec as specified in Section 9.3

ECOG Performance Status will be assessed at screening, day 1 of Cycle 1, then every 12 weeks (ie, every sixth cycle) alongside the tumor response assessments until the end of tumor response assessments per study protocol.

Anti-cancer therapy may include any systemic, regional, and local therapies for melanoma disease.
Refer to the applicable supplemental laboratory manuals for detailed collection and handling procedures for laboratory samples.

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. Only eligible subjects will be enrolled into the study.

During treatment, assessments and procedures can be performed within 3 days of the planned visit unless specified otherwise. It is recommended that dosing occur on the same day of the week (e.g., 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 following laboratory analytes in Table 3 will be assessed at various times throughout the study:

<table>
<thead>
<tr>
<th>Chemistry</th>
<th>Hematology</th>
<th>Biomarkers</th>
<th>Other Labs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>RBC</td>
<td>HSV Serostatus</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Potassium</td>
<td>Hemoglobin</td>
<td>Blood for biomarker analysis</td>
<td>LDH</td>
</tr>
<tr>
<td>Chloride</td>
<td>Hematocrit</td>
<td>Archived tumor tissue for biomarker analysis</td>
<td>qPCR for talimogene laherparepvec DNA</td>
</tr>
<tr>
<td>Total protein</td>
<td>Platelets</td>
<td>Tumor biopsy for biomarker analysis</td>
<td>PT (or INR), PTT</td>
</tr>
<tr>
<td>Albumin</td>
<td>WBC</td>
<td>Blood for biomarker analysis</td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td>Differentiala</td>
<td>Day 2: Basophils, Day 3: Lymphocytes, Day 4: Monocytes</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total bilirubin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST (SGOT)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT (SGPT)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 3-part differential if 5-part is unable to be performed

The chemistry, hematology, PT (or INR), PTT and pregnancy tests are to be performed at a local laboratory and test results are to be fully and routinely recorded on the electronic CRFs (eCRFs). Missed tests that are not done must be reported as such on the eCRFs and should not be completed as unscheduled tests between cycles. The real-time quantitative polymerase chain reaction (qPCR) and biomarker/antibody tests will be performed at a central laboratory and tests results will not be reported on the eCRFs.
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.

Where required by local laws and regulations additional assessments are defined in a country-specific protocol supplement at the end of the Appendix Section of the protocol.

### 7.2.1 Screening and Enrollment

The following procedures are to be completed during the screening period within 28 days of enrollment (unless otherwise noted) at time points designated in the Schedule of Assessments (Table 2):

- Confirmation that the Informed Consent Form has been signed
- Review of inclusion and exclusion criteria
- Demographic data including sex, date of birth, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness
- Review of medications and medical/surgical history
- Physical Examination as per standard of care
- Vital signs (eg, systolic/diastolic blood pressure, heart rate, and temperature)
- Determination of ECOG performance status (Appendix E)
- Local laboratory assessments
  - within ≤ 28 days prior to enrollment:
    - hematology panel: hemoglobin, hematocrit, white blood cells (WBC) with 5-part differential (3-part differential if 5-part unable to be performed), red blood cells (RBC), platelets
    - chemistry panel: sodium, potassium, chloride, total protein, albumin, calcium, creatinine, total bilirubin, alkaline phosphatase, AST, ALT
    - serum LDH
    - PT (or INR), PTT
  - within ≤ 3 days prior to enrollment:
    - serum or urine pregnancy test for female subjects of childbearing potential.
    - Note: Additional on-treatment pregnancy testing may be performed at the investigator’s discretion or as defined in a country-specific protocol supplement at the end of the Appendix Section of the protocol as required per local laws and regulations.
- Clinical tumor assessments, including clinical measurement of cutaneous, subcutaneous, or nodal tumor lesions by caliper (to be used as baseline)
- Radiographic tumor imaging (including computed tomography [CT] scan, positron emission tomography [PET]/CT scan, magnetic resonance imaging [MRI], or ultrasound) of the chest, abdomen, pelvis and all other sites of disease (to be used as baseline). Also, CT scan or MRI of the brain if symptoms or signs suggestive of CNS metastasis are present.
• Documentation of concomitant medications
• Reporting of serious adverse events (SAEs) that occur after subject signs informed consent form. SAEs will be reported to Amgen within 24 hours following the investigator’s knowledge of the event
• Registration in Electronic Trial Operation (ETO) system (see Section 5)

7.2.2 Treatment

Treatment begins when the first dose of talimogene laherparepvec is administered to a subject. Study treatment should begin as soon as possible after enrollment via ETO but no later than 5 days after enrollment. Study treatment is to be administered after all other procedures are completed during each visit, unless otherwise stated.

The following procedures will be completed during the treatment period at the times designated in the Schedule of Assessments (Table 2):

• Vital signs (eg, systolic/diastolic blood pressure, heart rate, and temperature) at day 1 of cycles 1, 2, and 4, then every other cycle until end of study treatment
• Determination of ECOG Performance Status at day 1 of Cycle 1, and then every 12 weeks (ie, every sixth cycle) in parallel with tumor response assessment and until the end of tumor assessment per study protocol (Appendix E)
• Physical exams as per standard of care at day 1 of Cycle 1, and then every 12 weeks (ie, every sixth cycle) until the end of study treatment
• Local laboratory assessments: Screening laboratory values may be used for day 1 cycle 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 must be reviewed prior to the administration of study treatment.
  - hematology panel: hemoglobin, hematocrit, WBC with 5-part differential (3-part differential if 5-part is unable to be performed), RBC, platelets
    o day 1 of cycles 1, 2, and 3, then every fourth (4th) cycle until end of study treatment
  - chemistry panel: sodium, potassium, chloride, total protein, albumin, calcium, creatinine, total bilirubin, alkaline phosphatase, AST, ALT
    o day 1 of cycles 1, 2, and 3, then every fourth (4th) cycle until end of study treatment
  - Note: Additional on-treatment pregnancy testing may be performed at the investigator’s discretion or as defined in a country-specific protocol supplement at the end of the Appendix Section of the protocol as required per local laws and regulations.
• Central laboratory assessments:
  - 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 within 28 days after enrollment for biomarker analyses
- **BRAF**\(^\text{V600E/K}\) mutation testing/status may be obtained in a number of ways as listed below:
  - previously known **BRAF**\(^\text{V600E/K}\) tumor status: **BRAF**\(^\text{V600E/K}\) tumor status result, obtained from a local laboratory prior to screening for this study will be acceptable and should be available within 28 days after enrollment
  - previously unknown **BRAF**\(^\text{V600E/K}\) tumor status: Archived formalin-fixed paraffin-embedded tumor tissue (block or unstained tumor slide) from either the primary tumor or a metastatic lesion (as described above) will be analyzed at a local laboratory or submitted to the central laboratory within 28 days after enrollment for **BRAF**\(^\text{V600E/K}\) tumor status determination

- swabs of cold sores, vesicles, and other lesions suspected to be herpetic in origin (if any) for qPCR testing:
  - 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 **herpetic** infection is suspected. A qPCR analysis will be performed on the swab sample to evaluate whether the talimogene laherparepvec DNA is detectable in the sample.

- blood sample for HSV serostatus (within 3 days prior to talimogene laherparepvec administration) at day 1 of week 1, week 6, and week 12.

- blood sample for biomarker analysis (within 3 days prior to talimogene laherparepvec administration) at day 1 of week 1, week 6, week 12 and week 24. **Note:** Lymphocyte subsets will be measured by flow cytometric determination.

- **all tumor biopsies in the study should be performed from easily accessible with or without ultrasound guidance cutaneous, subcutaneous or nodal lesions.** Tumor biopsy for biomarker analysis should not be collected prior to the subject being enrolled. **Tumor biopsy should be collected** (within 5 days prior to **first** talimogene laherparepvec administration) from one lesion at day 1 of week 1 and, if there are \(\geq 2\) lesions at baseline and one is left un.injected as described in Section 6.2.1.1, from an un.injected lesion within 7 days prior to talimogene laherparepvec injection at day 1 of week 6. Also within 7 days after documentation of disease progression (PDn or PDr) that resulted in treatment discontinuation, from the available and easily accessible for biopsy with or without ultrasound guidance cutaneous, subcutaneous or nodal lesion responsible for progression.
  
  **Note:** uninjected lesion biopsied at day 1 of week 6 must be a different lesion from the lesion biopsied at day 1 of week 1

- Radiographic tumor imaging assessments at day 1 of week 12 (± 1 week) and then every 12 (± 1 week) weeks, or more frequently if clinically indicated, until clinically relevant disease progression beyond 6 months of treatment, per modified WHO response criteria [Appendix D]), or until the start of a new anticancer treatment

  - radiographic imaging must include CT scan, PET/CT, MRI, or ultrasound (if applicable) of the chest, abdomen, and pelvis and all other sites of disease. In addition, CT scan or MRI of the brain 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 **throughout the study** for any individual subject.

- Clinical tumor assessments (clinical measurement of cutaneous, subcutaneous, or nodal tumor measurement by caliper) at day 1 of week 12 (± 1 week) and then every 12 (± 1 week) weeks or more frequently if clinically indicated, until clinically relevant disease progression beyond 6 months of treatment, per modified WHO response criteria (**Appendix D**), or until the start of a new anticancer therapy.

- Tumor response assessments at day 1 of week 12 (± 1 week) and then every 12 (± 1 week) weeks or more frequently if clinically indicated, until clinically relevant disease progression beyond 6 months of treatment, per modified WHO response criteria (**Appendix D**), or until the start of a new anticancer therapy.

- Photographs of **all** visible cutaneous and subcutaneous tumor lesions at **day 1 Cycle 1, day 1 Cycle 2, and day 1 of every second subsequent cycle** until end of tumor response assessment per protocol, always within 3 days prior to investigational product administration. (Select Sites Only: see Section 7.2.6)

- Recording of adverse events at each visit

- Recording of serious adverse events at each visit. Serious adverse events will be reported to Amgen within 24 hours following the investigator’s knowledge of the event

- Documentation of concomitant medications at each visit

- Reporting pregnancy in a female subject or a female partner of a male subject while the subject is taking talimogene laherparepvec treatment and through 3 months after end of treatment (Section 9.3)

- Reporting lactation case in a female subject while the subject is taking talimogene laherparepvec treatment and through 3 months after end of treatment (Section 9.3)

- Administration of talimogene laherparepvec treatment at day 1 of each cycle (Section 6.2.1.1)

### 7.2.3 Safety Follow-up Visit

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

- Physical examination as per standard of care

- Vital signs (eg, systolic/diastolic blood pressure, heart rate, and temperature)

- Determination of ECOG Performance Status **alongside the tumor response assessments until the end of tumor response assessments per study protocol** (**Appendix E**)

- Local laboratory assessments:
  - hematology panel: hemoglobin, hematocrit, WBC with 5-part differential (3-part differential if 5-part is unable to be performed), RBC, platelets
  - chemistry panel: sodium, potassium, chloride, total protein, albumin, calcium, creatinine, total bilirubin, alkaline phosphatase, AST, ALT
  - serum or urine pregnancy test for female subjects of childbearing potential
Central laboratory assessments:
- swabs of cold sores, vesicles, and other lesions suspected to be herpetic in origin (if any) for qPCR testing:
  - 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. A qPCR analysis will be performed on the swab sample to evaluate whether the talimogene laherparepvec DNA is detectable in the sample.

Radiographic tumor imaging, clinical tumor assessments, and tumor response assessments, will be performed as documented in Section 7.2.2 until documented clinically relevant disease progression beyond 6 months of treatment, per modified WHO response criteria (Appendix D), or until the start of a new anticancer therapy. (Only if subject has discontinued study treatment for reason other than disease progression or death and if not performed within 4 weeks [+1 week] of the safety visit.)

Recording of adverse events

Recording of serious adverse events. SAEs will be reported to Amgen within 24 hours following the investigator’s knowledge of the event.

Documentation of concomitant medications

7.2.4 Long-term Follow-up/End of Study
All subjects who permanently discontinue talimogene laherparepvec for any reason other than withdrawal of full consent or death will be contacted by telephone, or clinic visit, to assess survival status and, if applicable, commencement of any subsequent anticancer melanoma therapy. Adverse events deemed by the investigator to be potentially related to talimogene laherparepvec and use of anti-cancer therapies for melanoma will also be recorded. Follow-up will occur every 12 weeks (± 28 days) following the safety follow-up visit until death, subject withdraws full consent, or up to 24 months after the last subject is enrolled in the study.

If subject has discontinued talimogene laherparepvec for reason other than disease progression or death, radiographic tumor imaging, clinical tumor assessments, ECOG Performance Status assessments, reporting of pregnancy or lactation, assessment of swabs of lesions of suspected herpetic origin for presence of talimogene laherparepvec DNA by qPCR test, and tumor response assessments will be performed as documented in Section 7.2.2 until documented disease progression beyond 6 months of treatment, per modified WHO response criteria (Appendix D), until the start of a new anticancer therapy, or end of study, whichever the earliest.

After the long term follow-up period of this study has ended, subjects who end the study for any reason other than death or withdrawal of full consent will be followed for survival
under an ongoing separate registry protocol (Study 20120139) that is in place for the long-term follow-up of all 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 and use of anti-cancer therapies for melanoma.

7.2.5 Reporting Exposure to Talimogene Laherparepvec
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, have or 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 in a subject’s household member, caregiver, or healthcare provider as specified Section 9.4.

7.2.6 Optional Photography Substudy (Select Sites Only)
For sites selected to participate in the photography substudy, photographs of all visible (ie, visible protrusion from skin surface) cutaneous and subcutaneous tumor lesions will be performed as detailed in Section 7.2.2 until end of treatment (always within 3 days prior to investigational product administration). Amgen may use, copy, and/or distribute the photographs for educational purposes, in scientific lectures, journal articles, and textbooks. Amgen may also use the photographs for general commercial purposes and may have the photographs published, circulated or presented in any way either alone or with other written, printed, graphic, or audio matter to members of the medical, nursing, pharmaceutical and related professions, as well as to the public at large. The subjects’ identity will not be disclosed in any photographs. Amgen would only show the photographs of subjects from the neck down excluding face or scalp without identifying the subject facial characteristics. Any tattoos or other body marks that may identify the subjects will be covered. Amgen may edit, reduce, enlarge or otherwise change the photographs. The photographs may have commercial value to Amgen. Neither Amgen nor the investigator will compensate the subject for the photographs or the use of the photographs. Refer to the Photography Manual for further instructions.

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.

Amgen may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to talimogene laherparepvec.

7.3.1 Blood Samples
Blood samples are to be collected for biomarker development at time points designated in the Schedule of Assessments (Table 2) and as described in Section 7.2.2.

Blood samples (both cells and plasma) will be analyzed for changes in the immune system before and during treatment that correlate with clinical response. Tumor antigen specific cytotoxic T cells will be enumerated in blood samples. Changes in circulating immune cells will be characterized by flow cytometry to enumerate the number of immune cell subsets. T cell subsets will also be characterized for activation markers.

Refer to the Laboratory Manual for detailed collection and handling procedures for blood samples for biomarker development.

7.3.2 Tumor Tissue Samples
Archived Tumor Tissue Sample:
A block of formalin-fixed paraffin-embedded tumor tissue (from the current diagnosis) collected prior to the study is to be sent to the central laboratory along with the corresponding pathology report as described in the Schedule of Assessments (Table 2) and in Section 7.2.2.

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 the event that multiple tumor blocks with generous tumor tissue are available, the most recent block should be submitted. In lieu of a block, approximately 20 unstained sections on charged slides from the same block can be submitted.
Analyses of tumor specific mutations or epigenetic changes may be performed (eg somatic mutations) on tumor tissues.

Refer to Laboratory Manual for specific instructions on tumor block/slide preparation.

**Tumor Biopsy Samples:**

On study biopsies will be collected, as described in the Schedule of Assessments (Table 2) and in Section 7.2.2, to characterize the mechanism of systemic action of talimogene laherparepvec. Collecting a biopsy from an uninjected lesion during the treatment period (eg, **within 7 days prior to dosing** at week 6) is critical for identifying the changes in intratumoral CD8+ cell density that occur following talimogene laherparepvec treatment and that may be associated with clinical benefit. Refer to the Laboratory Manual for specific instructions on tumor biopsy procedures.

CD8+ cell density will be determined in tumor tissue samples by CD8 specific immunohistochemistry. The tissue samples will be analyzed by immunohistochemistry blinded to study outcomes at a central laboratory. The entire tissue slide will be stained and scanned to create a digital image. Image analysis software will be used to exclude areas of adjacent normal tissue, necrotic tissue and large blood vessels and to define the region of interest which will be measured in mm². Within the region of interest, the image analysis software will measure the number of CD8+ T cells and report the number of CD8+ T cells per square millimeter (eg, #CD8+ cells/mm²).

In addition to CD8 cells, a variety of other tumor infiltrating immune cell markers may be explored by immunohistochemistry.

The tumor samples will also be analyzed for mutations or other changes within the tumor that make it more resistant to talimogene laherparepvec viral replication.

### 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. 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 or tumor samples collected according to the Schedule of Assessments (Table 2) 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 coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. 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, 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.

Since the evaluations are not expected to be available in time to benefit the subject directly or to alter the treatment course, the results of qPCR testing from swabs of cold sores, vesicles, and other lesions suspected to be herpetic in origin will not be provided unless requested by the investigator or the subject. Results may not be available until the end of the study. Results of biomarker development or other exploratory studies are not placed in the subject’s medical record and are not to be 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 blood or tumor 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 (e.g., the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). 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.

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects’ Decision to Withdraw

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

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or 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 investigational product or other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments (Table 2) and collection of data, including endpoints and adverse events. The investigator must document the change to the Schedule of Assessments (Table 2) and the level of follow-up that is agreed to by the subject (e.g., 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.
8.2 Investigator or Sponsor Decision to Withdraw or Terminate Subjects’ Participation Prior to Study Completion

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion.

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol-required therapies by a separate protocol or as provided for by the local country’s regulatory mechanism, based on parameters consistent with Section 12.1.

8.3 Reasons for Removal From Treatment or Study

8.3.1 Reasons for Removal From Treatment

Reasons for removal from the protocol-required investigational product or procedural assessments may include any of the following:

- subject request
- safety concern (eg, due to an adverse event, ineligibility determined, protocol deviation, non-compliance (eg, procedural or dosing as defined in Section 6.2.1.1), requirement for alternative therapy, pregnancy)
- decision by sponsor (other than subject request or safety concern)
- death
- lost to follow-up
- clinically relevant disease progression beyond 6 months of treatment, per modified WHO response criteria (Appendix D)
- other protocol-specified criteria (Section 6.2.1.2)

8.3.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

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

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Adverse Events

9.1.1 Definition of Adverse Events

An adverse event 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 adverse events observed by the investigator or reported by the subject are recorded in the subject’s medical record.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition (e.g., diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome. A pre-existing 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 adverse event.

For situations when an adverse event or serious adverse event is considered to be due to melanoma, report all known signs and symptoms. Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (e.g., worsening of melanoma).

Note: The term “disease progression” should not be used to describe the adverse event.

The investigator’s clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject, or subject’s legally acceptable representative requests to withdraw from protocol-required therapies or the study due to an adverse event, refer to Section 8.1 for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

9.1.2 Definition of Serious Adverse Events

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

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

An adverse event would meet the criterion of “requires hospitalization”, if the event necessitated an admission to a health care facility (e.g., 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 serious adverse event 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.

9.2 Reporting of Adverse Events

9.2.1 Reporting Procedures for Adverse Events That do not Meet Serious Criteria

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after the first dose of talimogene laherparepvec through 30 (+ 7) days after the last dose of talimogene laherparepvec are reported using the applicable eCRF (eg, Adverse Event Summary). **Adverse events deemed by the investigator to be potentially related to talimogene laherparepvec that occur during and after the first dose of talimogene laherparepvec and through the survival follow-up are to be reported.**

The investigator must assign the following adverse event attributes:

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

The adverse event grading scale used will be the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. The grading scale used in this study is described in Appendix A. The investigator must assess whether the adverse event is possibly related to talimogene laherparepvec. 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 administration of investigational product?

The investigator must assess whether the adverse event is possibly related to any study-mandated activity and/or procedure (eg, including any screening procedures). 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 and/or procedure”?

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 adverse events. However, laboratory value changes that require treatment
or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

If the severity of an adverse event worsens from the date of onset to the date of resolution, record a single event for each increased level of severity on the Adverse Event Summary eCRF. The investigator is expected to follow reported adverse events until stabilization or reversibility.

9.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events 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 are recorded in the subject’s medical record and are submitted to Amgen. All serious adverse events must be submitted to Amgen within 24 hours following the investigator’s knowledge of the event via the applicable eCRF.

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 serious adverse event, the information is to be reported to Amgen via an electronic Serious Adverse Event (eSAE) Contingency Report Form within 24 hours of the investigator’s knowledge of the event. See Appendix B for a sample of the Serious Adverse Event Worksheet /electronic Serious Adverse Event Contingency Report Form. For EDC studies where the first notification of a Serious Adverse Event is reported to Amgen via the electronic Serious Adverse Event 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 talimogene laherparepvec. 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 the investigational product”? 
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 serious adverse event must be submitted to Amgen. All new information for serious adverse events must be sent to Amgen within 24 hours following knowledge of 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 serious adverse event must be consistent with that recorded on the applicable CRF (e.g., Adverse Event Summary eCRF).

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

Amgen will report serious adverse events 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 (GCP).

The investigator is to notify the appropriate IRB/IEC of serious adverse events occurring at the site and other adverse event 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-required therapies, report the pregnancy to Amgen as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should report pregnancies that occur after the last dose of talimogene laherparepvec through 3 months after the last dose of talimogene laherparepvec. The pregnancy should be reported to Amgen Global Patient Safety within 24 hours of the investigator’s knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix B).
If a lactation case occurs while the female subject is taking protocol-required therapies report the lactation case to Amgen as specified below.

In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur after the last dose of talimogene laherparepvec through 3 months after the last dose of talimogene laherparepvec.

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 B).

9.4 Reporting of 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 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. Please refer to your study specific documents for reporting details.

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 signs 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 in the lesion, within 3 days of the symptoms or signs occurring.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

10.1.1.1 Primary Endpoint

• Correlation between baseline intratumoral CD8+ cell density and objective response rate (ORR)
10.1.1.2 Secondary Endpoints

- Correlation between baseline intratumoral CD8+ cell density and durable response rate (DRR), and duration of response (DOR), and changes in tumor burden
- Correlation between changes in intratumoral CD8+ cell density during treatment and ORR, DRR, DOR, and changes in tumor burden
- Efficacy Endpoints: ORR, DOR, time to treatment failure (TTF), DRR, OS, and change in tumor burden during treatment
- Safety Endpoints: subject incidence of treatment-emergent and treatment-related adverse events (including all adverse events, grade ≥ 3 adverse events, serious adverse events, fatal adverse events, events of interest, adverse events requiring the discontinuation of study drug), clinically significant laboratory changes, and incidence of symptomatic herpetic lesions that are positive for talimogene laherparepvec

10.1.1.3 Exploratory Endpoints

- Correlation between the changes in the population of tumor specific cytotoxic T cells and immunoscore during treatment and clinical response
- Identification of other potential blood and tumor biomarkers which correlate with or predict clinical outcomes to talimogene laherparepvec

10.1.2 Analysis Sets

Safety Analysis Set: The safety analysis set will include all subjects who have received at least 1 dose of talimogene laherparepvec. The efficacy analysis and safety analysis will be performed on the safety analysis set.

Baseline Biomarker Analysis Set: The baseline biomarker analysis set will be defined separately for each baseline biomarker. The baseline biomarker analysis set includes all subjects who received at least 1 dose of talimogene laherparepvec and have the biomarker recorded at baseline. The correlation between a baseline biomarker and objective response rate, durable response rate, and duration of response will be conducted on the baseline biomarker analysis set.

Biomarker Evaluable Analysis Set: The biomarker evaluable analysis set will be defined separately for each biomarker. Lesions will be analyzed by injection status. The biomarker evaluable analysis set includes all subjects who received at least 1 dose of talimogene laherparepvec and have the biomarker recorded both at baseline and week 6. The correlation between biomarker changes during treatment and objective response rate, durable response rate, and duration of response will be conducted on the biomarker evaluable analysis set.
10.1.3 Covariates and Subgroups

The following covariates may be used to examine efficacy and safety in subgroups or in multivariate analyses:

- Region, if applicable
- Age at baseline: < 50, ≥ 50; < 65, ≥ 65; < 75, ≥ 75 years
- Disease stage at baseline: IIIB and IIIC vs IVM1a vs IVM1b vs IVM1c
- Baseline LDH ≤ ULN vs > ULN
- Sex (Female vs Male)
- ECOG Performance Status (0 vs 1)

10.2 Sample Size Considerations

All analyses will be descriptive with no formal hypothesis testing. The sample size was selected based on practical considerations. The primary objective of the study is to assess whether baseline intratumoral CD8+ cell density is correlated with the likelihood of response to talimogene laherparepvec. Analyses for the objective will focus on whether the response rate varies with baseline intratumoral CD8+ cell density. The functional manner in which the response rate may vary with the biomarker is unknown, therefore multiple functional relationships may be examined. It is assumed that 100 subjects (approximately 91% of the enrolled) will have an evaluable baseline intratumoral CD8+ cell density. The adequacy of the sample size was evaluated for one of several possible analyses that evaluates whether the response rate is positively correlated with a high baseline intratumoral CD8+ cell density where a low and high biomarker is defined as a value below versus at or above the sample median, respectively. A one-sided Fisher’s Exact test will be performed at a 5% nominal level to explore the hypothesis that the response rate is equal regardless of baseline intratumoral CD8+ cell density. The overall ORR is assumed to be 26.4%. The power for the test will depend on the true response rates in the biomarker subgroups.

Assuming the true response rate is 13.2% in the biomarker low subgroup, and 39.6% in the biomarker high subgroup, the power will be 88% to detect a positive association.

A secondary objective of this study is to estimate the objective response rate. Based on the analysis of the OPTiM study, the overall response rate for stage IIIB/C and IVM1c is assumed to be around 26.4% where, among responders, the probability of response onset after 12 months was < 5%. The expected exact 95% CIs for various true ORRs are listed in Table 4. The expected width of the 95% CI is around 18% under these scenarios.
Table 4. Expected 95% Confidence Intervals by Various True ORRs

<table>
<thead>
<tr>
<th>Subjects enrolled (N)</th>
<th>True</th>
<th>Expected 95% CI (width)</th>
</tr>
</thead>
<tbody>
<tr>
<td>110</td>
<td>20%</td>
<td>13% - 29% (16%)</td>
</tr>
<tr>
<td></td>
<td>30%</td>
<td>22% - 39% (18%)</td>
</tr>
<tr>
<td></td>
<td>40%</td>
<td>31% - 50% (19%)</td>
</tr>
<tr>
<td></td>
<td>50%</td>
<td>40% - 60% (19%)</td>
</tr>
</tbody>
</table>

Another secondary objective is to explore the correlation between changes in intratumoral CD8+ cell density during treatment and objective response rate. The primary focus will be on changes in tumor cell CD8+ density. It is assumed that 55 subjects (approximately 50% of all enrolled) will be evaluable with a pre- and on-treatment lesion biopsy that is sufficient to evaluate biomarker changes in uninjected lesions. In addition to correlating biomarker changes with objective response, Pearson’s correlation coefficient (r) will also be estimated between the biomarker change and the maximum decrease in index lesions. With 55 evaluable subjects, a value of $r \leq 0.30$ will be rejected at a nominal 1-sided 5% significance level with an observed $r > 0.49$ for which the power will be > 80% given a true value for $r \geq 0.60$.

10.3 Planned Analyses

10.3.1 Interim Analyses

An interim analysis to evaluate the study objectives of correlation between the biomarker (ie baseline intratumoral CD8+ cell density changes in intratumoral CD8+ cell density and other biomarkers) and ORR will be conducted on approximately the first 50 subjects only who received at least 1 dose of talimogene laherparepvec, with the biomarker recorded at baseline, and have had the opportunity to be on study (treatment or follow-up phase) for at least 6 months. The study will not be discontinued due to the results of this interim analyses; however, predictive hypotheses generated from the interim analysis may lead to subsequent changes to study conduct. For example, if the interim analysis suggests an enhanced effect in a biomarker-defined subgroup, then the protocol and statistical analysis plan may be revised to ensure the study can adequately evaluate the subgroup effect. Revisions may also happen due to obtaining new relevant data from external sources, such as scientific publications and communications.
10.3.2 Primary Analysis
The clinical study report (CSR) will be written based on the results of the primary analysis. The main goals of the primary analysis are to evaluate the ORR and correlation of baseline intratumoral CD8+ cell density and the likelihood of response to talimogene laherparepvec, in addition to the correlation between changes in intratumoral CD8+ cell density during treatment and objective response. The timing of the primary analysis will be when all subjects have had the opportunity to complete 12 months of treatment of talimogene laherparepvec.

10.3.3 Final Analysis
The final analysis will occur either 24 months after the last subject has been enrolled or when the last subject discontinues the study treatment and has had the opportunity to complete the safety follow-up, whichever is later. The CSR will be amended with the updated results from the final analysis at the completion of the study.

10.4 Planned Methods of Analysis
Descriptive statistics will be provided for demographic, safety, efficacy, and biomarkers as appropriate. In general, the safety analysis set will be used for all safety analyses. The safety analyses include incidence of treatment-emergent and treatment related adverse events (all adverse events, ≥ grade 3 adverse events, serious adverse events, fatal adverse events and adverse events defined as events of interest).

The efficacy analysis will be conducted using the safety analysis set as well unless otherwise specified. The ORR will be estimated with the associated 95% CI. Descriptive statistics for DRR, time to treatment failure and OS will be provided. In addition, DOR and changes in tumor burden for responders will also be summarized.

The correlation between a baseline biomarker and response rate will be evaluated. The functional manner in which the response rate may vary with the biomarker is unknown; therefore multiple functional relationships may be examined. Pearson’s correlation coefficient (r) will be estimated between the biomarker change and the maximum decrease in index lesions to evaluate the correlation between changes in a biomarker post-treatment and the effect of treatment on measurable lesions, in addition to correlating biomarker changes with objective response using logistic regression.

10.4.1 Primary Endpoint
The primary endpoint of the study is the correlation between baseline intratumoral CD8+ cell density and objective response rate (ORR). The correlation of intratumoral
CD8+ cell density and other biomarkers with ORR will be evaluated as described in Section 10.4 for ORR and DRR.

10.4.2 Secondary Endpoint (s)

Multiple biomarkers will be examined to assess the correlation between their baseline value and DRR, DOR, and changes in tumor burden as well as the changes in their value during treatment with ORR, DRR, DOR, and changes in tumor burden. The functional manner in which the ORR, DRR, DOR, and change in tumor burden may vary with each biomarker is unknown, therefore multiple functional relationships will be examined to assess overall evidence of an association. Combinations of biomarkers may be explored to assess their predictive value for patient selection. Example analyses include, but are not limited to: (a) the correlation of baseline value as a continuous variable with the odds of OR, DR or the hazard of ending response; (b) a trend test for an increasing ORR, DRR with pre-specified, ordered biomarker categories, (c) a test that the ORR, DRR or hazard of ending response is greater between subgroups of subjects with a high vs. low baseline biomarker value for all possible cut-points for a minimum high biomarker value, (d) a receiver operating characteristic (ROC) analysis (categorical and continuous biomarker values), and (e) calculation of negative predictive value (NPV) and positive predictive value (PPV) for each candidate cut-point for ORR and DRR.

In order to evaluate the correlation between changes in biomarkers during treatment and the effect of treatment on measurable lesions, Pearson’s correlation coefficient (r) will be estimated between the biomarker change and the maximum decrease in index lesions, in addition to correlating biomarker changes with ORR/DRR using logistic regression, and duration of response using Cox model regression.

Overall survival (OS), duration of response and time to treatment failure will be summarized by K-M methods. Durable response rate and objective response rate will be presented with 95% CI.

10.4.3 Safety Endpoints

Subject incidence rates of treatment-emergent adverse events (including all adverse events, grade ≥ 3 adverse events, serious adverse events, adverse events of interest and events requiring the discontinuation of study drug, and local effects on the tumor [ie, pain, inflammation and ulceration]) will be summarized. Medical Dictionary for Regulatory Activities (MedDRA) will be used to code adverse events 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 adverse events. 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, dose delay, study drug discontinuation, overall exposure, and changes in ECOG performance status. Tables and/or narratives of deaths after initiation of the study through 30 days since the last dose of talimogene laherparepvec will be provided.

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 descriptively.

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

10.4.4 Exploratory Endpoints
Correlation between the changes in the population of tumor specific cytotoxic T-cells and immunoscore during treatment and clinical response will be assessed by the same methods described in Section 10.4. In addition, other potential blood and tumor biomarkers which predict ORR will be explored similarly.

10.5 Handling of Missing and Incomplete Data
Partial or missing dates of adverse events and concomitant medications will be imputed. Adverse events with missing severity and/or possible relationship to talimogene laherparepvec will be included in the all adverse events analyses, except by severity grade and treatment-related. Every effort will be made to obtain complete dates for deaths. Details of the imputation algorithms will be specified in the study-specific 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(s) is/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 and does not have a legally acceptable representative, 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 serious adverse events occurring at the site and other adverse event 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 Serious Adverse Events 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 multi-center 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(s) 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(s) and by what mechanism, after termination of the study and before the product(s) is/are 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 eCRFs will be included on the Amgen Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject’s eCRF 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.

eCRF entries may be considered source data if the eCRF 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 eCRFs, 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, Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable.

In addition, all original source documents supporting entries in the eCRFs 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, eCRFs and other pertinent data) provided that subject confidentiality is respected.

The Amgen clinical monitor is responsible for verifying the eCRFs 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 eCRFs.

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing eCRFs, 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 R&D Compliance and Audit 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 eCRFs must be maintained and readily available.
- Updates to eCRFs 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 are checked for consistency, omissions, and any apparent discrepancies. In addition, the data are reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries are created in the EDC system database for site resolution and subsequently closed by the EDC system or by an Amgen (or designee) reviewer.
- The investigator signs only the Investigator Verification Form for this electronic data capture study. This signature indicates that the investigator inspected or reviewed the data on the eCRF, 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 visits) 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 for complying 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), 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

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 Guidelines).

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.
13. REFERENCES


Hart DN. Dendritic cells: unique leukocyte populations which control the primary immune response. *Blood*. 1997;90(9):3245-3287.


Tafinlar™ (dabrafenib) Prescribing Information. Research Triangle Park, NC, GlaxoSmithKline, USA, 2013.


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 adverse event grading. The CTCAE version 3.0 is available at the following location:

Appendix B. Sample Serious Adverse Event Report Form

<table>
<thead>
<tr>
<th>Amgen</th>
<th>Electronic Adverse Event Contingency Report Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study # 20120325</td>
<td>For Restricted Use</td>
</tr>
<tr>
<td>Talimogene Laherparepvec</td>
<td></td>
</tr>
</tbody>
</table>

**Reason for reporting this event via fax**

- [ ] Is not available due to internet outage at my site
- [ ] Is not yet available for this study
- [ ] Has been closed for this study

**Protocol specific reasons:**

- [ ] <<Note protocol instruction/reason here and change text from italics to standard.>>

**1. SITE INFORMATION**

<table>
<thead>
<tr>
<th>Site Number</th>
<th>Investigator</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reporter</th>
<th>Phone Number</th>
<th>Fax Number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**2. SUBJECT INFORMATION**

- Subject ID Number
- Age at event start
- Sex: [ ] F [ ] M
- Race

If applicable, provide End of Study date

**3. ADVERSE EVENT**

- Date started
- Date ended
- Is event serious? [ ] Yes [ ] No
- If event serious, provide date and details
- If protocol order was not followed, provide details
- If event occurred under study, provide details

**Serious Events**

- [ ] 01 Death
- [ ] 02 Required/prolonged hospitalization
- [ ] 03 Immediate life threatening
- [ ] 04 Persistent or significant disability/incapacity
- [ ] 05 Other medically important serious event

**4. Was subject hospitalized or was a hospitalization prolonged due to this event?**

- Date admitted
- Date discharged

**Protocol Number:** 20120325

**Date:** 21 September 2015

**Page 78 of 90**
## 5. Was the drug under study administered/taken prior to this event? 

No [ ]
Yes if yes, please complete all of Section 5

### Prior to, or at time of Event

<table>
<thead>
<tr>
<th>Site Number</th>
<th>Subject ID Number</th>
</tr>
</thead>
</table>

#### IP Drug/Amgen Device

- **Day**: 
- **Month**: 
- **Year**: 
- **Date of Initial Dose**: 
- **Date of Dose**: 
- **Dose**: 
- **Route**: 
- **Frequency**: 
- **Action Taken**: 
  - **Lot # and Serial #**: 
  - **Unknown**: 
  - **Unavailable**: 
  - **Unavailable / Unknown**: 

#### **If**:

- **Lot # and Serial #**: 
- **Unknown**: 
- **Unavailable**: 
- **Unavailable / Unknown**: 

### 6. Concomitant Medications (e.g., chemotherapy)

- **Any Medications?** [ ]
- **Yes** if yes, please complete:

<table>
<thead>
<tr>
<th>Medication Name(s)</th>
<th>Start Date</th>
<th>Stop Date</th>
<th>Co-administered</th>
<th>Continuing</th>
<th>Dose</th>
<th>Route</th>
<th>Treatment Mod</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 7. Relevant Medical History (include dates, allergies and any relevant prior therapy)

- 
- 
- 

### 8. Relevant Laboratory Values (include baseline values)

- **Any Relevant Laboratory values?** [ ]
- **Yes** if yes, please complete:

<table>
<thead>
<tr>
<th>Test</th>
<th>Date</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**FORM 05306**

Page 2 of 3  Version 6.0 Effective Date 07 JUL 2014
### Electronic Adverse Event Contingency Report Form

**Amgen**  
Study # 20120325  
Talimogene laherparepvec

### 9. OTHER RELEVANT TESTS (diagnostics and procedures)

<table>
<thead>
<tr>
<th>Date</th>
<th>Additional Tests</th>
<th>Results</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Any Other Relevant tests?**  
☐ No  ☐ Yes  ☐ If yes, please complete:

### 16. 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:

Title:

Date:

**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.**
Appendix C. Pregnancy and Lactation Notification Worksheets

**AMGEN Pregnancy Notification Worksheet**

Fax Completed Form to the Country-respective Safety Fax Line

**1. Case Administrative Information**

<table>
<thead>
<tr>
<th>Protocol/Study Number:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Design:</td>
<td>☐ Interventional</td>
</tr>
</tbody>
</table>

**2. Contact Information**

<table>
<thead>
<tr>
<th>Investigator Name</th>
<th>Site #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phone ( )</td>
<td>Fax ( )</td>
</tr>
<tr>
<td>Email</td>
<td></td>
</tr>
<tr>
<td>Institution</td>
<td></td>
</tr>
<tr>
<td>Address</td>
<td></td>
</tr>
</tbody>
</table>

**3. Subject Information**

| Subject ID # | Subject Gender: | Male ☐ Female ☐ | 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: |

Effective Date: March 27, 2011
### AMGEN Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

**1. Case Administrative Information**

Protocol/Study Number: ________________

Study Design: [ ] Intervventional  [ ] 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**

<table>
<thead>
<tr>
<th>Amgen Product</th>
<th>Dose at time of breast feeding</th>
<th>Frequency</th>
<th>Route</th>
<th>Start Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>mm/dd/yyyy</td>
</tr>
</tbody>
</table>

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: ________________________  Title: ________________________

Print Name: ________________________  Signature: ________________________

Date: ________________________

Effective Date: 03 April 2012, version 2.

CONFIDENTIAL
Appendix D. Modified World Health Organization (WHO) Response Criteria

A modified version of the World Health Organization (WHO) response criteria (WHO handbook for reporting results of cancer treatment, 1979) 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 ≥ 10 mm in at least 2 dimensions 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 preferred 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 nodal/soft tissue disease (including lymph nodes). Measurability of lesions on CT scans 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 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 noncontract 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 intravenous contrast for CT scans while on trial. 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 intravenous and oral contrast) then the CT portion of the PET/CT can be used for tumor measurements.

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

**Measurable Disease**
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 tumor’s 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:**
At baseline (the last assessment on or prior to the first dose of study drug being administered), tumor lesions will be categorized as follows:

- measurable or
- nonmeasurable but evaluable

**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 as measured by CT scan, MRI, or ultrasound for nodal/soft tissue disease (including lymph nodes)
- ≥ 10 mm caliper measurement by clinical exam for superficial cutaneous or subcutaneous melanoma lesion as measured by caliper
- multiple superficial melanoma lesions which in aggregate have a total diameter of ≥ 10 mm

**Nonmeasurable Lesions:**
All other lesions, including small lesions (longest diameter < 10 mm by CT/MRI/ultrasound for nodal/soft tissue disease [including lymph nodes] or < 10 mm caliper measurement by clinical exam for superficial cutaneous melanoma lesion) and
other truly nonmeasurable lesions are considered nonmeasurable and characterized as nonindex lesions. This will include any measurable lesions beyond the maximum number of 10 lesions that were not chosen 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.

Coalescing or splitting lesions:

- **Coalescing lesions:** When two or more index or new measurable lesions merge without distinct borders between tumors, the smaller lesion should have 0 x 0 mm recorded for the current and all future assessments with a comment indicating that the lesion coalesced with the specified lesion, and the larger lesion should have the size of the merged lesion recorded for the current assessment with a comment indicating that the lesion coalesced with the specified lesion and be followed for future assessments. When two or more nonindex or 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 (with a comment indicating that the lesion coalesced with the specified lesion) and followed for future assessments. If an index or new measurable lesion and a non-index or new non-measurable lesion merge, the non-index or new non-measurable lesion should be absent for the current and all future assessments while the index lesion or new measurable lesion should include both merged lesions for recording measurements with a comment indicating that the lesion coalesced with the specified lesion.

- **Splitting lesions:** When an index or new measurable lesion splits into two or more lesions the largest measurable part of the split lesion should be considered to be the previously recorded index or new measurable lesion with measurements provided for the current assessment with the comment indicating that the lesion split from the specified lesion, and followed for future assessments. The remaining lesions would be reported as a new measurable lesions or new non-measurable lesions depending on measurability with a comment indicating that the lesion split from the specified lesion. In this case, appearance of a new lesion from a previous lesion will not be considered a disease progression solely due to appearance of a new lesion (may be considered a disease progression due to > 25% increase in the sum of the products of the perpendicular diameters of all index tumors since baseline, or the unequivocal appearance of a new tumor, other than the product of the split tumor, since the last response assessment time point).

Measureable Tumor Assessment/Burden:
Baseline Documentation of “Index Lesions”:
All baseline evaluations should be performed as close as possible to enrollment and never more than 4 weeks (ie, 28 days) prior to enrollment.
At baseline, up to 10 measurable cutaneous, nodal, or soft tissue lesions 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 ultrasound) 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.

If subject has multiple small superficial melanoma lesions at baseline (less than 10 mm in longest diameter) which in aggregate have a total diameter of ≥ 10 mm, up to 10 largest lesions that were included in this measurement will be reported as "Index Lesions", and sum of the products of the two largest of perpendicular SPD of these lesions will be calculated and reported for tumor response assessments.

Baseline Documentation of “Nonindex 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. Nonindex lesions should be recorded and assessed qualitatively over the course of therapy.

Follow-up “Index Lesions”:
At each subsequent tumor assessment, the SPD of the index lesions are added together to provide the total tumor burden.

Follow-up “Nonindex Lesions”:
Nonindex disease measurements are not required and these lesions should be followed as “present,” “absent,” or in rare cases “unequivocal progression”.

Response Criteria
Evaluation of Objective Response:
The subject response will be assessed based on the response of the index lesions and nonindex lesion, and presence or absence of new lesions. Confirmation of complete or partial response is not required. The overall response is derived from time point response assessments as described in Table 5, Table 6, and Table 7.
### Table 5. Definition of Index Lesion Tumor Response Including New Lesions

<table>
<thead>
<tr>
<th>Response Type</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response (CR)</td>
<td>Complete disappearance of all index lesions, including any new tumors which might have appeared. Any residual cutaneous or subcutaneous index lesions must be documented by representative biopsy to not contain viable tumor.</td>
</tr>
<tr>
<td>Partial Response (PR)</td>
<td>Achieving a 50% or greater reduction in the SPD of the perpendicular diameters of all index lesions at the time of assessment as compared to the sum of the products of the perpendicular diameters of all index lesions at baseline. If any new lesions have appeared, the sum of products of the perpendicular diameters of new measurable lesions must have reduced by 50% or more from when first documented.</td>
</tr>
<tr>
<td>Disease Progression (PD)</td>
<td>A &gt; 25% increase in the sum of the products of the perpendicular diameters of all index tumors since baseline, or the unequivocal appearance of a new tumor since the last response assessment time point.</td>
</tr>
<tr>
<td></td>
<td><strong>There are 2 types of PD defined in this protocol:</strong>&lt;br&gt;<strong>Non-clinically relevant disease progression (PDn):</strong> PD in subjects who do not suffer a decline in performance status and/or in the opinion of the investigator do not require alternative therapy. Subjects showing overall response as PDn will be allowed to continue study treatment. &lt;br&gt;<strong>Clinically relevant disease progression (PDr):</strong> PD that is associated with a decline in performance status and/or in the opinion of the investigator the subject requires alternative therapy. Subjects with PDr will be allowed to remain on study until 24 weeks of therapy unless, in the opinion of the investigator, other treatment is warranted.</td>
</tr>
<tr>
<td>Stable Disease (SD)</td>
<td>Neither sufficient tumor shrinkage of index lesion to qualify for response (PR or CR) nor sufficient tumor increase of index lesion to qualify for PD.</td>
</tr>
<tr>
<td>Unable to Evaluate (UE)</td>
<td>Any index 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.</td>
</tr>
<tr>
<td>Not Done (ND)</td>
<td>Radiographic image or clinical measurement were not performed at this time point to evaluate the index lesions</td>
</tr>
</tbody>
</table>
### Table 6. Definition of Nonindex Lesion Tumor Response

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response (CR)</td>
<td>Disappearance of all nonindex lesions.</td>
</tr>
<tr>
<td>Incomplete Response/Stable Disease (SD):</td>
<td>Persistence of one or more nonindex tumor(s).</td>
</tr>
<tr>
<td>Disease Progression (PD):</td>
<td>Unequivocal progression of one or more nonindex lesions</td>
</tr>
<tr>
<td><strong>There are 2 types of PD defined in this protocol:</strong></td>
<td></td>
</tr>
<tr>
<td>Non-clinically relevant disease progression (PDn):</td>
<td>PD in subjects who do not suffer a decline in performance status and/or in the opinion of the investigator do not require alternative therapy. Subjects showing PDn as overall response will be allowed to continue study treatment.</td>
</tr>
<tr>
<td>Clinically relevant disease progression (PDr):</td>
<td>PD that is associated with a decline in performance status and/or in the opinion of the investigator the subject requires alternative therapy. Subjects with PDr will be allowed to remain on study until 24 weeks of therapy unless, in the opinion of the investigator, other treatment is warranted.</td>
</tr>
<tr>
<td>Unable to Evaluate (UE):</td>
<td>Any nonindex 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.</td>
</tr>
<tr>
<td>Not Applicable (NA)</td>
<td>No nonindex lesions were identified at baseline</td>
</tr>
<tr>
<td>Not Done (ND)</td>
<td>Radiographic image or clinical measurement were not performed at this time point to evaluate the nonindex lesions</td>
</tr>
<tr>
<td>Index Lesion Response Including New Lesions</td>
<td>Nonindex Lesion Response</td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>CR</td>
<td>CR</td>
</tr>
<tr>
<td>SD</td>
<td>PR</td>
</tr>
<tr>
<td>PDn</td>
<td>PDn</td>
</tr>
<tr>
<td>PDr</td>
<td>PDr</td>
</tr>
<tr>
<td>NA</td>
<td>CR</td>
</tr>
<tr>
<td>UE/ND</td>
<td>UE</td>
</tr>
<tr>
<td>PR</td>
<td>CR/SD</td>
</tr>
<tr>
<td>PDn</td>
<td>PDn</td>
</tr>
<tr>
<td>PDr</td>
<td>PDr</td>
</tr>
<tr>
<td>NA</td>
<td>PR</td>
</tr>
<tr>
<td>UE/ND</td>
<td>UE</td>
</tr>
<tr>
<td>SD</td>
<td>CR</td>
</tr>
<tr>
<td>SD</td>
<td>SD</td>
</tr>
<tr>
<td>PDn</td>
<td>PDn</td>
</tr>
<tr>
<td>PDr</td>
<td>PDr</td>
</tr>
<tr>
<td>NA</td>
<td>SD</td>
</tr>
<tr>
<td>UE/ND</td>
<td>UE</td>
</tr>
<tr>
<td>PDn</td>
<td>CR/SD/PDn/NA/UE/ND</td>
</tr>
<tr>
<td>PDr</td>
<td>PDr</td>
</tr>
<tr>
<td>PDr</td>
<td>Any</td>
</tr>
<tr>
<td>UE/ND</td>
<td>CR/SD/NA/UE/ND</td>
</tr>
<tr>
<td>PDn</td>
<td>PDn</td>
</tr>
<tr>
<td>PDr</td>
<td>PDr</td>
</tr>
</tbody>
</table>

Subjects with PDn as overall response will be allowed to continue study treatment.
Subjects with PDr will be allowed to remain on study until 24 weeks of therapy unless, in the opinion of the investigator, other treatment is warranted.

CR = complete response; PR = partial response; SD = stable disease; PD = disease progression; PDn = nonclinically disease progression; PDr = clinically relevant disease progression; UE = unable to evaluate; NA = not applicable; ND = not done.
### Appendix E. Eastern Cooperative Oncology Group Performance Status Scale

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all predisease performance without restriction.</td>
</tr>
<tr>
<td>1</td>
<td>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.</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about &gt; 50% of waking hours.</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to a bed or chair &gt; 50% of waking hours.</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>
Amendment 1

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

Talimogene Laherparepvec
Amgen Protocol Number (Talimogene Laherparepvec) 20120325

Amendment 1 Date: 31 August 2015
Superseding Date: 21 September 2015

This document summarizes the changes made to the protocol in both Amendment 1 and the superseding version.

Rationale:

- Removed Inclusion Criterion 105 to allow subjects to join the study after having received first-line therapy.
- Removed exclusion of subjects receiving any non-oncology vaccine therapies used for the prevention of infectious disease within 28 days prior to enrollment and during treatment period (Exclusion criterion 210).
- Clarified that if no viable cells were found following surgery, the response definition will be complete response (CR).
- Added testing for herpes simplex virus type 2 (HSV-2) within 3 days prior to dose at day 1 of week 1 [Cycle 1], week 6 [Cycle 3], and week 12 [Cycle 6].
- Increased the window to 5 days for tumor biopsy for biomarker analysis for the Week 1 biopsy, 7 days for the Week 6 biopsy, and to 7 days after documentation of disease progression at PD.
- Added assessment of Eastern Cooperative Oncology Group (ECOG) performance status every 3 months during treatment period.
- Revised photography assessments in the schedule of assessments to remove requirement at screening, update cycles, and removed the word “measurable.”
- In Schedule of Assessments, clarified that the week 1 biopsy should not be collected prior to the subject being enrolled.
- Removed word “uninjected” from the correlation between changes in intratumoral CD8+ cell density during treatment and objective response rate in the study endpoints.
- Revised the number of planned sites to be 50.
- Added exclusion criterion to avoid potential viral transmission during sexual contact.
- Specified how lesions that separate or merging are to be assessed.
• Added an interim analysis.
• Added reporting of treatment related adverse events during the long-term follow-up.
• Added addition of anti-cancer therapy for melanoma during long term period follow-up.
• In Table 5: Definition of Index Lesion Tumor Response Including New Lesions, removed the following text from the definition of partial response, “Any residual cutaneous or subcutaneous index or new lesions that must be tumor free for the subject to meet the criteria for partial response (PR) must be documented as such by representative biopsy”.
• Updated text throughout document to specify cycle number corresponding to study week.
• Implemented minor administrative and formatting changes.
• Added references in Section 2.2 and in the reference list.
• Added ECOG and physical examination during treatment period and follow-up period.
• Defined the final analysis after 24 months from LSE rather than keeping it open ended.
• Clarified that unless patient dies or withdraws full consent after they have completed the LTFU portion of the study they will then be transferred to the registry protocol where they will continue to be followed up, until death or full consent withdraw.
Description of Changes:

Section: Global

Replace:

5 December 2014

With:

21 September 2015

Section: Synopsis, Secondary Objective(s)

Bullet 2

Replace:

to explore the correlation between changes in intratumoral CD8+ cell density during treatment (in injected and uninjected lesions) and ORR, DRR, DOR, and changes in tumor burden

With:

to explore the correlation between changes in intratumoral CD8+ cell density during treatment and ORR, DRR, DOR, and changes in tumor burden

Section: Synopsis, Secondary Endpoints

Bullet 1

Replace:

correlation between changes in intratumoral CD8+ cell density during treatment (in injected and uninjected lesions) and ORR, DRR, DOR, and changes in tumor burden

With:

correlation between changes in intratumoral CD8+ cell density during treatment and ORR, DRR, DOR, and changes in tumor burden

Section: Synopsis, Study Design

Paragraph 3

Replace:

Subjects will be followed for safety 30 (+ 7) days after the last dose of talimogene laherparepvec and for survival every 12 weeks (± 28 days) for up to approximately
24 months after the last subject is enrolled. Thereafter, subjects will be followed under an ongoing separate registry protocol (Study 20120139) for the long-term survival follow-up of subjects treated with talimogene laherparepvec. The registry protocol will also monitor for late and long-term adverse events thought to be potentially related to talimogene laherparepvec.

With:

Subjects will be followed for safety 30 (+ 7) days after the last dose of talimogene laherparepvec and for survival every 12 weeks (± 28 days) for up to approximately 24 months after the last subject is enrolled in the study. Thereafter, subjects will be followed under an ongoing separate registry protocol (Study 20120139) for the long-term survival follow-up of subjects treated with talimogene laherparepvec. The registry protocol will also monitor for late and long-term adverse events thought to be potentially related to talimogene laherparepvec and use of anti-cancer therapy for melanoma.

Section: Synopsis, Study Design

Paragraph 4

Replace:

Blood and tumor tissue samples will be collected at timepoints outlined in the Schedule of Assessments (Table 2). Tumor biopsies will be performed on an uninjected lesion on day 1 of week 1, on a different uninjected lesion at week 6 (if available), and at disease progression (PDn or PDr beyond 6 months of treatment) on the lesion responsible for PD as outlined in Section 7.2.2. Samples will be analyzed to explore if intratumoral CD8+ cell density at baseline and its change during treatment is correlated with the objective response rate in subjects with unresected stage IIIB-IVM1c melanoma treated with talimogene laherparepvec.

With:

Blood and tumor tissue samples will be collected at timepoints outlined in the Schedule of Assessments (Table 2). Tumor biopsies (taken from accessible cutaneous, subcutaneous or nodal lesions) will be performed on an uninjected lesion on day 1 of week 1, on a different uninjected lesion at week 6 (if available), and at disease progression that results in treatment discontinuation from the lesion responsible for progression as outlined in Section 7.2.2. Samples will be analyzed to explore if intratumoral CD8+ cell density at baseline and its change during treatment is correlated
with the objective response rate in subjects with unresected stage IIIB-IVM1c melanoma treated with talimogene laherparepvec.

**Section: Synopsis, Key Inclusion Criteria**

Replace:

Male or female ≥ 18 years of age with histologically confirmed diagnosis of stage IIIB to IVM1c melanoma for whom surgery is not recommended. Subject must be treatment naïve with no prior systemic anticancer treatment for melanoma. Subject must have measurable disease and must be a candidate for intralesional therapy with at least 1 injectable cutaneous, subcutaneous, or nodal melanoma lesion (≥ 10 mm in longest diameter) or with multiple injectable lesions that in aggregate have a longest diameter of ≥ 10 mm. Also, subject must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and must have a serum lactate dehydrogenase (LDH) ≤ 1.5 X upper limit of normal and adequate hematologic, hepatic, and renal organ function.

With:

Male or female ≥ 18 years of age with histologically confirmed diagnosis of stage IIIB to IVM1c melanoma for whom surgery is not recommended. Subject who is treatment naïve or had received prior treatment for melanoma. Subject must have measurable disease and must be a candidate for intralesional therapy with at least 1 injectable cutaneous, subcutaneous, or nodal melanoma lesion (≥ 10 mm in longest diameter) or with multiple injectable lesions that in aggregate have a longest diameter of ≥ 10 mm. Also, subject must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and must have a serum lactate dehydrogenase (LDH) ≤ 1.5 X upper limit of normal and adequate hematologic, hepatic, and renal organ function.

**Section: Synopsis, Key Exclusion Criteria**

Replace:

Subject must not have clinically active cerebral metastases, greater than 3 visceral metastases (this does not include lung or nodal metastases associated with visceral organs), or any bone metastases, primary ocular or mucosal melanoma, or history or evidence of symptomatic autoimmune pneumonitis, glomerulonephritis, vasculitis, or other symptomatic autoimmune disease. Subject must not have evidence of clinically significant immunosuppression or active herpetic skin lesions or prior complications of
HSV-1 infection (eg, herpetic keratitis or encephalitis) and must not require intermittent or chronic systemic treatment with an antiherpetic drug (eg, acyclovir), other than intermittent topical use. Subjects known to have acute or chronic active hepatitis B, hepatitis C, or human immunodeficiency virus infection will also be excluded. Subjects must not have any nononcology vaccine therapies used for the prevention of infectious disease within 28 days prior to enrollment and must not have been treated previously with talimogene laherparepvec.

With:

Subject must not have clinically active cerebral metastases, greater than 3 visceral metastases (this does not include lung or nodal metastases associated with visceral organs), or any bone metastases, primary ocular or mucosal melanoma, history or evidence of symptomatic autoimmune disease (such as pneumonitis, glomerulonephritis, vasculitis, 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. Subject must not have evidence of clinically significant immunosuppression or active herpetic skin lesions or prior complications of HSV-1 infection (eg, herpetic keratitis or encephalitis) and must not require intermittent or chronic systemic treatment with an antiherpetic drug (eg, acyclovir), other than intermittent topical use. Subjects known to have acute or chronic active hepatitis B, hepatitis C, or human immunodeficiency virus infection will also be excluded. Subjects must not have been treated previously with talimogene laherparepvec.

Section: Synopsis, Screening

Bullet 8

Delete:

photographs of visible cutaneous and subcutaneous tumor lesions (select sites only)
Section: Synopsis, Treatment

Bullet 2
Add:

**physical examination**

Section: Synopsis, Treatment

Bullet 3
Add:

**ECOG Performance Status assessment**

Section: Synopsis, Treatment

Bullet 6, subbullet 2
Replace:

blood samples for herpes simplex virus (HSV-1) antibody serostatus

With:

blood samples for herpes simplex virus (HSV) serostatus

Section: Synopsis, Treatment

Bullet 8
Replace:

photographs of visible cutaneous and subcutaneous tumor lesions (select sites only)

With:

photographs of all visible cutaneous and subcutaneous tumor lesions (select sites only)
always within 3 days of the treatment visit starting from the first treatment visit

Section: Synopsis, Treatment

Bullet 10
Replace:

administration of talimogene laherparepvec at day 1 of each cycle
With:

administration of talimogene laherparepvec at day 1 of each treatment cycle

Section: Synopsis, Long-term Follow-up/End of Study

Paragraph 1

Replace:

All subjects who permanently discontinue talimogene laherparepvec for any reason other than withdrawal of full consent or death will be contacted by telephone or clinic visit to assess survival, adverse events thought by the investigator to be potentially related to talimogene laherparepvec, and use of anti-cancer therapies for melanoma every 12 weeks (± 28 days) following the safety follow-up visit until death, subject withdraws full consent, or up to 24 months after the last subject is enrolled.

With:

All subjects who permanently discontinue talimogene laherparepvec for any reason other than withdrawal of full consent or death will be contacted by telephone or clinic visit to assess survival, adverse events thought by the investigator to be potentially related to talimogene laherparepvec, and use of anti-cancer therapies for melanoma every 12 weeks (± 28 days) following the safety follow-up visit until death, subject withdraws full consent, or up to 24 months after the last subject is enrolled in the study.

Section: Synopsis, Long-term Follow-up/End of Study

Paragraph 2

Replace:

If subject has discontinued talimogene laherparepvec for reason other than disease progression or death, radiographic tumor imaging, clinical tumor assessments, and tumor response assessments will be performed until documented disease progression beyond 6 months of treatment, per modified WHO response criteria (Appendix D), or until the start of a new anticancer therapy.

With:

If subject has discontinued talimogene laherparepvec for reason other than disease progression or death, radiographic tumor imaging, clinical tumor assessments, ECOG Performance Status assessment, assessment of swabs of lesions of suspected
herpetic origin by qPCR for talimogene laherparepvec DNA, and tumor response assessments will be performed until documented disease progression beyond 6 months of treatment, per modified WHO response criteria (Appendix D), or until the start of a new anticancer therapy or end of study, whichever the earliest.

Section: Synopsis, Long-term Follow-up/End of Study

Paragraph 3

Replace:

After the long term follow-up period of this study has ended, subjects who end the study for any reason other than death or withdrawal of full consent will be followed for survival under an ongoing separate registry protocol (Study 20120139) that is in place for the long-term follow-up of all 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.

With:

After the long term follow-up period of this study has ended, subjects who end the study for any reason other than death or withdrawal of full consent will be followed for survival under an ongoing separate registry protocol (Study 20120139) that is in place for the long-term follow-up of all 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 and use of anti-cancer therapies for melanoma.

Section: Synopsis, Statistical Consideration

Paragraph 2

Replace:

The main goals of the primary analysis are to evaluate the correlation between baseline intratumoral CD8+ cell density and ORR, DRR, DOR, and changes in tumor burden, in addition to the correlation between changes in CD8+ cell density during treatment (in injected and uninjected lesions) and ORR, DRR, DOR, and changes in tumor burden. The timing of the primary analysis will be when all subjects have had the opportunity to complete 12 months of treatment with talimogene laherparepvec. The final analysis will
occur when the last subject discontinues the study treatment and has had the opportunity to complete the long term follow-up.

With:

The main goals of the primary analysis are to evaluate the correlation between baseline intratumoral CD8+ cell density and ORR, DRR, DOR, and changes in tumor burden, in addition to the correlation between changes in *intratumoral* CD8+ cell density during treatment and ORR, DRR, DOR, and changes in tumor burden. The timing of the primary analysis will be when all subjects have had the opportunity to complete 12 months of treatment with talimogene laherparepvec. The final analysis will occur when the last subject discontinues the study treatment and has had the opportunity to complete the long term follow-up.

**Section: Synopsis, Statistical Consideration**

**Paragraph 3**

Add:

*An interim analysis to evaluate the study objectives will be conducted on approximately the first 50 subjects who received at least 1 dose of talimogene laherparepvec, with the biomarker recorded at baseline, and have had the opportunity to be in the study (treatment or follow-up) for 6 months.*

**Section: Synopsis, Statistical Consideration**

**Paragraph 4**

Replace:

The final analysis will occur when the last subject discontinues the study treatment and has had the opportunity to complete the long term follow-up.

With:

The final analysis will occur *either 24 months after the last subject has been enrolled* or when the last subject discontinues the study treatment and has had the opportunity to complete the safety follow-up, *whichever is later.*
Section: Study Glossary

Delete:

| AE(s) | adverse event(s) |

Section: Study Glossary

Add:

| HLA | human leukocyte antigen |

Section: 1.2 Secondary

Bullet 2

Replace:

to explore the correlation between changes in intratumoral CD8+ cell density during treatment (in injected and uninjected lesions) and ORR, DRR, DOR, and changes in tumor burden

With:

to explore the correlation between changes in intratumoral CD8+ cell density during treatment and ORR, DRR, DOR, and changes in tumor burden

Section: 2.1 Melanoma

Paragraph 1, sentence 1

Replace:

Cutaneous melanoma is the fifth most common cancer in men and the seventh most common cancer in women in the United States of America (USA), with an estimated 76,100 new cases and 9,710 deaths expected in 2014 (Siegel et al, 2014).

With:

Cutaneous melanoma is the fifth most common cancer in men and the seventh most common cancer in women in the United States of America (USA), with an estimated 73,870 new cases and 9,940 deaths expected in 2015 (Siegel et al, 2015).
Section: 2.1 Melanoma

Paragraph 3, sentence 3

Delete:

For example, dacarbazine or temozolomide achieved a 7% to 12% objective response rate (ORR), but an objective response did not appear to be associated with a prolongation in overall survival.

Section: 2.1 Melanoma

Paragraph 4, sentence 1

Replace:

Recently, the Food and Drug Administration (FDA), European Commission, and other regulatory agencies have approved 4 novel therapies for advanced melanoma: an immune stimulatory agent, ipilimumab (Yervoy®, 2013), and 3 agents for use in patients with \textit{BRAF} mutant melanoma, a v-raf murine sarcoma viral oncogene homolog B1 (\textit{BRAF}) inhibitor, vemurafenib (Zelboraf®, 2013), the \textit{BRAF} inhibitor dabrafenib (Tafinlar™, 2013) and the \textit{MEK} inhibitor trametinib (Mekinist™, 2013).

With:

Recently, the Food and Drug Administration (FDA), European Commission, and other regulatory agencies have approved 6 novel therapies for advanced melanoma: an immune stimulatory agent, ipilimumab (Yervoy®, 2015), \textit{pembrolizumab} (Keytruda®, 2015) and \textit{nivolumab} (Opdivo®, 2015) and 3 agents for use in patients with \textit{BRAF} mutant melanoma, a v-raf murine sarcoma viral oncogene homolog B1 (\textit{BRAF}) inhibitor, vemurafenib (Zelboraf®, 2015), the \textit{BRAF} inhibitor dabrafenib (Tafinlar™, 2013) and the \textit{MEK} inhibitor trametinib (Mekinist™, 2014).

Section: 2.1 Melanoma

Paragraph 4, sentence 3

Replace:

The pivotal study of ipilimumab showed an overall survival (OS) improvement in subjects with HLA-A2*0201 genotype previously treated metastatic melanoma as compared with a gp100 peptide vaccine (Hodi et al, 2010; Yervoy® 2013).
With:

The pivotal study of ipilimumab showed an overall survival (OS) improvement in subjects with human leukocyte antigen (HLA)-A2*0201 genotype previously treated metastatic melanoma as compared with a gp100 peptide vaccine (Hodi et al, 2010; Yervoy® 2015).

Section: 2.1 Melanoma

Paragraph 6

Replace:

In 2013, regulatory agencies also approved the BRAF inhibitor dabrafenib (Tafinlar™, 2013) and the MEK inhibitor trametinib (Mekinist™, 2013), both in BRAFV600 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).

With:

In 2013, regulatory agencies also approved the BRAF inhibitor dabrafenib (Tafinlar™, 2013) and the MEK inhibitor trametinib (Mekinist™, 2014), both in BRAFV600 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). Additionally, dabrafenib and trametinib were approved recently as a combination therapy for BRAF-mutant (V600 E/K) unresectable or metastatic melanoma. (Flaherty et al, 2012b; Long et al, 2015; Robert et al, 2015).

Section: 2.1 Melanoma

Paragraph 7

Add:

Nivolumab, an anti-PD-1 monoclonal antibody, demonstrated improvement in 1-year OS in treatment naïve subjects with wild-type BRAF advanced melanoma compared to dacarbazine (73% versus 42%; HR 0.42, 99.8% CI 0.25-0.73) (Robert et al, 2015); improved ORR in subjects previously treated with either ipilimumab or BRAF inhibitor versus dacarbazine or carboplatin with paclitaxel (32% vs 10%)
(Weber et al, 2015), and improved PFS and ORR (either alone or in combination with ipilimumab) compared to ipilimumab alone in treatment naïve subjects (Larkin et al, 2015).

**Section: 2.1 Melanoma**

**Paragraph 8**

Add:

**Pembrolizumab,** is a monoclonal antibody that targets PD-1 protein, improved PFS and OS versus ipilimumab in subjects with advanced melanoma. Six-month progression-free rates were 47% and 46%, for pembrolizumab administered every 2 and 3 weeks, versus 27% for ipilimumab (HR 0.58; P<0.001 for both pembrolizumab regimens versus ipilimumab). Twelve-months OS rates were 74%, 68%, and 58%, respectively (HR 0.63, P=0.0005 for pembrolizumab every 2 weeks and 0.69, P=0.004 for pembrolizumab every 3 weeks) (Robert et al, 2015)

**Section: 2.1 Melanoma**

**Paragraph 9, sentence 3**

Add:

Although not as common and severe as with ipilimumab, a wide range of immune related toxicities has been reported with pembrolizumab and nivolumab, which include pneumonitis, hepatitis, colitis, nephritis, thyroid dysfunction and others (Larkin et al, 2015; Robert et al, 2015; Weber et al, 2015).

**Section: 2.1 Melanoma**

**Paragraph 9, sentence 3**

Replace:

The safety profiles of vemurafenib and dabrafenib include increased incidence of cutaneous squamous cell carcinoma or high grade keratoacanthoma in almost 20% of patients treated with vemurafenib and > 5% of patients treated with dabrafenib (Zelboraf®, 2013; Tafinlar™, 2013).

With:

The safety profiles of vemurafenib and dabrafenib include increased incidence of cutaneous squamous cell carcinoma or high grade keratoacanthoma in almost 20% of
patients treated with vemurafenib and > 5% of patients treated with dabrafenib (Zelboraf®, 2015; Tafinlar™, 2013).

Section: 2.1 Melanoma

Paragraph 9, sentence 7

Replace:

Trametinib is associated with cuneiform dermatitis, peripheral edema, hypertension, decreased cardiac ejection fraction, and ocular events (Mekinist™, 2013).

With:

Trametinib is associated with cuneiform dermatitis, peripheral edema, hypertension, decreased cardiac ejection fraction, and ocular events (Mekinist™, 2014).

Section: 2.1 Melanoma

Paragraph 10, sentence 7

Replace:

The prognostic value of immunoscores composed of a combination of immunohistochemical staining densities for both intratumoral CD3+ and CD8+ T cells, combined with the location of the cells either in the invasive margin or central tumor, has been well documented in colon cancer and was shown to have a prognostic significance superior to that of the AJCC TNM classification system (Galon et al, 2006, Galon et al, 2012).

With:

The prognostic value of immunoscores composed of a combination of immunohistochemical staining densities for both intratumoral CD3+/CD8+ T cells, combined with the location of the cells either in the invasive margin or central tumor, has been well documented in colon cancer and was shown to have a prognostic significance superior to that of the AJCC TNM classification system (Galon et al, 2006, Galon et al, 2012).
Section: 2.1 Melanoma

Paragraph 10, sentence 3

Replace:

In the current study we will measure tumor antigen-specific T cell responses induced by talimogene laherparepvec treatment in order to explore the association between the cytotoxic T cell response and response to treatment.

With:

In the current study we will measure tumor antigen-specific T cell responses induced by talimogene laherparepvec treatment in order to further explore mechanisms of action.

Section: 2.1 Melanoma

Paragraph 11

Add:

Furthermore, baseline tumor mutational load and corresponding neoantigen signatures have been shown to correlate with responsiveness to immunotherapy (Rizvi et al, 2015; Snyder et al, 2014). It will be important to understand if tumor mutational load can be predictive for response to talimogene laherparepvec as well.

Section: 2.2 Talimogene Laherparepvec Investigational Product Background

Paragraph 1, sentence 1

Replace:

Talimogene laherparepvec is an intralesionally delivered oncolytic immunotherapy comprised of a genetically engineered HSV-1(herpes simplex virus type 1) that selectively replicates in tumor tissue (Talimogene Laherparepvec Investigator’s Brochure, 2014).

With:

Talimogene laherparepvec is an intralesionally delivered oncolytic immunotherapy comprised of a genetically engineered HSV-1(herpes simplex virus type 1) that selectively replicates in tumor tissue (Talimogene Laherparepvec Investigator’s Brochure).
Section: 2.2 Talimogene Laherparepvec Investigational Product Background

Paragraph 3, sentences 1 and 2

Replace:

Clinical data currently available has provided evidence of talimogene laherparepvec’s efficacy in patients with regionally and distantly metastatic melanoma (Talimogene Laherparepvec Investigator’s Brochure, 2014). In particular, a high rate of complete response (CR) was achieved (16% in the phase 2 study with talimogene laherparepvec in stage III C to IV melanoma) (Senzer et al, 2009; Talimogene Laherparepvec Investigator’s Brochure, 2014).

With:

Clinical data currently available has provided evidence of talimogene laherparepvec’s efficacy in patients with regionally and distantly metastatic melanoma (Talimogene Laherparepvec Investigator’s Brochure). In particular, a high rate of complete response (CR) was achieved (16% in the phase 2 study with talimogene laherparepvec in stage III C to IV melanoma) (Senzer et al, 2009; Talimogene Laherparepvec Investigator’s Brochure).

Section: 2.2 Talimogene Laherparepvec Investigational Product Background

Paragraph 1, sentence 3

Replace:

The role of ICP47 is to block antigen presentation to major histocompatibility complex class I and II molecules by blocking the transporter associated with antigen processing 1 and 2.

With:

The role of ICP47 is to block antigen presentation to major histocompatibility complex class I molecules by blocking the transporter associated with antigen processing 1 and 2.
Section: 2.2 Talimogene Laherparepvec Investigational Product Background

Paragraph 5

Replace:

Primary analysis of the OPTiM Study 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 trend toward improved OS was also seen in a preplanned interim analysis (HR 0.79; 95% CI: 0.61, 1.02; p-value = 0.07) (Andtbacka et al, 2013). Survival at 12, 24, and 36 months in the talimogene laherparepvec arm was estimated to be 74%, 50%, and 41%, respectively, and 69%, 41%, and 28% in the GM-CSF arm, respectively. The most common side effects were fatigue, chills, and pyrexia. Serious adverse events occurred in 26% of the talimogene laherparepvec subjects and 13% of the GM-CSF subjects. No grade 3/4 adverse events occurred in ≥ 3% of subjects in either arm.

With:

Primary analysis of the OPTiM Study 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). Overall response rate was also improved from 6% with GM-CSF to 26% with talimogene laherparepvec (P < 0.0001, descriptive). Similarly, 11% of patients had a CR in the talimogene laherparepvec arm versus < 1% in the GM-CSF arm. In the event-driven primary OS analysis (secondary end point), median OS with talimogene laherparepvec treatment was 23.3 months compared with 18.9 months with GM-CSF treatment (HR, 0.79 [95% CI, 0.62–1.00]; P=0.051) (Andtbacka et al, 2015). At the final planned analysis of OS which happened when last enrolled subject completed 3 years of follow-up, median OS was 23.3 months in the talimogene laherparepvec arm and 18.9 months in the GM-CSF arm (HR, 0.79; 95% CI, 0.62–1.00; P=0.049, (descriptive) (Andtbacka et al, 2015).

The most common side effects were fatigue, chills, and pyrexia. Serious adverse events occurred in 36% of the talimogene laherparepvec subjects and 21% of the GM-CSF subjects. The only grade 3/4 adverse event occurring in ≥ 2% of patients was cellulitis (talimogene laherparepvec, n=6 [2.1%]; GM CSF, n=1 [< 1%]). Of 10 fatal
events in the talimogene laherparepvec arm, none were considered
treatment-related per investigator and most (80%) were associated with disease
progression with the exception of sepsis in the setting of salmonella infection and
myocardial infarction (Andtbacka et al, 2015).

Section: 2.2 Talimogene Laherparepvec Investigational Product Background

Paragraph 7

Replace:

Refer to the Talimogene Laherparepvec Investigator’s Brochure, 2014, for additional
information.

With:

Refer to the latest version of the Talimogene Laherparepvec Investigator’s Brochure,
for additional information.

Section: 2.3 Rationale

Paragraph 1, sentence 8

Replace:
Section: 3.1 Study Design

Paragraph 2, sentence 3

Replace:

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.

With:

Due to the mechanism of action, subjects may experience transient growth of existing tumors or the appearance of new tumors prior to achieving maximal clinical benefit of talimogene laherparepvec.

Section: 3.1 Study Design

Paragraph 3

Replace:

Subjects will be followed for safety 30 (+ 7) days after the last dose of talimogene laherparepvec and for survival every 12 weeks (± 28 days) for up to approximately 24 months after the last subject is enrolled. Thereafter, subjects will be followed under an ongoing separate registry protocol (Study 20120139) for the long-term survival follow-up of subjects treated with talimogene laherparepvec. The registry protocol will also monitor for late and long-term adverse events thought to be potentially related to talimogene laherparepvec.

With:

Subjects will be followed for safety 30 (+ 7) days after the last dose of talimogene laherparepvec for survival, adverse events thought by the investigator to be potentially related to talimogene laherparepvec, and use of anticancer therapies for melanoma every 12 weeks (± 28 days) for up to approximately 24 months after the last subject is enrolled in the study. Thereafter, subjects will be followed under an ongoing separate registry protocol (Study 20120139) for the long-term survival follow-up of subjects treated with talimogene laherparepvec. The registry protocol will also monitor for late and long-term adverse events thought by the investigator to be potentially related to talimogene laherparepvec and use of anti-cancer therapies for melanoma.
Section: 3.1 Study Design

Replace:

Blood and tumor tissue samples will be collected at timepoints outlined in the Schedule of Assessments (Table 2). Tumor biopsies will be performed on an uninjected lesion on day 1 of week 1, on a different uninjected lesion at week 6 (if available), and at disease progression (PDn or PDr beyond 6 months of treatment) on the lesion responsible for PD as outlined in Section 7.2.2. Samples will be analyzed to explore if intratumoral CD8+ cell density at baseline and its change during treatment is correlated with the objective response rate in subjects with unresected stage IIIB-IVM1c melanoma treated with talimogene laherparepvec.

With:

Blood and tumor tissue samples will be collected at timepoints outlined in the Schedule of Assessments (Table 2). Tumor biopsies will be performed from an uninjected lesion on day 1 of week 1, from a different uninjected lesion at week 6 (if available), and from the lesion responsible for progression at the time of disease progression that results in treatment discontinuation as outlined in Section 7.2.2. Samples will be analyzed to explore if intratumoral CD8+ cell density at baseline and its change during treatment is correlated with the objective response rate in subjects with unresected stage IIIB-IVM1c melanoma treated with talimogene laherparepvec.

Section: 3.2 Number of Sites

Replace:

Approximately 35 sites in Europe and the USA will participate in the study. Additional sites and regions may be added to the study as necessary. Sites that do not enroll subjects within 4 months of site initiation may be closed.

With:

Approximately 50 sites in Europe and the USA will participate in the study. Additional sites and regions may be added to the study as necessary. Sites that do not enroll subjects within 6 months of site initiation may be closed.
Section: 3.5.1 Study Duration for Subjects

Paragraph 2

Replace:

The duration of the screening period for each subject will be up to 28 days. The duration of treatment will vary for each subject. Subjects will be treated with talimogene laherparepvec until the subject has achieved a CR, all injectable tumors have disappeared, clinically relevant (resulting in clinical deterioration or requiring change in therapy) disease progression beyond 6 months of treatment, per modified WHO response criteria (Appendix D), or intolerance of study treatment, whichever occurs first. Subjects will be followed for safety 30 (+ 7) days after the last dose of talimogene laherparepvec and for survival every 12 weeks (± 28 days) for up to approximately 24 months after the last subject is enrolled. The estimated average per-subject study duration is approximately 32 months.

With:

The duration of the screening period for each subject will be up to 28 days. The duration of treatment will vary for each subject. Subjects will be treated with talimogene laherparepvec until the subject has achieved a CR, all injectable tumors have disappeared, clinically relevant (resulting in clinical deterioration or requiring change in therapy) disease progression beyond 6 months of treatment, per modified WHO response criteria (Appendix D), or intolerance of study treatment, whichever occurs first. Subjects will be followed for safety 30 (+ 7) days after the last dose of talimogene laherparepvec and for survival, adverse events thought by the investigator to be potentially related to talimogene laherparepvec, and use of anti-cancer therapy for melanoma every 12 weeks (± 28 days) for up to approximately 24 months after the last subject is enrolled in the study. The estimated average per-subject study duration is approximately 32 months.

Paragraph 3

Add:

After the end of the long term follow up subjects who end the study for any reason other than death or withdrawal of full consent will continue to be followed for survival under an ongoing separate registry protocol (Study 20120139). The
registry protocol will also monitor for adverse events thought by the investigator to be potentially related to talimogene laherparepvec and use of anti-cancer therapies for melanoma.

Section: 3.5.2 End of Study

Paragraph 2

Replace:

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 talimogene laherparepvec and has had the opportunity to complete the safety follow-up visit or the last long term follow-up visit, whichever occurs later.

With:

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 24 months after the last subject has been enrolled or when the last subject discontinues talimogene laherparepvec and has had the opportunity to complete the safety follow-up visit, whichever occurs later.

Section: 4.1.1 Inclusion Criteria

Criterion 105

Replace:

Subject who is treatment naïve: must not have received any prior systemic anticancer treatment consisting of chemotherapy, immunotherapy, or targeted therapy for unresected stage IIIB to IVM1c melanoma

• subjects who received prior adjuvant therapy for melanoma may be eligible as long as prior adjuvant therapy was completed at least 6 months prior to enrollment

With:

Subject who is treatment naïve or had received prior treatment for melanoma. Any systemic treatment for melanoma must have been completed at least 28 days prior to enrollment
Section: 4.1.2 Exclusion Criteria

Criterion 201

Replace:

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

With:

Clinically active cerebral metastases. Subjects with up to 3 cerebral metastases may be enrolled, provided that all lesions have been adequately treated with stereotactic radiation therapy (including Gamma Knife) or resection, with no evidence of progression and have not required steroids for at least two months prior to enrollment.

Section: 4.1.2 Exclusion Criteria

Criterion 205

Replace:

History or evidence of symptomatic autoimmune pneumonitis, glomerulonephritis, vasculitis, or other symptomatic autoimmune disease

With:

History or evidence of symptomatic autoimmune disease (such as pneumonitis, glomerulonephritis, vasculitis, or other), or history of autoimmune disease that required systemic treatment (i.e., use of corticosteroids, immunosuppressive drugs or biological agents used for treatment of autoimmune diseases) in past 2 months prior to enrollment. Replacement therapy (e.g., thyroxine for hypothyroidism, insulin for diabetes mellitus) is not considered a form of systemic treatment for autoimmune disease.
Section: 4.1.2 Exclusion Criteria

Criterion 206, bullet 3

Replace:

- receiving systemic immunosuppressive therapy (> 2 weeks), including oral steroid doses > 10 mg/day of prednisone or equivalent

With:

- receiving systemic immunosuppressive therapy (> 2 weeks), including oral steroid doses > 10 mg/day of prednisone or equivalent during the 2 months prior to enrollment

Section: 4.1.2 Exclusion Criteria

Criterion 210

Delete:

Any nononcology vaccine therapies used for the prevention of infectious disease within 28 days prior to enrollment and during treatment period

Section: 4.1.2 Exclusion Criteria

Criterion 216, bullet 2

Replace:

adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease

With:

adequately treated non-melanoma skin cancer without evidence of disease

Section: 4.1.2 Exclusion Criteria

Criterion 223

Add:

Sexually active subjects and their partners unwilling to use male or female latex condom to avoid potential viral transmission during sexual contact while on treatment and within 30 days after treatment with talimogene laherparepvec.
Section: 6.1 Classification of Product

Paragraph 2

Replace:

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, and administration of talimogene laherparepvec.

With:

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the description, storage, preparation, and administration of talimogene laherparepvec.

Section: 6.2.1 Amgen Investigational Product Talimogene Laherparepvec

Paragraph 1, sentence 3

Replace:

Each vial contains a minimum of 1.0 mL talimogene laherparepvec at either $10^6$ PFU/mL (green cap) or $10^8$ PFU/mL (blue cap) concentrations.

With:

Each vial contains a minimum of 1.0 mL talimogene laherparepvec at either $10^6$ PFU/mL or $10^8$ PFU/mL concentrations.

Section: 6.2.1 Amgen Investigational Product Talimogene Laherparepvec

Paragraph 1, sentence 5

Add:

Additional details on talimogene laherparepvec packaging and formulation are provided in the Investigational Product Instruction Manual.

Section: 6.2.1.1 Dosage, Administration, and Schedule

Paragraph 1

Replace:

Talimogene laherparepvec must be prepared and administered by a qualified healthcare professional. Subjects should be assessed clinically for adverse events/toxicity prior to
each dose using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (Appendix A). Complete blood count with differential and chemistry panels including liver function laboratory tests (such as ALT, AST, and total bilirubin) should be obtained according to the Schedule of Assessments (see Table 2) and the results should be checked before each scheduled dose. Dosing will occur only if these test values are acceptable, per Section 6.2.1.2.

With:

Talimogene laherparepvec must be prepared and administered by a qualified healthcare professional. Subjects should be assessed clinically for adverse events/toxicity prior to each dose using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (Appendix A). Complete blood count with differential and chemistry panels including liver function laboratory tests (such as ALT, AST, and total bilirubin) should be obtained according to the Schedule of Assessments (see Table 2) and the results should be checked before scheduled doses as per the requirements described in the Schedule of Assessments. Dosing will occur only if these test values are acceptable, per Section 6.2.1.2.

Section: 6.2.1.1 Dosage, Administration, and Schedule

Paragraph 6, sentence 1

Replace:

At baseline, if there are ≥ 2 lesions, one lesion (ie, the lesion considered lowest priority for injection) should be left uninjected at least until it is biopsied at week 6 (see Section 7.2.2).

With:

At baseline, if there are ≥ 2 lesions, one cutaneous, subcutaneous or nodal lesion (ie, the lesion considered lowest priority for injection) should be left uninjected at least until it is biopsied at week 6 (see Section 7.2.2).

Section: 6.2.1.1 Dosage, Administration, and Schedule

Paragraph 6, sentence 2

Add:

(No biopsy will be taken at week 6 for subjects with 1 lesion present at baseline).
Section:  6.2.1.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

Paragraph 3

Replace:

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. Dosing 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).

With:

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. If a subject requires treatment with systemic antiherpetic drugs (eg, acyclovir, valacyclovir, famciclovir) talimogene laherparepvec should be withheld and the investigator or designee should notify the Amgen medical monitor as soon as possible. Subject may be allowed to continue treatment after discussion between the Amgen medical monitor and the investigator to determine the appropriateness of treatment resumption.

Dosing 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).

Section:  6.2.1.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

Paragraph 5

Replace:

If the subject requires corticosteroid dosing of > 10 mg prednisone daily (or equivalent) for related toxicities, talimogene laherparepvec dosing must be withheld until the corticosteroid dose has decreased to < 10 mg prednisone daily (or equivalent).
With:

If the subject requires corticosteroid dosing of > 10 mg prednisone daily (or equivalent) for related toxicities, talimogene laherparepvec dosing must be withheld until the corticosteroid dose has decreased to ≤ 10 mg prednisone daily (or equivalent).

Section: 6.2.1.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

Paragraph 10, bullet 6

Replace:

A female subject becomes pregnant or fails to use acceptable method(s) of effective contraception (for those subjects who are able to conceive).

With:

A female subject becomes pregnant or fails to use acceptable method(s) of effective contraception (for those subjects who are able to conceive) including but not limited to male or female latex condom to avoid potential viral transmission during sexual contact.

Section: 6.2.1.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

Paragraph 11

Replace:

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, 2014.

With:

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.
Section: 6.4 Concomitant Therapy

Paragraph 2

Replace:

All prescription and nonprescription concomitant medication administered up to 28 days prior to enrollment, on an ongoing basis at enrollment, 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 case report form (CRF) until 30 days (+ 7 days) after the last dose of talimogene laherparepvec. The therapy name, indication, dose, unit, frequency, start date, and stop date will be collected.

With:

All prescription and nonprescription concomitant medication administered up to 28 days prior to enrollment, on an ongoing basis after enrollment, 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 case report form (CRF) until 30 days (+ 7 days) after the last dose of talimogene laherparepvec. The therapy name, indication, dose, unit, frequency, start date, and stop date will be collected.

Section: 6.5 Other Treatment Procedures

Paragraph 1, sentence 3

Replace:

Additionally, biopsies will be taken of cutaneous or subcutaneous lesions for tumor analysis during study.

With:

Additionally, biopsies will be taken of cutaneous, subcutaneous or nodal lesions for tumor analysis during study.

Section: 6.5 Other Treatment Procedures

Paragraph 1, sentence 4

Replace:

In the event of a complete response, any residual cutaneous or subcutaneous index lesions must be documented by representative biopsy to not contain viable tumor.
With:

In the event of a complete response, residual **visible** cutaneous or subcutaneous index lesions must be documented by representative biopsy to not contain viable tumor.

**Section: 6.5 Other Treatment Procedures**

**Paragraph 1, sentence 7**

Replace:

If no residual disease remains following surgery, this should also be noted in the eCRF, the response definition again being PR.

With:

If no residual disease remains following surgery, this should also be noted in the eCRF, the response definition again being PR with the **date of surgery as the date of response**.

**Section: 6.5 Other Treatment Procedures**

**Paragraph 1, sentence 8**

Add:

If no viable melanoma was found in the surgical specimen, and all other tumor lesions resolved completely (if were present), the response definition will be CR with the **date of surgery as the date of response**.

**Section: 6.5 Other Treatment Procedures**

**Paragraph 3, sentences 2 and 3**

Replace:

Subjects may be allowed to remain on protocol after discussion between the Amgen medical monitor and the investigator to determine the appropriateness of treatment resumption provided CNS lesions can be treated with stereotactic radiotherapy (including GammaKnife) or craniotomy and if there is no change in the baseline ECOG performance status. Subjects may be allowed to reinitiate talimogene laherparepvec following treatment of CNS metastases while receiving dexamethasone or a similar corticosteroid at no more than 1.5 mg dexamethasone (or 10 mg prednisone) per day.
With:

Subjects may be allowed to remain on protocol after discussion between the Amgen medical monitor and the investigator to determine the appropriateness of treatment resumption provided CNS lesions can be treated with stereotactic radiotherapy (including GammaKnife) or **resection** and if there is no change in the baseline ECOG performance status. Subjects may be allowed to reinitiate talimogene laherparepvec following treatment of CNS metastases while receiving dexamethasone or a similar corticosteroid at no more than 1.5 mg dexamethasone (or 10 mg prednisone, or **equivalent**) per day.

**Section: 6.8 Excluded Treatments and/or Procedures During Study Period**

**Bullet 4**

Replace:

antiherpetic drugs (eg, acyclovir), other than if topically administered > 20 cm from a talimogene laherparepvec injection site.

With:

antiherpetic drugs (eg, acyclovir), other than if topically administered > 20 cm from a talimogene laherparepvec injection site. **If a subject requires treatment with a systemic antiherpetic drugs (eg, acyclovir, valacyclovir, famciclovir) talimogene laherparepvec should be withheld and the investigator or designee should notify the Amgen medical monitor as soon as possible. Subject may be allowed to continue treatment after discussion between the Amgen medical monitor and the investigator to determine the appropriateness of treatment resumption.**

**Section: 6.8 Excluded Treatments and/or Procedures During Study Period**

**Bullet 5**

Delete:

any nononcology vaccine therapies used for the prevention of infectious disease within 28 days prior to enrollment or randomization and during treatment period
Section: 6.8 Excluded Treatments and/or Procedures During Study Period

Bullet 6

Delete:

any surgery for melanoma (other than the exceptions noted in Section 6.5)
## Section: 7.1 Schedule of Assessments

### Replace:

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Screening&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Treatment Period&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Follow-up Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day</td>
<td>≤ 28 days</td>
<td>1 2 3 4 5 6 7 8</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cycle and Beyond</th>
<th>Safety&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Survival&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30 (+7) Days</td>
<td>12 (±28 days) Weeks</td>
</tr>
</tbody>
</table>

### GENERAL & SAFETY ASSESSMENTS

- Concomitant Medications<sup>e</sup>
  - X

- Physical Exam<sup>f</sup>
  - X

- ECOG Performance Status
  - X

- Swab of Herpetic Lesion for qPCR<sup>m</sup>
  - Within 3 days of occurrence of suspected lesion of herpetic origin
  - X

- Blood for HSV-1 Antibody Serostatus<sup>i</sup>
  - Within 3 days prior to dose at day 1 of week 1, week 6, and week 12

- Tumor Biopsy for Biomarker Analysis<sup>p</sup>
  - Within 3 days prior to dose at day 1 of week 1 and week 6 and at disease progression (beyond 6 months of treatment)

- Photographs of Visible Tumor Lesions<sup>s</sup>
  - (Select Sites Only)
  - X
  - Monthly until End of Treatment
With:

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Screening</th>
<th>Treatment Period</th>
<th>Follow-up Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 28 days</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Day</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

GENERAL & SAFETY ASSESSMENTS

Concomitant Medications

Adverse Events Thought to Be Related to Talimogene Laherparepvec

Physical Exam

ECOG Performance Status

Anti-cancer therapy for melanoma

Swab of Herpetic Lesion for qPCR

Blood for HSV Serostatus

Tumor Biopsy for Biomarker Analysis

Photographs of all Visible Tumor Lesions (Select Sites Only)
Section: 7.1 Schedule of Assessments

Footnote b

Replace:

During the treatment period assessments and procedures can be performed within 3 days of the planned visit.

With:

During the treatment period assessments and procedures can be performed within 3 days of the planned visit unless otherwise specified.

Section: 7.1 Schedule of Assessments

Footnote d

Replace:

All subjects who permanently discontinue talimogene laherparepvec for any reason other than withdraw of full consent or death will be contacted by telephone, or clinic visit, to assess survival. Follow-up will occur every 12 weeks (± 28 days) following the safety follow-up visit until death, subject withdraws full consent, or up to 24 months after the last subject is enrolled. After the long term follow-up period has ended, subjects who end the study for any reason other than death or withdrawal of full consent will be followed for survival under an ongoing separate registry protocol (Study 20120139) that is in place for the long-term follow-up of subjects treated with talimogene laherparepvec in clinical trials.

With:

All subjects who permanently discontinue talimogene laherparepvec for any reason other than withdraw of full consent or death will be contacted by telephone, or clinic visit, to assess survival. **Adverse events deemed by the investigator to be potentially related to talimogene laherparepvec will also be recorded.** Follow-up will occur every 12 weeks (± 28 days) following the safety follow-up visit until death, subject withdraws full consent, or up to 24 months after the last subject is enrolled in the study. After the long term follow-up period has ended, subjects who end the study for any reason other than death or withdrawal of full consent will be followed for survival under an ongoing separate registry protocol (Study 20120139) that is in place for the long-term follow-up of subjects treated with talimogene laherparepvec in clinical trials.
Section: 7.1 Schedule of Assessments

Footnote e

Replace:

All concomitant medications that are administered after the subject has signed informed consent through 30 (+7) days after the last administration of talimogene laherparepvec will be recorded in the case report form. Concomitant medications should be assessed on an ongoing basis and recorded at each subject visit. Only subsequent anticancer therapy will be recorded during the long term follow-up survival assessment period.

With:

All concomitant medications that are administered after the subject has signed informed consent through 30 (+7) days after the last administration of talimogene laherparepvec will be recorded in the case report form. Concomitant medications should be assessed on an ongoing basis and recorded at each subject visit. Only subsequent anticancer therapy for melanoma will be recorded during the long term follow-up survival assessment period.

Section: 7.1 Schedule of Assessments

Footnote f

Replace:

All nonserious adverse events that occur after enrollment through 30 (+7) days after the last administration of talimogene laherparepvec will be recorded in the case report form. Adverse events should be assessed on an ongoing basis and recorded at each subject visit. All serious adverse events that occur after the subject has signed the informed consent through 30 (+7) days after the last administration of talimogene laherparepvec will be reported to Amgen and recorded in the case report form. Serious adverse events must be reported to Amgen within 24 hours of discovery.

With:

All nonserious adverse events (related or not related to talimogene laherparepvec) that occur after the first dose through 30 (+7) days after the last administration of talimogene laherparepvec will be recorded in the case report form. In addition, all adverse events deemed by the investigator to be potentially related to talimogene laherparepvec will be recorded in the case report form through the survival
follow-up. Adverse events should be assessed on an ongoing basis and recorded at each subject visit. All serious adverse events that occur after the subject has signed the informed consent through 30 (+7) days after the last administration of talimogene laherparepvec will be reported to Amgen and recorded in the case report form. Serious adverse events must be reported to Amgen within 24 hours of discovery.

Section: 7.1 Schedule of Assessments

Footnote m

Replace:

Swabs of any lesion suspected to be herpetic in origin will be collected as follows: 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. A qPCR analysis will be performed at a central lab on the swab to evaluate whether the talimogene laherparepvec DNA is detectable in the sample.

With:

Swabs of any lesion suspected to be herpetic in origin will be collected as follows: 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 herpetic infection is suspected. A qPCR analysis will be performed at a central lab on the swab to evaluate whether the talimogene laherparepvec DNA is detectable in the sample.

Section: 7.1 Schedule of Assessments

Footnote n

Replace:

Blood sample for HSV-1 antibody serostatus will be collected (within 3 days prior to talimogene laherparepvec administration) at day 1 of week 1, week 6, and week 12.

With:

Blood sample for HSV serostatus will be collected (within 3 days prior to talimogene laherparepvec administration) at day 1 of week 1 [Cycle 1], week 6 [Cycle 3], and week 12 [Cycle 6].
Section: 7.1 Schedule of Assessments

Footnote o

Replace:

Blood sample for biomarker analysis will be collected (within 3 days prior to talimogene laherparepvec administration) at day 1 of week 1, week 6, week 12, and week 24.

With:

Blood sample for biomarker analysis will be collected (within 3 days prior to talimogene laherparepvec administration) at day 1 of week 1 [Cycle 1], week 6 [Cycle 3], week 12 [Cycle 6], and week 24 [Cycle 12].

Section: 7.1 Schedule of Assessments

Footnote p

Replace:

Tumor biopsy for biomarker analysis (within 3 days prior to talimogene laherparepvec administration). from one lesion at day 1 of week 1 and, if there are ≥ 2 lesions at baseline and one is left uninjected as described in Section 6.2.1.1, from an uninjected lesion at day 1 of week 6. Also at disease progression (beyond 6 months of treatment) from the lesion responsible for PD. Note: uninjected lesion biopsied at day 1 of week 6 must be different lesion from the lesion biopsied at day 1 of week 1.

With:

Tumor biopsy from cutaneous, subcutaneous or nodal lesions for biomarker analysis should not be collected prior to the subject being enrolled. Tumor biopsy should be collected (within 5 days prior to first talimogene laherparepvec administration) from one lesion at day 1 of week 1 [Cycle 1] and, if there are ≥ 2 lesions at baseline and one is left uninjected as described in Section 6.2.1.1, from an uninjected lesion within 7 days prior to dose at day 1 of week 6 [Cycle 3]. Also within 7 days after documentation of disease progression followed by treatment discontinuation from the available cutaneous, subcutaneous or nodal lesion responsible for PD and easily accessible for biopsy with or without ultrasound guidance. Note: uninjected lesion biopsied at day 1 of week 6 [Cycle 3] must be different lesion from the lesion biopsied at day 1 of week 1 [Cycle 1].
Section: 7.1 Schedule of Assessments

Footnote q, sentence 1

Replace:

Investigator’s clinical measurement of cutaneous, subcutaneous, or nodal tumor by caliper at screening, day 1 of week 12 (± 1 week) and then every 12 weeks (± 1 week), or more frequently if clinically indicated, until clinically relevant disease progression beyond 6 months of treatment (per modified WHO response criteria, Appendix D) or until the start of a new anticancer therapy.

With:

Investigator’s clinical measurement of cutaneous, subcutaneous, or nodal tumor by caliper at screening, day 1 of week 12 (± 1 week) [Cycle 6] and then every 12 weeks (± 1 week), or more frequently if clinically indicated, until clinically relevant disease progression beyond 6 months of treatment (per modified WHO response criteria, Appendix D) or until the start of a new anticancer therapy.

Section: 7.1 Schedule of Assessments

Footnote r, sentence 1

Replace:

Radiographic imaging (CT, PET/CT, MRI, or US) of the chest, abdomen, and pelvis, and all other sites of disease, and CT scan or MRI of brain (only if symptoms or signs suggestive of CNS metastasis are present) at screening, day 1 of week 12 (± 1 week) and then every 12 weeks (± 1 week), or more frequently if clinically indicated, until clinically relevant disease progression beyond 6 months of treatment (per modified WHO response criteria, Appendix D) or until the start of a new anticancer therapy.

With:

Radiographic imaging (CT, PET/CT, MRI, or US) of the chest, abdomen, and pelvis, and all other sites of disease, and CT scan or MRI of brain (only if symptoms or signs suggestive of CNS metastasis are present) at screening, day 1 of week 12 (± 1 week) [Cycle 6] and then every 12 weeks (± 1 week), or more frequently if clinically indicated, until clinically relevant disease progression beyond 6 months of treatment (per modified WHO response criteria, Appendix D) or until the start of a new anticancer therapy.
Section: 7.1 Schedule of Assessments

Footnote s

Replace:

At select sites only, photographs of visible cutaneous and subcutaneous tumor lesions at screening and then monthly until end of treatment. See Section 7.2.6

With:

At select sites only, photographs of all visible cutaneous and subcutaneous tumor lesions at **Cycle 1, Cycle 2, and every second subsequent cycle** until end of treatment (always within 3 days prior to investigational product administration). See Section 7.2.6.

Section: 7.1 Schedule of Assessments

Footnote v

Replace:

Reporting of pregnancy or lactation: If a pregnancy occurs in a female subject, or female partner of a male subject, or a lactation case occurs while the subject is taking talimogene laherparepvec, the case must be reported to Amgen through 3 months after the last dose of talimogene laherparepvec as specified in Section 9.3

With:

Reporting of pregnancy or lactation: If a pregnancy occurs in a female subject, or female partner of a male subject, or a lactation case occurs while the subject is taking talimogene laherparepvec, the case must be reported to Amgen **Global Patient Safety** through 3 months after the last dose of talimogene laherparepvec as specified in Section 9.3.

Section: 7.1 Schedule of Assessments

Footnote w

Add:

**ECOG Performance Status** will be assessed at screening, **day 1 of Cycle 1**, then **every 12 weeks** (ie, every sixth cycle) alongside the tumor response assessments until the end of tumor response assessments per study protocol.
Section: 7.1 Schedule of Assessments

Footnote x

Add:

**Anti-cancer therapy may include any systemic, regional, and local therapies for melanoma disease.**

Section: 7.2 General Study Procedures

Paragraph 2

Replace:

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.

With:

During treatment, assessments and procedures can be performed within 3 days of the planned visit **unless specified otherwise**. 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.

Section: 7.2 General Study Procedures, Table 3, Biomarkers

Replace:

HSV-1 Antibody

With:

HSV **Serostatus**

Section: 7.2 General Study Procedures

Paragraph 4

Replace:

The chemistry, hematology, PT (or INR), PTT and pregnancy tests are to be performed at a local laboratory and test results are to be fully and routinely recorded on the
electronic CRFs (eCRFs). Missed tests that are not done must be reported as such on the eCRFs. The real-time polymerase chain reaction (qPCR) and biomarker tests will be performed at a central laboratory and tests results will not be reported on the eCRFs.

With:

The chemistry, hematology, PT( or INR), PTT and pregnancy tests are to be performed at a local laboratory and test results are to be fully and routinely recorded on the electronic CRFs (eCRFs). Missed tests that are not done must be reported as such on the eCRFs and should not be completed as unscheduled tests between cycles. The real-time quantitative polymerase chain reaction (qPCR) and biomarker/antibody tests will be performed at a central laboratory and tests results will not be reported on the eCRFs.

Section: 7.2.1 Screening and Enrollment

Bullet 11

Delete:

Photographs of visible (ie, visible protrusion from skin surface) cutaneous and subcutaneous tumor lesions (Select Sites Only: see Section 7.2.6)

Section: 7.2.2 Treatment

Paragraph 2, bullet 2

Add:

Determination of ECOG Performance Status at Day 1 of Cycle 1 and then every 12 weeks (ie every sixth cycle) in parallel with tumor response assessment and until the end of study treatment (Appendix E)

Section: 7.2.2 Treatment

Paragraph 2, bullet 3

Add:

Physical exams as per standard of care at day 1 of Cycle 1, and then every 12 weeks (ie, every sixth cycle) until the end of tumor assessment per study protocol
Section: 7.2.2 Treatment

Paragraph 2, bullet 5, subbullets 3, 4, 5, and 6

Replace:

swabs of cold sores, vesicles, and other lesions suspected to be herpetic in origin (if any) for qPCR testing:

  o 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. A qPCR analysis will be performed on the swab sample to evaluate whether the talimogene laherparepvec DNA is detectable in the sample.

blood sample for HSV-1 antibody serostatus (within 3 days prior to talimogene laherparepvec administration) at day 1 of week 1, week 6, and week 12.

blood sample for biomarker analysis (within 3 days prior to talimogene laherparepvec administration) at day 1 of week 1, week 6, week 12, and week 24. Note: Lymphocyte subsets will be measured by flow cytometric determination of the following markers including but not limited to: T cells: CD3, CD4, CD8; B cells; CD19; activation markers: HLA-DR; T-regs: CD25, CD127.

tumor biopsy for biomarker analysis (within 3 days prior to talimogene laherparepvec administration) from one lesion at day 1 of week 1 and, if there are ≥ 2 lesions at baseline and one is left uninjected as described in Section 6.2.1.1, from an uninjected lesion at day 1 of week 6. Also at disease progression (PDn or PDr) beyond 6 months of treatment, from the lesion responsible for PD

With:

swabs of cold sores, vesicles, and other lesions suspected to be herpetic in origin (if any) for qPCR testing:

  o 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 herpetic infection is suspected. A qPCR analysis will be performed on the swab sample to evaluate whether the talimogene laherparepvec DNA is detectable in the sample.

blood sample for HSV serostatus (within 3 days prior to talimogene laherparepvec administration) at day 1 of week 1, week 6, and week 12.

blood sample for biomarker analysis (within 3 days prior to talimogene laherparepvec administration) at day 1 of week 1, week 6, week 12 and week 24. Note: Lymphocyte
subsets will be measured by flow cytometric determination of the following markers including but not limited to: T cells: CD3, CD4, CD8; B cells; CD19; activation markers: HLA-DR; T-regs: CD25, CD127.

**all tumor biopsies in the study should be performed from easily accessible with or without ultrasound guidance cutaneous, subcutaneous or nodal lesions.** Tumor biopsy for biomarker analysis should not be collected prior to the subject being enrolled. Tumor biopsy should be collected (within 5 days prior to first talimogene laherparepvec administration) from one lesion at day 1 of week 1 and, if there are ≥ 2 lesions at baseline and one is left uninjected as described in Section 6.2.1.1, from an uninjected lesion within 7 days prior to talimogene laherparepvec injection at day 1 of week 6. Also within 7 days after documentation of disease progression (PDn or PDr) that resulted in treatment discontinuation, from the available and easily accessible for biopsy with or without ultrasound guidance cutaneous, subcutaneous or nodal lesion responsible for progression

Section: 7.2.2 Treatment

Bullet 6, subbullet 1

Replace:

radiographic imaging must include CT scan, PET/CT, MRI, or ultrasound of the chest, abdomen, and pelvis and all other sites of disease. In addition, CT scan or MRI of the brain 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.

With:

radiographic imaging must include CT scan, PET/CT, MRI, or ultrasound (if applicable) of the chest, abdomen, and pelvis and all other sites of disease. In addition, CT scan or MRI of the brain 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 throughout the study for any individual subject.
Section: 7.2.2 Treatment

Bullet 9

Replace:

- Photographs of visible cutaneous and subcutaneous measurable tumor lesions monthly until end of treatment. (Select Sites Only: see Section 7.2.6)

With:

- Photographs of all visible cutaneous and subcutaneous tumor lesions at day 1 Cycle 1, day 1 Cycle 2, and day 1 of every second subsequent cycle until end of tumor response assessment per protocol, always within 3 days prior to investigational product administration. (Select Sites Only: see Section 7.2.6)

Section: 7.2.3 Safety Follow-up Visit

Bullet 3

Replace:

- Determination of ECOG performance status (Appendix E)

With:

- Determination of ECOG Performance Status alongside the tumor response assessments until the end of tumor response assessments per study protocol (Appendix E)

Section: 7.2.3 Safety Follow-up Visit

Bullet 8

Replace:

- Recording of serious adverse events at each visit. SAEs will be reported to Amgen within 24 hours following the investigator’s knowledge of the event.

With:

- Recording of serious adverse events. SAEs will be reported to Amgen within 24 hours following the investigator’s knowledge of the event
Section: 7.2.4 Long-term Follow-up/End of Study

Paragraph 1

Replace:

All subjects who permanently discontinue talimogene laherparepvec for any reason other than withdrawal of full consent or death will be contacted by telephone, or clinic visit, to assess survival status and, if applicable, commencement of any subsequent anticancer melanoma therapy. Follow-up will occur every 12 weeks (± 28 days) following the safety follow-up visit until death, subject withdraws full consent, or up to 24 months after the last subject is enrolled.

With:

All subjects who permanently discontinue talimogene laherparepvec for any reason other than withdrawal of full consent or death will be contacted by telephone, or clinic visit, to assess survival status and, if applicable, commencement of any subsequent anticancer melanoma therapy. **Adverse events deemed by the investigator to be potentially related to talimogene laherparepvec and use of anti-cancer therapies for melanoma will also be recorded.** Follow-up will occur every 12 weeks (± 28 days) following the safety follow-up visit until death, subject withdraws full consent, or up to 24 months after the last subject is enrolled in the study.

Section: 7.2.4 Long-term Follow-up/End of Study

Paragraph 2

Replace:

If subject has discontinued talimogene laherparepvec for reason other than disease progression or death, radiographic tumor imaging, clinical tumor assessments, and tumor response assessments will be performed as documented in Section 7.2.2 until documented disease progression beyond 6 months of treatment, per modified WHO response criteria (Appendix D), or until the start of a new anticancer therapy.

With:

If subject has discontinued talimogene laherparepvec for reason other than disease progression or death, radiographic tumor imaging, clinical tumor assessments, **ECOG Performance Status assessments, reporting of pregnancy or lactation, assessment of swabs of lesions of suspected herpetic origin for presence of**
talimogene laherparepvec DNA by qPCR test, and tumor response assessments will be performed as documented in Section 7.2.2 until documented disease progression beyond 6 months of treatment, per modified WHO response criteria (Appendix D), until the start of a new anticancer therapy, or end of study, whichever the earliest.

Section: 7.2.4 Long-term Follow-up/End of Study

Paragraph 3

Replace:

After the long term follow-up period of this study has ended, subjects who end the study for any reason other than death or withdrawal of full consent will be followed for survival under an ongoing separate registry protocol (Study 20120139) that is in place for the long-term follow-up of all 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.

With:

After the long term follow-up period of this study has ended, subjects who end the study for any reason other than death or withdrawal of full consent will be followed for survival under an ongoing separate registry protocol (Study 20120139) that is in place for the long-term follow-up of all 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 and use of anti-cancer therapies for melanoma.

Section: 7.2.6 Optional Photography Substudy (Select Sites Only)

Paragraph 1, sentence 1

Replace:

For sites selected to participate in the photography substudy, photographs of visible (ie, visible protrusion from skin surface) cutaneous and subcutaneous measurable tumor lesions will be performed as detailed in Section 7.2.1 and Section 7.2.2 until end of treatment.

With:

For sites selected to participate in the photography substudy, photographs of all visible (ie, visible protrusion from skin surface) cutaneous and subcutaneous tumor lesions will
be performed as detailed in Section 7.2.2 until end of treatment (always within 3 days prior to investigational product administration).

Section: 7.3.1 Blood Samples

Paragraph 2, sentence 2

Section: 7.3.2 Tumor Tissue Samples

Paragraph 1

Replace:

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 the Schedule of Assessments (Table 2) and in Section 7.2.2.

With:

A block of formalin-fixed paraffin-embedded tumor tissue (from the current diagnosis) collected prior to the study is to be sent to the central laboratory along with the corresponding pathology report as described in the Schedule of Assessments (Table 2) and in Section 7.2.2.

Section: 7.3.2 Tumor Tissue Samples

Paragraph 4

Replace:

On study biopsies will be collected, as described in the Schedule of Assessments (Table 2) and in Section 7.2.2, to characterize the mechanism of systemic action of
talimogene laherparepvec. Collecting a biopsy from an uninjected lesion during the treatment period (eg, at week 6) is critical for identifying the changes in intratumoral CD8+ cell density that occur following talimogene laherparepvec treatment and that may be associated with clinical benefit. Refer to the Laboratory Manual for specific instructions on tumor biopsy procedures.

With:

On study biopsies will be collected, as described in the Schedule of Assessments (Table 2) and in Section 7.2.2, to characterize the mechanism of systemic action of talimogene laherparepvec. Collecting a biopsy from an uninjected lesion during the treatment period (eg, within 7 days prior to dosing at week 6) is critical for identifying the changes in intratumoral CD8+ cell density that occur following talimogene laherparepvec treatment and that may be associated with clinical benefit. Refer to the Laboratory Manual for specific instructions on tumor biopsy procedures.

Section: 9.2.1 Reporting Procedures for Adverse Events That do not Meet Serious Criteria

Paragraph 1

Replace:

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after the first dose of talimogene laherparepvec through 30 (+ 7) days after the last dose of talimogene laherparepvec are reported using the applicable eCRF (eg, Adverse Event Summary).

With:

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after the first dose of talimogene laherparepvec through 30 (+ 7) days after the last dose of talimogene laherparepvec are reported using the applicable eCRF (eg, Adverse Event Summary). Adverse events deemed by the investigator to be potentially related to talimogene laherparepvec that occur during and after the first dose of talimogene laherparepvec and through the survival follow-up are to be reported.
Section: 9.3 Pregnancy and Lactation Reporting

Paragraph 2

Replace:

In addition to reporting any pregnancies occurring during the study, investigators should monitor for pregnancies that occur after the last dose of talimogene laherparepvec through 3 months after the last dose of talimogene laherparepvec. The pregnancy should be reported to Amgen’s global Pregnancy Surveillance Program (PSP) within 24 hours of the investigator’s knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C). The PSP will seek to follow the pregnant woman throughout her pregnancy and her baby up to 12 months after birth.

With:

In addition to reporting any pregnancies occurring during the study, investigators should report pregnancies that occur after the last dose of talimogene laherparepvec through 3 months after the last dose of talimogene laherparepvec. The pregnancy should be reported to Amgen Global Patient Safety within 24 hours of the investigator’s knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C).

Section: 9.3 Pregnancy and Lactation Reporting

Paragraph 5

Replace:

Any lactation case should be reported to Amgen’s global Lactation Surveillance Program within 24 hours of the investigator’s knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix C).

With:

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 C).
Section: 9.4 Reporting of Exposure to Talimogene Laherparepvec

Paragraph 1, sentence 3

Add:

Please refer to your study specific documents for reporting details.

Section: 9.4 Reporting of Exposure to Talimogene Laherparepvec

Paragraph 2, sentence 3

Replace:

If the exposed individual is reporting signs 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 in the lesion.

With:

If the exposed individual is reporting signs 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 in the lesion, **within 3 days of the symptoms or signs occurring**.

Section: 10.1.1.2 Secondary Endpoints

Bullet 2

Replace:

Correlation between changes in intratumoral CD8+ cell density during treatment (in injected and uninjected lesions) and ORR, DRR, DOR, and changes in tumor burden

With:

Correlation between changes in intratumoral CD8+ cell density during treatment and ORR, DRR, DOR, and changes in tumor burden
Section: 10.1.2 Analysis Sets

Paragraph 3, sentence 4

Replace:

The correlation between biomarker changes during treatment (in injected and uninjected lesions) and objective response rate, durable response rate, and duration of response will be conducted on the biomarker evaluable analysis set.

With:

The correlation between biomarker changes during treatment and objective response rate, durable response rate, and duration of response will be conducted on the biomarker evaluable analysis set.

Section: 10.1.3 Covariates and Subgroups

Bullet 1

Replace:

Region, if applicable (USA or non-USA)

With:

Region, if applicable

Section: 10.1.3 Covariates and Subgroups

Bullet 6

Replace:

ECOG (0 vs 1)

With:

ECOG Performance Status (0 vs 1)

Section: 10.3.1 Interim Analyses

Replace:

No interim analysis is planned.
With:

An interim analysis to evaluate the study objectives of correlation between the biomarker (ie baseline intratumoral CD8+ cell density changes in intratumoral CD8+ cell density and other biomarkers) and ORR will be conducted on approximately the first 50 subjects only who received at least 1 dose of talimogene laherparepvec, with the biomarker recorded at baseline, and have had the opportunity to be on study (treatment or follow-up phase) for at least 6 months. The study will not be discontinued due to the results of this interim analyses; however, predictive hypotheses generated from the interim analysis may lead to subsequent changes to study conduct. For example, if the interim analysis suggests an enhanced effect in a biomarker-defined subgroup, then the protocol and statistical analysis plan may be revised to ensure the study can adequately evaluate the subgroup effect. Revisions may also happen due to obtaining new relevant data from external sources, such as scientific publications and communications.

Section: 10.3.3 Final Analysis

Replace:

The final analysis will occur when the last subject discontinues the study treatment and has had the opportunity to complete the long term follow-up. 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 either 24 months after the last subject has been enrolled or when the last subject discontinues the study treatment and has had the opportunity to complete the safety follow-up, whichever is later. The CSR will be amended with the updated results from the final analysis at the completion of the study.

Section: 13 References

Delete:

Add:


Add:

*Keytruda® (Pembrolizumab) Prescribing Information.* Merck & Co, Whitehouse Station, USA; 2015.

Add:


Replace:


With:

Section: 13 References

Add:


Section: 13 References

Add:


Section: 13 References

Add:


Section: 13 References

Add:


Section: 13 References

Replace:


With:

Section: 13 References

Add:


Section: 13 References

Replace:


Zelboraf® (vemurafenib) Prescribing Information. South San Francisco, CA; Genentech USA, Inc: 2013.

With:


Section: 14 Appendices, Appendix B

Complete the following instructions:

**Electronic Serious Adverse Event (eSAE) Contingency Reporting Form**

*Note: this form is to be used under restricted conditions outlined on page 1 of the form. If you must fax an event report to Amgen, do not enter that event into the EDC system (e.g., Rave) unless directed to do so by Amgen.*

**Header Information**
Complete either Section A or Section B and follow the instructions provided within the applicable section.

**Section A:**
- Complete this section and complete only page 1 of the SAE Report Form if the EDC system (e.g., Rave) is active and your site does not have access for reasons such as internet connectivity issues, the EDC system is down, etc.

**Section B:**
- Complete this section and complete all pages of the SAE Report Form:
  - You are submitting a screening serious adverse event report and the database is not active yet
  - You are submitting a serious adverse event report and your site access has been removed

**1. Site Information**
- Site Number – Enter your assigned site number for this study
- Investigator, Country, Reporter, Phone No., and Fax No. – Enter information requested

**2. Subject Information**
- Subject ID Number – Enter the entire number assigned to the subject
- Date of Birth, Sex, and Race – Enter the subject’s demographic information
- End of Study date – If the subject has already completed the study or terminated the study early, enter the End of Study date

**If you are submitting follow-up information to a previous report, provide the adverse event term for the previous report as well as the start date for the initial event.**

**3. Serious Adverse Event**
Provide the date the investigator became aware of this Serious Adverse Event Information

**Serious Adverse Event Diagnosis or Syndrome**
- If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
- If a diagnosis is not known, the relevant signs/symptoms meeting serious criteria should be entered.
- If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available.

**Date Started** – Enter date the adverse event first started, not when the event met serious criteria, when a diagnosis was made or when the subject was hospitalized. This is a mandatory field.

**Date Ended** – Enter date the adverse event ended, not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.

**If event occurred before the first dose of IP** add a check mark in the corresponding box.

**Serious Criteria Code** – This is a mandatory field. Enter all reasons why the reported event has met serious criteria:
- Immediately life-threatening – Use only if the subject was at immediate risk of death from the event as it occurred.
- Emergency treatment is often required to sustain life in this situation.
- If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious criteria, “Other Medically Important Serious Event” may be the appropriate serious criteria.

**Relationship to IP** – The Investigator must determine and enter the relationship of the event to the IP at the time the event is initially reported. This is a mandatory field.

**Relationship to Amgen device** – The Investigator must determine and enter the relationship of the event to the Amgen device at the time the event is initially reported. If the study involves an Amgen device, this is a mandatory field.

**Outcome of Event** – Enter the code for the outcome of the event at the time the form is completed. This is a mandatory field.
- Resolved – End date is known
- Not resolved/Unknown – End date is unknown
- Fatal – Event led to death

If event is related to a study procedure, such as a biopsy, radiotherapy or withdrawal of a current drug treatment during a wash-out period, add a check mark to the corresponding box. This does not include relationship to IP or concomitant administration – only diagnostic tests or activities mandated by the protocol.

If you completed Section A of the form header, stop here. Complete the signature section at the bottom of page 1 and fax the form to Amgen. Otherwise, complete the remainder of the form. If the reporter is not the investigator, designate must be identified on the Delegation of Authority form.
Completion Instructions

Electronic Serious Adverse Event (eSAE) Contingency Reporting Form
[for use for Studies using Electronic Data Capture (EDC)]

Note. This form is to be used under restricted conditions outlined on page 1 of the form. If you must fax an event report to Amgen, do not enter that event into the EDC system (eg, Rave) unless directed to do so by Amgen.

At the top of Page 2, provide your Site Number and the Subject ID Number in the designated section.

4. Hospitalization
If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did not worsen while on study which involved a hospitalization for an elective treatment, is not considered an adverse event.

Protocol specified hospitalizations are exempt.

5. Investigational Product Administration
Blinded or open-label – If applicable, indicate whether the investigational product is blinded or open-label
Initial Start Date – Enter date the product was first administered, regardless of dose.
Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.
Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.
Action Taken with Product – Enter the status of the product administration.

6. Relevant Concomitant Medications
Indicate if there are any relevant medications.

Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other relevant medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.
Co-suspect – Indicate if the medication is co-suspect in the event
Continuing – Indicate if the subject is still taking the medication
Event Treatment – Indicate if the medication was used to treat the event.

7. Relevant Medical History
Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event or allergies and any relevant prior therapy, such as radiation. Include dates if available.

8. Relevant Laboratory Tests
Indicate if there are any relevant laboratory values.
For each test type, enter the test name, units, date the test was run and the results.

Provide your Site Number and the Subject ID Number in the designated section at the top of Page 3.

9. Other Relevant Tests
Indicate if there are any tests, including any diagnostics or procedures.
For each test type, enter the date, name, results and units (if applicable).

10. Case Description
Describe Event – Enter a summary of the event. Provide narrative details of the events listed in section 3. Include any therapy administered, such as radiotherapy, (excluding medications, which will be captured in section 5). If necessary, provide additional pages to Amgen.

Complete the signature section at the bottom of page 3 and fax the form to Amgen. If the reporter is not the investigator, designee must be identified on the Delegation of Authority Form.
Electronic Serious Adverse Event (eSAE) Contingency Reporting Form
For Restricted Use

Complete either Section A or Section B and follow the instructions provided:

Section A
- EDC system (e.g., Rave) is active for this study but is not accessible to allow reporting within 24 hours of the Investigator's knowledge of the event. I am submitting (check/completed all that apply):
  - An event that applies to a specialty CRF page titled ___ (e.g., clinical fracture)
  - Screening event (as defined by the protocol)
  - OR
  - On-study event (as defined by the protocol)
- Complete ONLY Sections 1, 2, and 3 (page 1)
- Sign and date the signature section following Section 3
- Fax completed page of the form to the number noted in the header above Section 1

Section B
- Access to the EDC system (e.g., Rave) has either not begun or has ended for this study. I am submitting (check all that apply):
  - Event after access to the EDC system (e.g., Rave) has ended (provide subject's End of Study date in Section 2)
  - This is a new event report
  - This is follow-up information for a previously reported event
- Complete ALL sections of the form (all 3 pages)
- Sign and date the signature section at the end of the form
- Fax completed form (all 3 pages) to the number noted in the header above Section 1

1. SITE INFORMATION
   - Site Number
   - Investigator
   - County
   - Reporter
   - Phone Number
   - Fax Number

2. SUBJECT INFORMATION
   - Subject ID Number
   - Date of Birth
   - Day
   - Month
   - Year
   - Sex
   - Male (M)
   - Female (F)

If this is a follow-up to an event reported in the EDC system (e.g., Rave), provide the adverse event term:

3. SERIOUS ADVERSE EVENT
   - Provide the date the investigator became aware of this Serious Adverse Event Information: Day
   - Month
   - Year

   Serious Adverse Event Diagnosis or Syndrome
   - When Final Diagnosis is known, enter diagnosis/symptoms
   - List one event per line. If event is fatal, enter the Cause of Death. Entry of "Death" is not acceptable, as this is an outcome.

   Date Started
   - Day
   - Month
   - Year
   - Date Ended
   - Day
   - Month
   - Year
   - Event Code
   - Cause of Death

   Check only if event occurred before date of IP
   - Relationship
   - Is there a reasonable possibility that the event may have been caused by an Amgen device?
   - Yes
   - No
   - If yes, list event type, date of study onset, and device type

   Serious Criteria:
   - 01 Death
   - 02 Immediate life-threatening
   - 03 Prostration requiring hospitalization
   - 04 Persistent or significant disability
   - 05 Congenital anomaly/birth defect
   - 06 Other medically important serious event

   If you temporarily lost access to the EDC system (e.g., Rave), sign below and submit ONLY this page to the number noted in the header above Section 1.

   Signature of Investigator or Designee:

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.

CONFIDENTIAL
### Electronic Serious Adverse Event (eSAE) Contingency Reporting Form

For Restricted Use

If access to the EDC system (e.g., Rave) has either not begun or has ended for this study, complete the remainder of this form.

<table>
<thead>
<tr>
<th>Site Number</th>
<th>Subject ID Number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4. Was subject hospitalized or was a hospitalization prolonged due to this event?  

- [ ] No
- [ ] Yes, if yes, please complete all of Section 4

<table>
<thead>
<tr>
<th>Date Admitted</th>
<th>Date Discharged</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day</td>
<td>Month</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5. Was IP administered prior to this event?  

- [ ] No
- [ ] Yes, if yes, please complete all of Section 5

**IMP:**

- [ ] Blinded
- [ ] Open Label

<table>
<thead>
<tr>
<th>Initial Start Date</th>
<th>Prior to, or at time of Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day</td>
<td>Month</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medication Name(s)</th>
<th>Start Date</th>
<th>Stop Date</th>
<th>Co-administered</th>
<th>Continuing</th>
<th>dose</th>
<th>route</th>
<th>freq</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day</td>
<td>Month</td>
<td>Year</td>
<td>Day</td>
<td>Month</td>
<td>Year</td>
<td>No/Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

- [ ]

9. RELEVANT LABORATORY VALUES (Include baseline values) Any Relevant Laboratory values?  

- [ ] No
- [ ] Yes, if yes, please complete:

<table>
<thead>
<tr>
<th>Test</th>
<th>Date</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day</td>
<td>Month</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**FORM-058006**

Version 3.0 Effective Date: 04-FEB-2013
## Electronic Serious Adverse Event (eSAE) Contingency Reporting Form

### For Restricted Use

<table>
<thead>
<tr>
<th>Site Number</th>
<th>Subject ID Number</th>
</tr>
</thead>
</table>

### 9. OTHER RELEVANT TESTS (diagnostics and procedures)

<table>
<thead>
<tr>
<th>Date</th>
<th>Additional Tests</th>
<th>Results</th>
<th>Units</th>
</tr>
</thead>
</table>

### 10. CASE DESCRIPTION

(Provide narrative details of events listed in section 3) Provide additional pages if necessary. For each event in section 3, where relationships are not clear, please provide rationale.

---

Signature of Investigator or Designee:  

Title:  

Date:  

---

Amgen

Study 20120325
Talimogene Laherparepvec

CONFIDENTIAL

Product: Talimogene Laherparepvec
Protocol Number: 20120325
Date: 21 September 2015
Page 62 of 69
With:

**Amgen**

**Study # 20120325**

**Talimogene laherparepvec**

---

**Electronic Adverse Event Contingency Report Form**

**For Restricted Use**

---

**Reason for reporting this event via fax**

- The Clinical Trial Database (e.g., Rave):
  - [ ] Not available due to internet outage at my site
  - [ ] 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 those 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**

<table>
<thead>
<tr>
<th>Site Number</th>
<th>Investigator</th>
<th>Reporter</th>
<th>Phone Number</th>
<th>Country</th>
</tr>
</thead>
</table>

---

**2. SUBJECT INFORMATION**

<table>
<thead>
<tr>
<th>Subject ID Number</th>
<th>Age at event onset</th>
<th>Sex</th>
<th>Race</th>
<th>If applicable, provide End of Study date: Day Month Year</th>
</tr>
</thead>
</table>

If this is a follow-up to an event reported in the EDC system (e.g., 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.

- Data Started
- Data Ended

Check any if event occurred before first dose of Protocol under study.

- Vital signs
- Clinical laboratory
- Safety criteria: 61 Fatal 62 Unexpected death in non-related manner

- Other: 63 Unrelated 64 Other medically important serious event

Was subject hospitalized or was a hospitalization prolonged due this event? [ ] Yes [ ] No

- Date Admitted
- Date Discharged

---

FORM 056006

Page 1 of 3

Version 5.0 Effective Date: 07 JUL 2014

CONFIDENTIAL
## Electronic Adverse Event Contingency Report Form

**For Restricted Use**

### Site Number

<table>
<thead>
<tr>
<th>Site Number</th>
<th>Subject ID Number</th>
</tr>
</thead>
</table>

### 5. Was the drug under study administered/taken prior to this event? [ ] No [ ] Yes

- **If Yes:** Please complete all of Section 5.

#### Prior to or at time of event:

<table>
<thead>
<tr>
<th>Initial Dose</th>
<th>Date of Dose</th>
<th>Date of Event</th>
<th>Route</th>
<th>Frequency</th>
<th>Action Taken</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Additional Details:

- [ ] Lot # and Serial #
- [ ] Unavailable / Unknown

### 6. CONCOMITANT MEDICATIONS (e.g., chemotherapy)

- **Any Medications?** [ ] No [ ] Yes

   - **If Yes:** Please complete.

<table>
<thead>
<tr>
<th>Medication Name(s)</th>
<th>Start Date</th>
<th>Stop Date</th>
<th>Co-treatment</th>
<th>Continuing</th>
<th>Dose</th>
<th>Route</th>
<th>Freq</th>
<th>Treatment Mod</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 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.

<table>
<thead>
<tr>
<th>Test</th>
<th>Date</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Form:** FORM-056006

**Version:** 6.0

**Effective Date:** 07 JUL 2014

Page 2 of 3
9. OTHER RELEVANT TESTS (diagnostics and procedures)

<table>
<thead>
<tr>
<th>Date</th>
<th>Additional Tests</th>
<th>Results</th>
<th>Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Site Number

Subject ID Number

16. 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 -

Title

Date

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.

FORM-056006

Page 3 of 3

Version 6.0 Effective Date 07 JUL 2014
**AMGEN Pregnancy Notification Worksheet**

Fax Completed Form to the Country-respective Safety Fax Line

**1. Case Administrative Information**
- Protocol/Study Number: 20120325
- 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**

<table>
<thead>
<tr>
<th>Amgen Product</th>
<th>Done at time of conception</th>
<th>Frequency</th>
<th>Route</th>
<th>Start Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Talimogene Laherparepvec</td>
<td></td>
<td></td>
<td></td>
<td>mm/dd/yyyy</td>
</tr>
</tbody>
</table>

- 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
# Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

**1. Case Administrative Information**

<table>
<thead>
<tr>
<th>Protocol/Study Number:</th>
<th>Site #</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Design:</td>
<td>Interventional</td>
<td>Observational (If Observational: Prospective Retrospective)</td>
</tr>
</tbody>
</table>

**2. Contact Information**

<table>
<thead>
<tr>
<th>Investigator Name</th>
<th>Site #</th>
<th>Phone</th>
<th>Fax</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>Institution</td>
<td>Address</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**3. Subject Information**

<table>
<thead>
<tr>
<th>Subject ID #</th>
<th>Subject Gender: Female Male</th>
<th>Subject DOB: mm dd yyyy</th>
</tr>
</thead>
</table>

**4. Amgen Product Exposure**

<table>
<thead>
<tr>
<th>Amgen Product</th>
<th>Dose at time of conception</th>
<th>Frequency</th>
<th>Route</th>
<th>Start Date</th>
</tr>
</thead>
</table>

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**

<table>
<thead>
<tr>
<th>Pregnant female’s LMP: mm dd yyyy</th>
<th>Estimated date of delivery: mm dd yyyy</th>
</tr>
</thead>
</table>

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:

<table>
<thead>
<tr>
<th>Name:</th>
<th>Title:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signature:</td>
<td>Date:</td>
</tr>
</tbody>
</table>

---

Effective Date: March 27, 2011
Section: 14 Appendices, Appendix D

paragraph 2

Replace:

Clinical Examination Using Caliper: All measurements will be determined using a ruler or calipers and reported in metric notation (mm) and will be recorded biimensionally. Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in at least 2 dimensions 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 preferred since it is more objective).

With:

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 ≥ 10 mm in at least 2 dimensions 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 preferred since it is more objective).

Section: 14 Appendices, Appendix D

Add:

Coalescing or splitting lesions:

• Coalescing lesions: When two or more index or new measurable lesions merge without distinct borders between tumors, the smaller lesion should have 0 x 0 mm recorded for the current and all future assessments with a comment indicating that the lesion coalesced with the specified lesion, and the larger lesion should have the size of the merged lesion recorded for the current assessment with a comment indicating that the lesion coalesced with the specified lesion and be followed for future assessments. When two or more non-index or 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 (with a comment indicating that the lesion coalesced with the specified lesion) and followed for future assessments. If an index or new measurable lesion and a non-index or new non-measurable lesion merge, the non-index or new non-measurable lesion should be absent for the current and all future assessments while the index lesion or new measurable lesion should include
both merged lesions for recording measurements with a comment indicating
that the lesion coalesced with the specified lesion.

- **Splitting lesions**: When an index or new measurable lesion splits into two or
two or more lesions the largest measurable part of the split lesion should be
considered to be the previously recorded index or new measurable lesion with
measurements provided for the current assessment with the comment
indicating that the lesion split from the specified lesion, and followed for future
assessments. The remaining lesions would be reported as a new measurable
lesions or new non-measurable lesions depending on measurability with a
comment indicating that the lesion split from the specified lesion. In this case,
appearance of a new lesion from a previous lesion will not be considered a
disease progression solely due to appearance of a new lesion (may be
considered a disease progression due to > 25% increase in the sum of the
products of the perpendicular diameters of all index tumors since baseline, or
the unequivocal appearance of a new tumor, other than the product of the split
tumor, since the last response assessment time point)

Section: 14 Appendices, Appendix D

Add:

If subject has multiple small superficial melanoma lesions at baseline (less than
10 mm in longest diameter) which in aggregate have a total diameter of ≥ 10 mm,
up to 10 largest lesions that were included in this measurement will be reported as
"Index Lesions", and sum of the products of the two largest of perpendicular SPD
of these lesions will be calculated and reported for tumor response assessments.

Section: 14 Appendices, Appendix D

Replace:

| Partial Response (PR): | Achieving a 50% or greater reduction in the SPD of the perpendicular
diameters of all index lesions at the time of assessment as compared
to the sum of the products of the perpendicular diameters of all index
lesions at baseline. If any new lesions have appeared, the sum of
products of the perpendicular diameters of new measurable lesions
must have reduced by 50% or more from when first documented. Any
residual cutaneous or subcutaneous index or new lesions that must
be tumor free for the subject to meet the criteria for PR must be
documented as such by representative biopsy. |
|------------------------|----------------------------------------------------------------------------------------------------------|

With:

| Partial Response (PR): | Achieving a 50% or greater reduction in the SPD of the perpendicular
diameters of all index lesions at the time of assessment as compared
to the sum of the products of the perpendicular diameters of all index
lesions at baseline. If any new lesions have appeared, the sum of
products of the perpendicular diameters of new measurable lesions
must have reduced by 50% or more from when first documented. |
|------------------------|----------------------------------------------------------------------------------------------------------|