Title: A Phase 2, Multicenter, Single-arm Trial to Evaluate the Biodistribution and Shedding of Talimogene Laherparepvec in Subjects With Unresected, Stage IIIB to IVM1c Melanoma

Amgen Protocol Number (Talimogene Laherparepvec) 20120324

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

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Amendment 1 Date:	30 July 2014
Amendment 2 Date:	06 April 2015
Amendment 3 Date:	**18 August 2015**

Investigator's Agreement

I have read the attached protocol entitled A Phase 2, Multicenter, Single-arm Trial to Evaluate the Biodistribution and Shedding of Talimogene Laherparepvec in Subjects With Unresected, Stage IIIB to IVM1c Melanoma, dated **18 August 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 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, Single-arm Trial to Evaluate the Biodistribution and Shedding of Talimogene Laherparepvec in Subjects With Unresected, Stage IIIB to IVM1c Melanoma

Study Phase: 2

Indication: Unresected stage IIIB to IVM1c melanoma

Primary Objective: The primary objective is to estimate the proportion of subjects with detectable talimogene laherparepvec DNA in the blood and urine any time after administration of talimogene laherparepvec within the first 3 cycles.

Secondary Objectives:

- to estimate the incidence of clearance of talimogene laherparepvec DNA from blood and urine overall and by baseline herpes simplex virus type 1 (HSV-1) serostatus (seronegative versus seropositive) during each of the first 3 cycles
- to estimate the rate of detection and subject incidence of talimogene laherparepvec DNA and virus from exterior of occlusive dressing and surface of injected lesion
- to estimate the rate of detection and subject incidence of talimogene laherparepvec DNA and virus in oral mucosa swabs during treatment and after end of treatment
- to estimate the rate of detection and subject incidence of talimogene laherparepvec DNA and virus in swabs from the anogenital area during treatment and after the end of treatment
- to estimate the incidence of detection of talimogene laherparepvec DNA in lesions suspected to be herpetic in origin
- to describe the efficacy of talimogene laherparepvec as assessed by objective response rate (ORR), best overall response rate (BORR), duration of response (DOR), and durable response rate (DRR) achieved in subjects with unresected, stage IIIB-IVM1c melanoma
- to describe the safety profile of talimogene laherparepvec in subjects with unresected, stage IIIB-IVM1c melanoma

Hypothesis:

No formal statistical hypothesis will be tested. The study will provide estimates of the proportions of subjects with detectable talimogene laherparepvec in the blood and urine any time after the administration of talimogene laherparepvec within the first 3 cycles as assessed by real-time quantitative polymerase chain reaction (qPCR) analysis of talimogene laherparepvec DNA in subjects with unresected stage IIIB to IVM1c melanoma.

Primary Endpoint:

Prevalence of detectable talimogene laherparepvec DNA in the blood and urine any time after administration of talimogene laherparepvec within the first 3 cycles.

Secondary Endpoints:

- Incidence of clearance of talimogene laherparepvec DNA from blood and urine after receiving talimogene laherparepvec
- Rate and subject incidence of talimogene laherparepvec DNA detection and viral detection on the exterior of the occlusive dressing during treatment
- Rate and subject incidence of talimogene laherparepvec DNA detection and viral detection from the surface of injected lesions during treatment
- Rate and subject incidence of talimogene laherparepvec DNA detection and viral detection in oral mucosa swabs during treatment
- Rate and subject incidence of talimogene laherparepvec DNA and viral detection in swabs from the anogenital area during treatment
- Rate and subject incidence of talimogene laherparepvec DNA detection in oral mucosa swabs after the end of treatment

- Rate and subject incidence of talimogene laherparepvec DNA in swabs from the anogenital area after the end of treatment
- Rate and subject incidence of talimogene laherparepvec DNA detection in lesions suspected to be herpetic in origin
- Best overall response rate (BORR), Objective response rate (ORR), DRR, duration of response (DOR)
- 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, adverse events of interest, adverse events requiring permanent discontinuation of study drug), and clinically significant laboratory changes.

Study Design:

This is a phase 2, multicenter, and single-arm study to investigate the biodistribution and shedding of talimogene laherparepvec in subjects with unresected, stage IIIB to IVM1c melanoma. **Approximately** 50 to 60 subjects will be enrolled in this study.

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 of therapy) disease progression per modified World Health Organization (WHO) response criteria (WHO handbook for reporting results of cancer treatment, 1979; refer to Appendix D) beyond 6 months of therapy, or intolerance of study treatment, whichever occurs first.

Subjects will be followed for safety approximately 30 (+ 7) days and 60 (+ 7) days after the last dose of talimogene laherparepvec, respectively. Thereafter, subjects will be followed under an ongoing separate registry protocol for the long-term survival follow-up of subjects treated with talimogene laherparepvec in clinical trials **(Study 20120139)**. The registry protocol will also monitor for late and long-term adverse events thought to be potentially related to talimogene laherparepvec **and anti-cancer therapy for melanoma**.

Samples (blood, urine, swab from oral mucosa, swab from the anogenital area, swab from exterior of the occlusive dressing and surface of injected lesions, and swab of lesions suspected to be of herpetic origin) will be collected to evaluate the biodistribution and shedding of talimogene laherparepvec during the treatment period and safety follow-up at time points designated in the Schedule of Assessments (Table 2, Section 7.1) and the General Study Procedures (Section 7.2).

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

Sample Size: Between 50 to 60 subjects will enroll in this study

Summary of Subject Eligibility Criteria:

Key Inclusion Criteria:

Male or female age ≥ 18 years with histologically confirmed diagnosis of melanoma and unresected stage IIIB, IIIC, IVM1a, IVM1b, or IVM1c regardless of prior line of therapy. Subject is candidate for intralesional therapy administration into cutaneous, subcutaneous, or nodal disease and must also have measurable disease, serum lactate dehydrogenase ≤ 1.5 x upper limit of normal, and Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, 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 metastases or any nodal metastases associated with visceral organs) or any bone metastases melanoma, primary ocular or mucosal melanoma, history or evidence of symptomatic autoimmune pneumonitis, glomerulonephritis, vasculitis, or symptomatic autoimmune disease, or evidence of immunosuppression for any reason. Subject known to have acute or chronic active hepatitis B or hepatitis C infection, or human immunodeficiency virus infection will also be excluded. Subject who has active herpetic skin lesions or prior

complications of HSV-1 infection (eg, herpetic keratitis or encephalitis), and/or requires intermittent or chronic systemic (intravenous or oral) treatment with an antiherpetic drug (eg, acyclovir), other than intermittent topical use will also be **excluded**. Subject must not have received previous treatment 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 days after the initial dose (ie, no sooner than day 22, but should not be delayed more than 5 days after the day-22 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 procedures will be performed during screening:

- 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
- medication and medical history review, concomitant medication(s)
- physical examination, including vital signs and ECOG performance status assessment
- radiographic tumor imaging and clinical tumor assessment
- record any serious adverse events that occur after subject signs informed consent
- local laboratory tests:
  - hematology panel
  - chemistry panel
  - serum or urine pregnancy test for female subjects of childbearing potential.

For a full list of screening procedures, including the timing of each procedure, please refer to Section 7.2.1 and the Schedule of Assessments (Table 2).

Treatment:

The following procedures will be completed during the treatment period:

- recording of concomitant medication(s) and adverse events/serious adverse events at each visit
- vital signs
- local laboratory tests
  - hematology panel
  - chemistry panel
- archived tumor tissue for v-raf murine sarcoma viral oncogene homolog B1 V600 ($BRAF^{V600}$) mutation testing and biomarker analyses
- central laboratory tests
  - blood and urine samples for qPCR analysis of talimogene laherparepvec DNA
  - swabs of exterior of occlusive dressing and surface of injected lesion for qPCR analysis of talimogene laherparepvec DNA. If the qPCR testing is positive, then a TCID50 assay

will be performed on the swab sample to measure viral infectivity. The exterior of the selected occlusive dressing(s) and the surface of selected injected lesion(s) will be swabbed starting on day 2 of cycle 1 at time points designated in Section 7.2.2 and only re-swabbed if the lesion is injected subsequently up to and including day 1 cycle 4.

- swabs of oral mucosa for qPCR analysis of talimogene laherparepvec DNA. If the qPCR testing is positive, then a TCID50 assay will be performed on the swab sample to measure viral infectivity. Up to 3 injected lesions will be selected at baseline (ie, on day 1 of cycle 1).
- swabs from the anogenital area for qPCR analysis of talimogene laherparepvec DNA. If the qPCR testing is positive, then a TCID50 assay will be performed on the swab sample to measure viral infectivity. Note: collection of swabs from the anogenital area is optional for subjects enrolled into the study prior to the investigator obtaining institutional review board (IRB) approval of amendment 1. Collection of swabs from the anogenital area for subjects injected any time during the study into a melanoma lesion above the waist, ie above the line that connects the tops of left and right iliac crests is optional for subjects enrolled into the study prior to the investigator obtaining IRB approval of amendment 2.
- swabs of cold sore, vesicles and other lesions suspected to be herpetic origin (if any) for qPCR analysis of talimogene laherparepvec DNA.
- blood sample for HSV antibody serostatus
- blood samples for biomarker analysis
- tumor biopsy for biomarker analyses (at limited number of sites).

- radiographic tumor imaging, clinical tumor assessment, and tumor response.

For a full list of procedures required during treatment period, including the timing of each procedure, please refer to Section 7.2.2 and the Schedule of Assessments (Table 2).

Safety Follow-up Procedures:

30-Day Safety Follow-up Visit:

The following procedures will be completed during the 30-day safety follow-up visit:

- recording of concomitant medication(s) and AE(s)/SAE(s)
- physical examination including 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
  - blood and urine samples for qPCR analysis of talimogene laherparepvec DNA
  - swabs of the surface of up to 3 most recently injected lesion(s) for qPCR analysis of talimogene laherparepvec DNA (if a lesion is in CR, the place of the prior injection will be swabbed). If the qPCR testing is positive, then a TCID50 assay will be performed on the swab sample to measure viral infectivity.
  - swabs of oral mucosa for qPCR analysis of talimogene laherparepvec DNA. If the qPCR testing is positive, then a TCID50 assay will be performed on the swab sample to measure viral infectivity.
  - swabs from the anogenital area for qPCR analysis of talimogene laherparepvec DNA. If the qPCR testing is positive, then a TCID50 assay will be performed on the swab sample to measure viral infectivity. Note: collection of swabs from anogenital area is optional for subjects enrolled into the study prior to the investigator obtaining IRB approval of amendment 1. Collection of swabs from anogenital area for subjects injected any time

during the study into a melanoma lesion above the waist, ie above the line that connects the tops of left and right iliac crests is optional for subjects enrolled into the study prior to the investigator obtaining IRB approval of amendment 2.

- swabs of cold sore, vesicles, and other lesions of suspected herpetic origin (if any) for qPCR analysis of talimogene laherparepvec DNA
- blood sample for HSV antibody serostatus

Procedures Performed Between 30-Day and 60-Day Safety Follow-up Visits:

- recording of SAE(s) and concomitant medication(s) associated with SAE(s)
- central laboratory tests:

  The following samples will be collected daily by the subject at home between 30 (+7) days and 60 (+7) days after the last dose of talimogene laherparepvec starting approximately 1 day after the 30-day safety follow-up visit:

  - Swabs of oral mucosa for qPCR testing: Samples will be collected at home by the subject.
  - swabs from the anogenital area for qPCR analysis of talimogene laherparepvec DNA. Note: collection of swabs from anogenital area is optional for subjects enrolled into the study prior to the investigator obtaining IRB approval of amendment 1. Collection of swabs from the anogenital area for subjects injected any time during the study into a melanoma lesion above the waist, ie above the line that connects the tops of left and right iliac crests is optional for subjects enrolled into the study prior to the investigator obtaining IRB approval of amendment 2.

  The following samples will be collected weekly at home between 30 (+7) days and 60 (+7) days after the last dose of talimogene laherparepvec starting approximately 7 days after the 30-day safety follow-up visit:

  - swabs of the surface of up to 3 most recently injected lesion(s) for qPCR analysis of talimogene laherparepvec DNA (if a lesion is in CR, the place of the prior injection will be swabbed).

60-Day Safety Follow-up Visit:

The following procedures will be completed approximately 60 (+7) days after last dose of talimogene laherparepvec:

- recording of SAE(s) and concomitant medication(s) associated with SAE(s)
- central laboratory tests
  - swabs of the surface of most recently injected lesion(s) for qPCR analysis of talimogene laherparepvec DNA (if a lesion is in CR, the place of the prior injection will be swabbed). If the qPCR testing is positive, then a TCID50 assay will performed on the swab sample to measure viral infectivity
  - swabs of oral mucosa for qPCR analysis of talimogene laherparepvec DNA.
  - swabs from anogenital area for qPCR analysis of talimogene laherparepvec DNA. Note: collection of swabs from anogenital area is optional for subjects enrolled into the study prior to the investigator obtaining IRB approval of amendment 1. Collection of swabs from anogenital area for subjects injected any time during the study into a melanoma lesion above the waist, ie above the line that connects the tops of left and right iliac crests is optional for subjects enrolled into the study prior to the investigator obtaining IRB approval of amendment 2.
  - swabs of cold sore, vesicles, and other lesions of suspected herpetic origin (if any) for qPCR analysis of talimogene laherparepvec DNA

For a full list of safety follow-up procedures, including the timing of each procedure, please refer to Section 7.2.3 and the Schedule of Assessments (Table 2).

Reporting Exposure to Talimogene Laherparepvec:

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

Long-term Follow-up:

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

For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedule of Assessments (Table 2).

Statistical Considerations: The primary analysis will be triggered once all enrolled subjects have had a chance to complete their **cycle 4 day 1 blood and urine** sample collection for the qPCR assay. Mean, standard deviation, median, first and third quartiles, minimum and maximum will be calculated for continuous variables; frequency and percent will be calculated for binary and categorical variables.

For the primary endpoint, the proportion of subjects that meets the criteria of detectable talimogene laherparepvec DNA in the blood and urine, respectively, after investigational product administration during the first 3 cycles will be calculated. The point-wise exact 95% confidence intervals (CI) for binomial proportions will be provided using F-distributions. The primary analysis will be based on the Blood/Urine Evaluable Analysis Set (see Section 10.1.2).

The estimate of the incidence of clearance of talimogene laherparepvec DNA in each of the first 3 cycles of treatment will be presented. The point-wise exact 95% CI for the binomial proportions will be provided using F-distributions. Analysis of clearance will be based on the Blood/Urine Clearance Analysis Set (see Section 10.1.2).

Summary statistics of the rate and subject incidence of talimogene laherparepvec DNA detection (and viral detection by TCID50 assay) in swabs collected from oral mucosa and in swabs from anogenital area, exterior of the occlusive dressing, and surface of injected lesions for each subject will be presented. Incidence of talimogene laherparepvec DNA detection in lesions suspected to be herpetic in origin will be presented and the 95% CI will be calculated using the F-distribution.

Subject incidence rates of treatment-emergent and treatment-related adverse events (including all adverse events, grade ≥ 3 adverse events, serious adverse events, fatal adverse events, adverse events of interest, and adverse events requiring permanent discontinuation of study drug) after initiation of the study therapy through the 30-day safety follow-up visit will be summarized. In addition, subject incidence rates of serious adverse events from the 30-day safety follow-up visit through the 60-day safety follow-up visit will be summarized. Potential or known unintended exposure to talimogene laherparepvec, suspected related signs or symptoms, and detection of talimogene laherparepvec DNA in a subject's household member, caregiver, or healthcare provider will be reported.

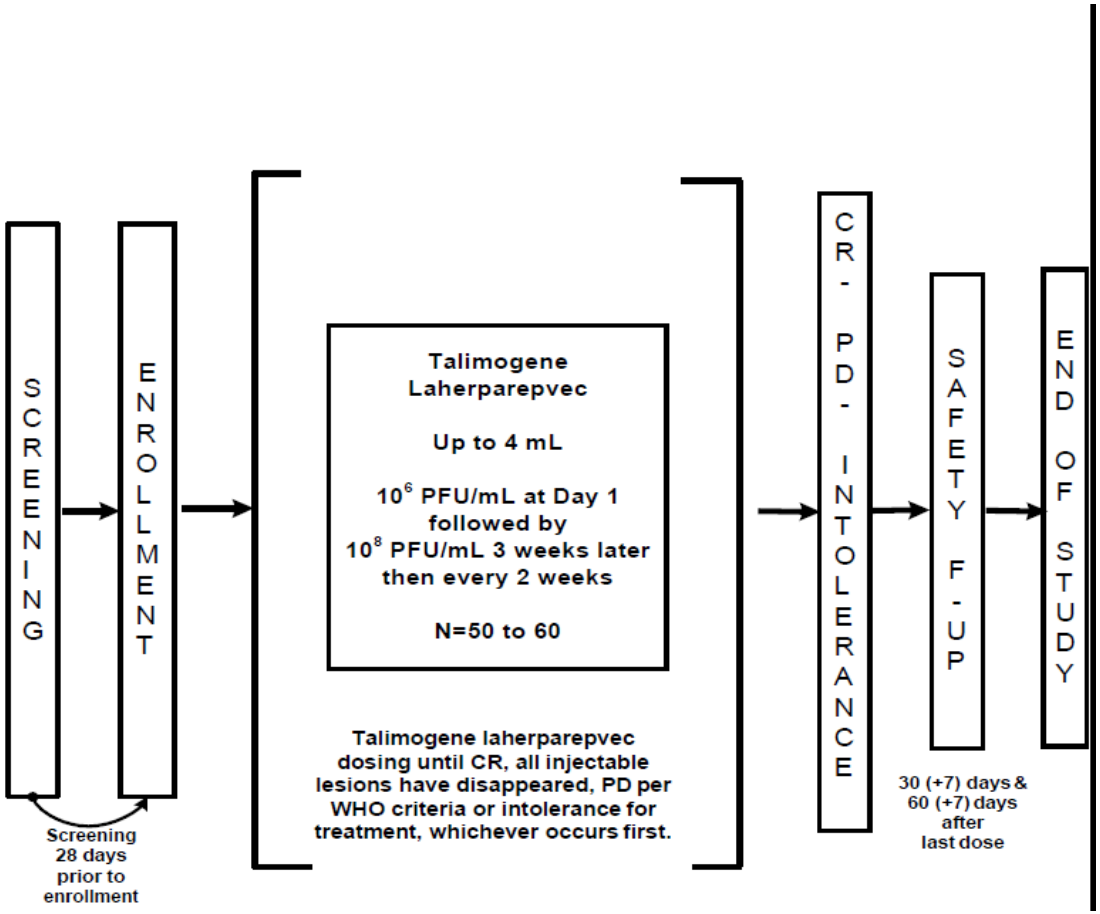
A final analysis will be performed after all enrolled subjects have had a chance to complete their 60-day safety follow up visit.

For a full description of **statistical** analysis methods, please refer to Section 10.

Sponsor: Amgen Inc.

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

Study Design and Treatment Schema



Study Glossary

Abbreviation or Term	Definition/Explanation
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BORR	best overall response rate
BRAF, $BRAF^{V600}$, $BRAF^{V600E}$	v-raf murine sarcoma viral oncogene homolog B1, BRAF V600, BRAF V600E
CNS	central nervous system
CR	complete response
CRF	case report form
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
End of Study for Individual Subject	defined as the date the subject withdraws full consent from the study, completes the 60-day safety follow-up visit, or dies, whichever is earlier
End of Study (primary completion)	defined the time when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary analysis
End of Study (end of trial)	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 the study treatment and has had the opportunity to complete the 60-day safety follow-up visit or withdraws full consent from the study, whichever is earlier
End of Treatment	defined as the last dose of the protocol-specified treatment
ETO system	electronic trial operation system: An electronic system that is used to facilitate the operations of a clinical trial through the collection of study related data.
GCP	Good Clinical Practice
GM-CSF	granulocyte macrophage colony-stimulating factor
HLA	human leukocyte antigen
HSV, HSV-1, HSV-2	herpes simplex virus, herpes simplex virus type 1, herpes simplex virus type 2
ICH	International Conference on Harmonisation
IgG	immunoglobulin G
IgM	immunoglobulin M
IPIM	Investigational Product Instruction Manual
IRB	institutional review board
LDH	lactate dehydrogenase
MRI	magnetic resonance imaging
NA	not applicable

Abbreviation or Term	Definition/Explanation
ND	not done
ORR	objective response rate
OS	overall survival
p_a	true event probability
PD	progression disease
PDn	nonclinically relevant disease progression
PDr	clinically relevant disease progression
PET	positron emission tomography
PFU	plaque-forming unit
PR	partial response
Q1C	every cycle
qPCR	real-time quantitative polymerase chain reaction
Q2C	every second/other cycle
RBC	red blood cells
SD	stable disease
Source Data	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.
SPD	sum of the products of the two largest perpendicular diameters
Study Day 1	defined as the first day that protocol-specified investigational product is administered to the subject
TCID50	50% Tissue Culture Infective Dose
ULN	upper limit of normal
UE	unable to evaluate
US	ultrasound
USA	United States of America
WBC	white blood cells
WHO	World Health Organization

TABLE OF CONTENTS

List of Tables

List of Appendices

1. OBJECTIVES

1.1 Primary

The primary objective is to estimate the proportion of subjects with detectable talimogene laherparepvec DNA in the blood and urine any time after administration of talimogene laherparepvec within the first 3 cycles.

1.2 Secondary

The secondary objectives are as follows:

- to estimate the incidence of clearance of talimogene laherparepvec DNA from blood and urine overall and by baseline herpes simplex virus type 1 (HSV-1) serostatus (seronegative versus seropositive) during each of the first 3 cycles
- to estimate the rate of detection and subject incidence of talimogene laherparepvec DNA and virus from exterior of occlusive dressing and surface of injected lesion
- to estimate the rate of detection and subject incidence of talimogene laherparepvec DNA and virus in oral mucosa during treatment and after end of treatment
- to estimate the rate of detection and subject incidence of talimogene laherparepvec DNA and virus in anogenital swabs from anogenital area during treatment and after end of treatment
- to estimate the incidence of detection of talimogene laherparepvec DNA in lesions suspected to be herpetic in origin
- to describe the efficacy of talimogene laherparepvec as assessed by objective response rate (ORR), best overall response rate (BORR), duration of response (DOR), and durable response rate (DRR) achieved in subjects with unresected, stage IIIB-IVM1c melanoma
- to describe the safety profile of talimogene laherparepvec in subjects with unresected, stage IIIB-IVM1c melanoma.

1.3 Exploratory

The exploratory objectives are as follows:

- to assess blood and tumor for potential biomarkers (eg, proteins and [RNA transcripts) which predict clinical outcomes to talimogene laherparepvec
- to assess fresh tumor biopsy samples for infiltrating immune cells induced by talimogene laherparepvec and clinical response or resistance to talimogene laherparepvec.

2. BACKGROUND AND RATIONALE

2.1 Melanoma

In adults, 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 76,690 new cases and 9,480 deaths expected in 2013 (American Cancer Society, 2013). 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 (GLOBOCAN 2008). In Europe as a whole, approximately 85,927 new cases were diagnosed in 2008 (GLOBOCAN 2008). The incidence of melanoma is increasing rapidly worldwide. 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 nodal metastases or in-transit/satellite lesions (stages IIIB and IIIC), the 5-year survival rate ranges between 40% (for stage IIIC disease) to 59% (for stage IIIB 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 abysmal, ranging from 20% for stage M1a disease (skin or nodes only), 5% to 10% for stage M1b disease (lung only), and < 5% for stage M1c disease (other visceral lesions or high 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. For example, dacarbazine or temozolomide achieved a 7% to 12% ORR, but an objective response did not appear to be associated with a prolongation in survival (Anderson et al, 1995; Chapman et al, 1999; Wagner et al, 2000; Middleton et al, 2000). Response rates for interleukin-2 ranged from 10% to 20% (Rosenberg et al, 1994; Sparano et al, 1993; Atkins et al, 1999), with a small proportion achieving prolonged response, but its administration requires specialized facilities and well-trained staff.

Recently, the 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 v-raf murine sarcoma viral oncogene homolog B1 (*BRAF)* mutant melanoma, a *BRAF* inhibitor, vemurafenib (Zelboraf®, 2013), the *BRAF* inhibitor dabrafenib (Tafinlar™, 2013) and the *MEK* inhibitor trametinib (Mekinist™, 2013). 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 HLA-A2*0201 genotype

previously treated metastatic melanoma as compared with a gp100 peptide vaccine (Hodi et al, 2010; Yervoy® 2013). The median 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 ORR 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 *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 HR 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 *BRAF* inhibitor dabrafenib (Tafinlar™, 2013) and the *MEK* inhibitor trametinib (Mekinist™, 2013), both in *BRAF*^{V600} mutant advanced melanoma. Each agent showed a benefit in progression-free survival compared to dacarbazine in phase 3 trials (Hauschild et al, 2012; Flaherty et al, 2012a), though cross-over and short duration of follow-up to date limits interpretation of overall survival. Additionally, dabrafenib and trametinib were approved recently as a combination therapy for *BRAF*-mutant unresectable or metastatic melanoma (Flaherty et al, 2012b).

While the approval of these newer agents represents a clear milestone in the treatment of advanced melanoma, limitations still exist. The 2-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). Vemurafenib, dabrafenib, and trametinib are indicated only in patients with *BRAF*^{V600} 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®, 2013; 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™, 2013). Thus, the need remains for additional treatment options for patients with advanced melanoma (including those with regional and/or distant metastases).

2.2 Talimogene Laherparepvec Investigational Product Background

Talimogene laherparepvec is an intralesionally delivered oncolytic immunotherapy comprised of a genetically engineered HSV-1 that selectively replicates in tumor tissue (Talimogene Laherparepvec Investigator's Brochure, 2014). 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 ICP34.5 functional deletion allows the virus to replicate selectively in tumors. 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. 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. Extensive experimental studies of the biological activity of GM-CSF established it having a major role in promoting the generation of dendritic cells from blood monocytes (Demir et al, 2003; Lonial, 2004; Conti and Gessani, 2008). Dendritic cells have the capacity to capture antigens, migrate in response to chemotactic stimuli, and induce proliferative responses and Th1 cytokine production in CD4+ and CD8+ T-lymphocytes (Hart, 1997; Steinman, 2001; Ikeda et al, 2004; Paul, 2007). Th1-type cytokines have the capacity to produce proinflammatory responses, eradicate tumors, and perpetuate autoimmune responses (Nishimura et al, 2000; Ikeda et al, 2004; Knutson and Disis, 2005).

A proposed 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 enhancement of a systemic antitumor immune response by expression of GM-CSF in the tumor microenvironment. This therapeutic strategy is

intended to induce antitumor effects through both direct tumor lysis and secondary initiation of systemic tumor-specific immune responses.

Talimogene laherparepvec was tested in an open-label ascending-dose study (Study 001-01) with single doses of either 10^6, 10^7, or 10^8 PFU/mL (up to 4 mL), injected directly into a single metastatic skin or subcutaneous lesion of breast cancer, head and neck cancer, gastrointestinal cancer, or melanoma (Talimogene Laherparepvec Investigator's Brochure, 2014; Hu et al, 2006).

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

In a subsequent multidose part of the study, talimogene laherparepvec was injected, again into single lesions, at 3 different time points. In this part of the study, in both seronegative and seropositive subjects who received a lower initial dose of 10^6 PFU/mL, followed by two doses of 10^8 PFU/mL, febrile responses were minimal, there was no further detection of virus on the surface of the injected tumors, and vesicles were not seen.

Intralesional administration of talimogene laherparepvec resulted in seroconversion in all baseline-seronegative subjects within 3 weeks after a single dose of ≥ 10^6 PFU/mL. Necrosis of injected tumors, confirmed on histopathology, was observed in both seropositive and seronegative subjects. These data supported the conclusion that an initial dose of 10^6 PFU/mL, followed by doses of 10^8 PFU/mL, was appropriate for use in further trials. This dose regimen has been tested in phase 2 trial (Study 002/03; Senzer et al, 2009) and versus subcutaneous GM-CSF in recently completed open-label, randomized, phase 3 trial (OPTiM study, Study 005/05), where subjects with stages IIIB, IIIC and IV unresectable melanoma were treated at least until week 24, complete response (CR), clinically significant disease progression, intolerable side effects, 12 months of therapy without an objective response, or withdrawal of consent. The primary endpoint of the OPTiM study was DRR, defined as the rate of subjects with an objective response (CR or partial response [PR]) by central review starting any time within 12 months of initiating therapy and lasting continuously for at least 6 months.

Secondary endpoints included OS, best overall response, time-to-treatment failure, changes in tumor burden and safety.

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: 16%, 2%) (p-value < 0.0001). An improvement that closely approached statistical significance was seen in the intent-to-treat population in the primary analysis of the secondary endpoint of OS with HR of 0.79 (95% CI: 0.62-1.00), p = 0.051. Median OS of subjects treated with talimogene laherparepvec was 4.4 months longer than those treated with GM-CSF (23.3 months for talimogene laherparepvec versus 18.9 months for GM-CSF) (Kaufman et al, 2014). Survival at 12, 24, 36 and 48 months in the talimogene laherparepvec arm was estimated to be 74%, 50%, 39% and 33%, respectively, and 69%, 40%, 30% and 21% in the GM-CSF arm, respectively. Median (range) time to response among the 78 subjects in the talimogene laherparepvec arm with a response was 4.1 (1.2 to 16.7) months, whereas among the 8 in the GM-CSF arm with a response, it was 3.7 (1.9 to 9.1) months. Fifty-four percent of talimogene laherparepvec objective responders and 48% of talimogene laherparepvec durable responders exhibited “interval progression”, which is transient locoregional or distant progression including appearance of new lesions, before ultimately achieving response (Kaufman et al, 2013).

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

2.3 Shedding and Transmissibility of HSV-1 and Talimogene Laherparepvec

Wild type HSV-1, the parent virus of talimogene laherparepvec, is capable of causing lifelong but rarely serious oro-labial or anogenital recurrent disease in immunocompetent

individuals. HSV-1 infection is a prevalent infection with approximately 60 to 80% of the adult population in the United States having evidence of past exposure to HSV-1 (Corey et al, 2012; Scott et al, 1997). This is explained by fact that HSV-1 is transmitted not only from close contact (by kissing, sharing of towels or glasses and/or silverware, sexual contact, etc) with persons who have active ulcerative lesions but also with persons who have no clinical signs of disease but who are "shedding" HSV-1 from mucocutaneous (oro-labial or anogenital) surfaces (Scott et al, 1997). Rate of shedding is highest during the initial years after acquisition, with viral shedding occurring on as many as 30 to 50% of days during this period. Rate of shedding of HSV-1 is highly variable among individuals, ranging from 0 to 90% of days tested, and occurs both in seronegative and seropositive subjects (Miller and Danaher, 2008). In a systematic review of 22 reports which included 3,500 asymptomatic subjects, the rate of HSV-1 shedding in the oral cavity was 33.3% (Miller and Danaher, 2008). The rate of shedding of HSV-1 in the anogenital region (where HSV-2 infection is more prevalent) in symptomatic and asymptomatic individuals is similar to HSV-2 (Corey et al, 2012). In the study on 60,000 clinical cervicovaginal specimens derived from samples originating from generally healthy women in 43 continental USA states, 14% were positive for HSV-1 (Peña et al, 2010). In the study on 498 immunocompetent HSV-2-seropositive subjects, the rate of HSV-2 shedding was 20.1% in persons with symptomatic anogenital HSV-2 infection and 10.2% in subjects with asymptomatic infection (Tronstein et al, 2011). With increased sampling frequency and use of ultra-sensitive techniques based on PCR, the rates of detected reactivation increase, with many episodes lasting several hours only (Sacks et al, 2004). HSV-1 can remain latent in neural sensory ganglia in the anatomic region of the initial infection, such as trigeminal ganglia in the oral herpes or sacral nerve root ganglia (S2–S5) with genital infection (Corey et al, 2012). It is assumed that these ganglia are the source of viral particles for both recurrent infection and asymptomatic shedding. The transit interval from inoculation of virus in peripheral tissue to spread to the neural ganglia is unknown. During periods of reactivation the virus replicates initially at the sensory ganglion and contiguous neural tissue and then spreads in an anterograde fashion along sensory nerves to the innervated skin or mucosa (Corey et al, 2012). This mode of spread explains the high frequency of new lesions distant from the area of initial inoculation. HSV-1 can reactivate and shed under a variety of stimuli, such as fever, ultraviolet irradiation, trauma, and immunosuppression. The mechanism of reactivation of HSV-1 from latency as well as asymptomatic shedding is unknown. Additional mode of spread of HSV infection

through the body is viremia, which was demonstrated in approximately 30 to 40% of persons with primary HSV-2 infection (Corey et al, 2012).

Due to specific considerations relating to nature of the parent virus, biodistribution, tumoral shedding (shedding from the tumor injected with talimogene laherparepvec) and transmissibility of talimogene laherparepvec have been studied in previous studies. Anogenital or oral mucosal shedding while on treatment with talimogene laherparepvec and mucosal and tumoral shedding following reactivation after the end of treatment with talimogene laherparepvec are planned to further understand the pattern of viral shedding and reactivation.

In the preclinical setting, biodistribution of talimogene laherparepvec was evaluated in a BALB/c murine model. Overall, the biodistribution of talimogene laherparepvec was predominantly restricted to tumor, blood, and tissues likely associated with immune-mediated viral clearance (spleen, lymph node, liver). Low levels of viral DNA occasionally found in heart, kidney, lung, ovary and salivary gland occurred in animals with the highest concurrent blood levels, suggesting contribution of viral DNA contamination by residual blood in these tissues; these results also suggest a low risk of viral transmission from salivary or anogenital secretions following intratumoral administration of talimogene laherparepvec. The absence of viral DNA in lacrimal glands, nasal mucosa or feces demonstrates a low likelihood of secondary exposure to viral DNA from tears, saliva or feces following intratumoral administration. Viral DNA found in two samples collected from brain (both treated with $1x10^5$ PFU, detected at 635 and 13,325 copies/µg genomic DNA) were not associated with observed adverse effects in these animals.

Biodistribution/shedding was also studied in the first-in-human study (Hu et al, 2006). In the single dosing portion of the study, virus was detected at low levels on the tumor surface for up to 2 weeks in 3 of 13 subjects, which, because detectable virus levels initially reduced following injection, suggested virus replication. In the multidosing portion, virus was only detected on the surface of the tumor of 1 of 17 subjects at a single time point at a very low level (7.5 PFU per swab). This difference between the single and multidose subjects was attributed to the optimized dosing regimens used (ie, initially dosing with 10^6 PFU/mL before moving to higher doses), and the absence of a biopsies of tumors during the multidose portion, which prevented virus leakage through the puncture site. A vesicle adjacent to the tumor and under the occlusive dressing also tested positive at a similarly low level in 1 patient, which could have been due to

cross-contamination from the tumor as all other vesicles from this or other patients tested negative for the presence of the virus. Virus was not detected outside the occlusive dressing in any case during the study.

In the single-dose portion of the study, viral DNA was only detected in the blood of two of 13 patients between 8 hours and 1 week after injection. In the multidose portion of the study, virus was detected in the blood of eight of 17 patients 1 to 8 hours postdose, which was somewhat more evident in HSV-1 seronegative patients. Virus DNA was even more rarely detected in urine with only two of 13 patients testing positive at very low levels 8 hours to 1 week after injection in the single-dose group, and no patient tested positive in the multidose group.

This phase 1 study also evaluated the effect of the virus on HSV-1 serostatus. All patients who were HSV-1 seronegative at baseline seroconverted 3 to 4 weeks after their first dose to a similar level to patients who were originally seropositive. For seropositive patients, the general trend was an increase in anti-HSV antibody index with each injection, which eventually plateaued.

Viral transmissibility was evaluated as a part of the phase 3 study. Patients and health care providers were administered monthly surveys to evaluate whether providers or subject contacts had experienced symptoms or signs consistent with talimogene laherparepvec infection.

Research has also been conducted to determine the ability of talimogene laherparepvec to cause disease in humans. Internal and published studies demonstrate that ICP34.5 deletion (as in talimogene laherparepvec) significantly reduces HSV-1 neurovirulence and reduces viral burden in normal (ie, non-tumour) tissues in animals (Study 4648-00014; MacLean et al, 1991; Chou et al, 1990) and humans (Harrington et al, 2010; Markert et al, 2009; Senzer et al, 2009; Mace et al, 2008; Hu et al, 2006; Harrow et al, 2004; Papanastassiou et al, 2002; MacKie et al, 2001; Markert et al, 2000; Rampling et al, 2000).

Clinical data to date are consistent with decreased virulence of talimogene laherparepvec. During the phase 3 study, there were 14 documented instances of cold sores or oral herpes that occurred among subjects who received talimogene laherparepvec and two instances of herpetic keratitis (of 292 treated subjects). None of these lesions were tested for the presence of talimogene laherparepvec. Two instances of herpetic keratitis were reported in the same subject who had a history of herpetic

keratitis before treatment initiation. The majority of these patients were documented as seropositive for HSV-1 at the start of the study, and among those who were seronegative, no pathologic confirmation of a herpetic infection was obtained. However, comprehensive reactive swabbing program (in the event of herpes-like symptoms) was not implemented for suspicious cases.

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

2.4 Rationale

Though the above described studies have characterized the biodistribution, transmissibility, and possibility of virulence of talimogene laherparepvec, tumoral shedding of talimogene laherparepvec has not been routinely tested at the frequency of administration given in the phase 3 trial and pattern of shedding (ie duration, including the period when shedding stops after the treatment, changes during the treatment and dependence on the immune status) were not evaluated to a full extent. Additionally, oral mucosal and anogenital area shedding while on treatment with talimogene laherparepvec and tumoral and mucosal shedding after the end of treatment with talimogene laherparepvec have not been evaluated yet. While transmissibility of the virus has been studied using questionnaires, it is anticipated that such questionnaires may lack sensitivity and specificity. As such, additional determination of whether there may be a possibility of exposure of subjects, close contacts, and health care providers would be useful. Taken together, these data will provide important information as to the safety profile of talimogene laherparepvec.

2.5 Clinical Hypotheses

No formal statistical hypothesis will be tested. The study will provide estimates of the proportions of subjects with detectable talimogene laherparepvec in the blood and urine any time after the administration of talimogene laherparepvec within the first 3 cycles as assessed by real-time quantitative polymerase chain reaction (qPCR) analysis of talimogene laherparepvec DNA in subjects with unresected stage IIIB to IVM1c melanoma.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a phase 2, multicenter, and single-arm study to investigate the biodistribution and shedding of talimogene laherparepvec in subjects with unresected, stage IIIB to IVM1c melanoma. **Approximately** 50 to 60 subjects will be enrolled in this study. **The final**

number of subjects in the study (with the minimal number of approximately 50 and the maximal number of approximately 60 subjects) will depend on enrollment of approximately 20 subjects evaluable for the estimation of detection of talimogene laherparepvec DNA in any set of swabs (ie, swabs from the surface of injected lesions, exterior of the occlusive dressing, oral mucosa, or anogenital area). For a full description of determination of the final number of subjects in the study, please refer to Section 10.2.

Talimogene laherparepvec will be administered by intralesional injection into injectable cutaneous, subcutaneous, and nodal tumors initially at a dose of 10^6 PFU/mL at study day 1 followed by a dose of 10^8 PFU/mL 21 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 relevant (resulting in clinical deterioration or requiring change of therapy) disease progression per modified World Health Organization (WHO) response criteria (WHO handbook for reporting results of cancer treatment, 1979; refer to Appendix D) beyond 6 months of therapy, 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 regardless of progression provided that the subject does not develop deterioration of health status requiring other treatment, and is able to tolerate the treatment.

Subjects will be followed for safety approximately 30 (+7) days and 60 (+7) days after the after the last dose of talimogene laherparepvec, respectively. Thereafter, subjects will be followed under an ongoing separate registry protocol for the long-term survival follow-up of subjects treated with talimogene laherparepvec in clinical trials. The registry protocol will also monitor for late and long-term adverse events thought to be potentially related to talimogene laherparepvec.

The following samples will be collected to evaluate the biodistribution of talimogene laherparepvec during the treatment period and safety follow-up at time points designated in the Schedule of Assessments (Table 2, Section 7.1) and the General Study Procedures (Section 7.2):

- Blood sample to quantify the number of the talimogene laherparepvec DNA copies in the blood using qPCR analysis
- Urine sample to quantify the number of the talimogene laherparepvec DNA copies in the urine using qPCR analysis

The following samples will be collected to evaluate the shedding of talimogene laherparepvec during the treatment period and safety follow-up at time points designated in the Schedule of Assessments (Table 2. Section 7.1) and the General Study Procedures (Section 7.2):

- Swabs of the exterior of the occlusive dressing and the surface of injected lesion for qPCR analysis and 50% Tissue Culture Infective Dose (TCID50) testing assay. During treatment up to 3 injected lesions will be selected at baseline (ie, on day 1 of cycle 1). The exterior of the selected occlusive dressing(s) and the surface of the selected injected lesion(s) will be swabbed starting on day 2 of cycle 1 at time points designated in Section 7.2.2 and only re-swabbed if the lesion is injected subsequently up to and including day 1 cycle 4.
- During safety follow-up only the surface of up to 3 most recently injected lesion(s) will be swabbed starting on day-30 (+ 7) safety follow-up visit at time points designated in Section 7.2.3 (if a lesion is in CR, the place of the prior injection will be swabbed). Initially, a qPCR analysis will be performed on the swab sample to quantify the number of talimogene laherparepvec DNA copies in order to evaluate whether the talimogene laherparepvec DNA is detectable in the sample. If the qPCR testing is positive, then a TCID50 assay will be performed on the swab sample to measure the viral infectivity (ie, the concentration of the infective talimogene laherparepvec virus in the sample).
- Swabs of oral mucosa for qPCR analysis and TCID50 assay during treatment at time points designed in the Section 7.2.3. Initially, a qPCR analysis will be performed on the swab sample to quantify the number of talimogene laherparepvec DNA copies in order to evaluate whether the talimogene laherparepvec DNA is detectable in the sample. If the qPCR testing is positive, then a TCID50 assay will be performed on the swab sample to measure the viral infectivity.
- Swabs from anogenital area for qPCR analysis and TCID50 assay during treatment at time points designed in the Section 7.2.3. Initially, a qPCR analysis will be performed on the swab sample to quantify the number of talimogene laherparepvec DNA copies in order to evaluate whether the talimogene laherparepvec DNA is detectable in the sample. If the qPCR testing is positive, then a TCID50 assay will be performed on the swab sample to measure the viral infectivity (ie, the concentration of the talimogene laherparepvec virus in the sample). Note: collection of swabs from the anogenital area is optional for subjects enrolled into the study prior to the investigator obtaining institutional review board (IRB) approval of amendment 1. Collection of swabs from the anogenital area for subjects injected

any time during the study into a melanoma lesion above the waist, ie above the line that connects the tops of left and right iliac crests is optional for subjects enrolled into the study prior to the investigator obtaining IRB approval of amendment 2.

- Swabs of oral mucosa for qPCR analysis after end of treatment. Samples will be collected daily for approximately 30 days starting 30 (+7) days after end of treatment until 60 (+7) days after end of treatment (refer to Section 7.2.3 for additional information regarding logistics of sample collection). At each time point a qPCR analysis will be performed on the swab sample to quantify the number of talimogene laherparepvec DNA copies in order to evaluate whether the talimogene laherparepvec DNA is detectable in the sample.
- Swabs from the anogenital area after end of treatment. Samples will be collected daily for approximately 30 days starting 30 (+ 7) days after end of treatment until 60 (+ 7) days after end of treatment (refer to Section 7.2.3 for additional information regarding logistics of sample collection). At each time point a qPCR analysis will be performed on the swab sample to quantify the number of talimogene laherparepvec DNA copies in order to evaluate whether the talimogene laherparepvec DNA is detectable in the sample. Note: collection of swabs from anogenital area is optional for subjects enrolled into the study prior to the investigator obtaining IRB approval of amendment 1. Collection of swabs from the anogenital area for subjects injected any time during the study into a melanoma lesion above the waist, ie above the line that connects the tops of left and right iliac crests is optional for subjects enrolled into the study prior to the investigator obtaining IRB approval of amendment 2.
- Swabs of any lesion regardless of location that is suspected to be herpetic in origin for qPCR analysis during treatment and safety follow-up. 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 quantify the number of talimogene laherparepvec DNA copies in order to evaluate whether talimogene laherparepvec DNA is detectable in the sample.

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

The study will be conducted at approximately 15 to 20 sites in the USA and Canada.

Sites that do not enroll subjects within 4 to 6 months of site initiation may be closed.

3.3 Number of Subjects

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

A**pproximately** 50 to 60 subjects will be enrolled in this study. Refer to Section 10.2 for sample size considerations.

3.4 Replacement of Subjects

Subjects who withdraw from treatment before the first dose of talimogene laherparepvec or have received the first dose talimogene laherparepvec but have not provided blood and urine samples 1 hour after cycle 1 dosing and at 8 hours or beyond may be replaced in order to obtain approximately **50** subjects evaluable for the estimation of the biodistribution of talimogene laherparepvec in the blood and urine. Evaluable subjects are defined as those who have received the first dose of talimogene laherparepvec and have blood and urine samples collected approximately 1 hour after cycle 1 dosing and at or beyond 8 hours.

Refer to Section 10.2 for sample size considerations for additional information.

The final number of subjects needed to be enrolled in the study (with the minimal number of approximately 50 and the maximal number of approximately 60 subjects) will depend on enrollment of approximately 20 subjects evaluable for the estimation of detection of talimogene laherparepvec DNA in any set of swabs (ie, swabs from oral mucosa, swabs from the anogenital area, swabs from injected lesions, or swabs from exterior of occlusive dressing). For a full description of determination of the final number of subjects in the study, please refer to Section 10.2.

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

The duration for the study is approximately 30 months. The duration of screening for each subject will be approximately 28 days. The subject accrual period is planned for approximately 20 months. The duration of treatment will vary for each subject. Subjects will be treated with talimogene laherparepvec until the subject has achieved a complete response, all injectable tumors have disappeared, clinically relevant (resulting in clinical deterioration or requiring change of therapy) disease progression per modified WHO response criteria (WHO handbook for reporting results of cancer treatment, 1979; refer to Appendix D) beyond 6 months of therapy, or intolerance of study treatment, whichever occurs first. Subjects will be followed for safety approximately 30 (+ 7) days and 60 (+ 7) days after the last dose of talimogene laherparepvec.

The end of the study for each subject is defined as the date the subject withdraws full consent from the study, completes the 60-day (+ 7) safety follow-up visit, or dies, whichever is earlier.

At the end of study subject will be asked to participate in an ongoing separate registry protocol for the long-term survival follow-up of subjects treated with talimogene laherparepvec in clinical trials. The registry protocol **(Study 20120139)** will also monitor for long-term adverse events thought to be potentially related to talimogene laherparepvec **and use of anti-cancer therapy for melanoma**.

3.5.2 End of Study

Primary Completion: The time when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary analysis. The primary completion is anticipated to occur after all treated subjects have had the opportunity to complete the blood and urine sample collection through day 1 of cycle 4.

End of Trial: The time when the last subject is assessed or receives an intervention for evaluation in the study. The end of study will occur when the last subject discontinues the study treatment and has had the opportunity to complete the 60-day (+7) safety follow-up visit or withdraws full consent from the study, whichever is earlier.

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/procedure, 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

110 Subjects with unresected stage IIIB, IIIC, IVM1a, IVM1b, or IVM1c regardless of prior line of therapy

105 Candidate for intralesional therapy (ie, disease is appropriate for direct injection or through the use of ultrasound guidance) defined as one either of the following:

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

106 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

111 Serum LDH levels ≤ 1.5 x upper limit of normal (ULN) within 28 days prior to enrollment

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

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

- absolute neutrophil count ≥ 1500/mm^3
- platelet count ≥ 75,000/mm^3
- 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

4.1.2 Exclusion Criteria

222 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 therapy, craniotomy, with no evidence of progression, and have not required steroids, for at least two (2) months prior to enrollment.

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

224 Bone metastases

202 Primary ocular or mucosal melanoma

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

204 Evidence of immunosuppression for any reason such as the following:

- chronic oral or systemic steroid medication use at a dose of > 10 mg/day of prednisone or equivalent (steroids with low systemic absorption [eg, triamcinolone hexacetonide] injected into a joint space is allowed)
- other signs or symptoms of clinical immune system suppression

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

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

207 Previous treatment with talimogene laherparepvec

225 Currently receiving treatment in another investigational device or drug study besides talimogene laherparepvec, or less than 28 days since ending treatment on another investigational device or drug study(s).

210 Other investigational procedures while participating in this study are excluded.

211 Known to have acute or chronic active hepatitis B infection

212 Known to have acute or chronic active hepatitis C infection

213 Known to have human immunodeficiency virus infection

214 History of other malignancy within the past 3 years. Consider allowing 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

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

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

217 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.

218 Subject previously has entered this study.

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

227 Sexually active subjects who are unwilling to use a barrier method (male or female condom) to avoid potential viral transmission during sexual contact during and within 30 days after treatment with talimogene laherparepvec.

226 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. (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 < 55 years but no spontaneous menses for at least 2 years, or less than 55 years and spontaneous menses within the past year, but currently amenorrheic (eg, spontaneous or secondary to hysterectomy), and with postmenopausal gonadotropin levels (luteinizing hormone and follicle-stimulating hormone levels > 40 IU/L) or postmenopausal estradiol levels (< 5 ng/dL) or according to the definition of "postmenopausal range" for the laboratory involved], or who have had a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy). Acceptable methods of effective contraception are defined in the informed consent form (ICF). Where required by local laws and regulations, additional country-specific contraception requirements may be outlined in a country-specific protocol supplement at the end of the Appendix Section of the protocol).

5. SUBJECT ENROLLMENT

Before subjects may be entered into the study, Amgen requires a copy of the site's written IRB approval of the protocol, informed consent form, and all other subject information and/or recruitment material (see Section 11.1*)*. All subjects must personally sign and date the consent form before commencement of study-specific procedures (ie, nonstandard 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 that are determined not eligible after screening must be screen-failed in the ETO system and the reason for the screen-failure provided. Subjects who do not meet all eligibility criteria may be rescreened once at the discretion of the investigator. If a subject is being rescreened, he or she may need to reconsent to the study to ensure that the IRB approved main informed consent form is signed within 28 days of enrollment. Subjects that are determined not eligible after rescreen must be screen-failed in the ETO

system and the reason for the screen-failure provided. Subjects may only be enrolled 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 upon registering the subject as enrolled in the ETO system.

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 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 10^6 PFU/mL or 10^8 PFU/mL concentrations. The supply for 10^6 PFU/mL concentration will be packaged separately from the supply for 10^8 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 and, where applicable, licensed healthcare professional. Subjects should be assessed clinically for toxicity prior to each dose using the Common Terminology Criteria for Adverse Events (CTCAE) version 3 (Appendix A). Complete blood count with differential and chemistry panels including liver function laboratory tests (ALT, AST, and total bilirubin) must be obtained according to the Schedule of Assessments (see Section 7.1), and the results must be checked before each treatment. Dosing will occur only if these test values are acceptable, per Section 6.2.1.2.

Talimogene laherparepvec will be administered by intralesional injection 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 10^6 PFU/mL. Subsequent doses of talimogene laherparepvec are up to 4.0 mL of 10^8 PFU/mL.

The first cycle of talimogene laherparepvec will be 21 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 10^6 PFU/mL. The second injection up to 4.0 mL of 10^8 PFU/mL should be administered 21 days after the initial injection (ie, no sooner than day 22 but should not be delayed more than 5 days after the 22-day time point). Subsequent injections up to 4.0 mL of 10^8 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 one 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 events 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.

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

Tumor Size (longest dimension)	Maximum Injection Volume
> 5.0 cm	4.0 mL
> 2.5 cm to 5.0 cm	2.0 mL
> 1.5 cm to 2.5 cm	1.0 mL
> 0.5 cm to 1.5 cm	0.5 mL
≤ 0.5 cm	0.1 mL

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

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

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

Subjects will be treated with talimogene laherparepvec until CR, all injectable tumors have disappeared, clinically relevant (resulting in clinical deterioration or requiring change of therapy) disease progression per the modified WHO response criteria (Appendix D) **beyond 6 months of treatment**, 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 and is able to tolerate the treatment.

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

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:

- 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 may not receive systemic antiherpetic drugs (eg, acyclovir, valacyclovir, famciclovir), but may receive a topically administered antiherpetic drug at least 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).

If the subject requires corticosteroid dosing of > 10 mg prednisone daily (or equivalent, eg, 1.5 mg dexamethasone) for any reason, talimogene laherparepvec dosing must be held 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 risk/benefit assessment of the subject.

If talimogene laherparepvec treatment was delayed by > 1 week, that dose will be deemed to have been missed and the subject will proceed to the next scheduled treatment visit.

If 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 taken off 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 anti-cancer 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 occurs as defined per the modified WHO response criteria (Appendix D).
- Immune-mediated adverse events have been observed in subjects receiving talimogene laherparepvec. These have included pauci-immune glomerulonephritis, vasculitis, and pneumonitis; however, immune-mediated adverse events can

potentially involve any organ system. Permanently discontinue talimogene laherparepvec if 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 a grade 2 or greater immune-mediated adverse event (with the exception of vitiligo), allergic reactions, or urticaria attributed to talimogene laherparepvec.

- Plasmacytoma has been observed with the administration of talimogene laherparepvec. Permanently discontinue talimogene laherparepvec if development of a plasmacytoma is observed.
- 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).
- A female subject becomes pregnant or fails to use 2 highly effective methods of contraception (for those subjects who are able to conceive).
- A female subject breast feeds while on study treatment.
- Intercurrent medical illness that, in the judgment of the investigator, would make continued treatment with talimogene laherparepvec dangerous for the subject.

Subjects who discontinue talimogene laherparepvec are to continue to return for all other study procedures and measurements until the end of the 60-day safety follow-up visit (ie, until approximately 60 [+ 7] days after the last dose of talimogene laherparepvec).

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 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 CRF until 60 (+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 may be taken of cutaneous or subcutaneous lesions for tumor analysis during study. 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. If a subject undergoes resection of the lesion in the event other than CR, the investigator or designee should notify the sponsor medical monitor and the procedure should be recorded in the source document and CRF. 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 CRF, the response definition again being PR if viable melanoma was noted in the surgical specimen, and CR if no viable melanoma was identified in the surgical specimen. Best response of CR or PR due to surgeries will not be considered for assessment of OR or BOR.

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 CRF.

If a subject demonstrates evidence of new or worsening central nervous system (CNS) metastases, talimogene laherparepvec treatment should be withheld and the investigator or designee should notify the sponsor's medical monitor as soon as possible. Subjects may be allowed to remain on study after discussion between the sponsor's medical monitor and the investigator to determine the appropriateness of treatment resumption provided CNS lesions can be treated with stereotactic radiotherapy (including Gamma

Knife) or craniotomy and if there is no change in the baseline ECOG performance status. Subjects may be allowed to resume talimogene laherparepvec treatment per Section 6.2.1.1 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. If higher doses of corticosteroid 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 (1.5 mg/day dexamethasone) 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)
- antiherpetic drugs, other than if topically administered > 20 cm from a talimogene laherparepvec injection site
- any surgery for melanoma (other than the exceptions noted in Section 6.5)
- Subjects must not schedule any elective nonmelanoma-related 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.

7. STUDY PROCEDURES

7.1 Schedule of Assessments

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

Table 2. Schedule of Assessments

Schedule of Assessments																	
	Screening[a]	Treatment Period[a]												Follow-up Period		
Cycle		1	1	1	1	1	2	2	2	2	3	3	Cycle 4	Cycle 5 and Subsequent Cycles	Safety[b] Follow-up		
Day		1	2	3	8	15	1	2	3	8	1	8	1	1	30 (+7)	30 to 60	60 (+7)
GENERAL & SAFETY ASSESSMENTS																	
Informed Consent & Review of Eligibility Criteria	X																
Medical/Surgical History & Demographics	X																
Concomitant Medications[c]	X	→	→	→	→	→	→	→	→	→	→	→	→	→			X
Adverse Events[d]		X	→	→	→	→	→	→	→	→	→	→	→	→	X		
Serious Adverse Events[e]	X	→	→	→	→	→	→	→	→	→	→	→	→	→			X
Physical Exam[f]	X														X		
Vital Signs[g]	X	X					X						Q2C		X		
ECOG Performance Status	X														X		
LOCAL LABORATORY ASSESSMENTS																	
Urine or Serum Pregnancy Test[h]	X														X		
Hematology[i]	X	X					X						Q2C		X		
Chemistry[j]	X	X					X						Q2C		X		
Serum LDH	X																
Archived Tumor Tissue for $BRAF^{V600}$ [k]		X															
CENTRAL LABORATORY ASSESSMENTS																	
Blood and Urine for qPCR[l]		X	X	X	X	X	X	X	X	X	X	X	X		X		
Swab of Oral Mucosa for qPCR and TCID50[m]		X			X	X	X			X	X	X	X	X	X	X	X
Anogenital Swab for qPCR and TCID50[n]		X			X	X	X			X	X	X	X	X	X	X	X
Swab of Exterior of Occlusive Dressing for qPCR and TCID50[o]			X	X	X	X	X	X	X	X	X	X	X				
Swab of Surface of Injected Lesion for qPCR and TCID50[o]			X	X	X	X	X	X	X	X	X	X	X		**X**		**X**

Footnote defined on the next page of the table

Table 2. Schedule of Assessments

Schedule of Assessments																	
	Screening[a]	Treatment Period[a]													Follow-up Period		
Cycle		1	1	1	1	1	2	2	2	2	3	3	Cycle 4	Cycle 5 and Subsequent Cycles	Safety[b] Follow-up		
Day		1	2	3	8	15	1	2	3	8	1	8	1	1	30 (+7)	30 to 60	60 (+7)
CENTRAL LABORATORY ASSESSMENTS (Continued)																	
Swab of Herpetic Lesion for qPCR[p]		X		Within 3 days of occurrence of suspected lesion of herpetic origin											X		X
Blood for HSV Serostatus[q]		X				X	X				X		Q2C		X		
Blood for Biomarker Analysis[r]		X					X										
Archived Tumor Tissue for Biomarker Analysis[k]		X															
Tumor Biopsy for Biomarker Analysis (at limited number of sites)[s]		X									X						
REPORTING EXPOSURE TO TALIMOGENE LAHERPAREPVEC																	
Exposure of Subject's Household member or Caregiver[t]		X	→														X
Exposure of Subject's Healthcare Provider[t]		X	→														X
DOSING																	
Talimogene Laherparepvec Administration[u]		X					X				X		Q1C				
TUMOR STAGING ASSESSMENTS																	
Clinical Tumor Assessment[v]	X	Week 12 (± 7 days), week 24 (± 7 days), then at least every 3 months (± 15 days)															
Radiological (CT, PET/CT, MRI, or ultrasound) Tumor Assessment[w]	X	Week 12 (± 7 days), week 24 (± 7 days), then at least every 3 months (± 15 days)															
Tumor Response Assessment		Week 12 (± 7 days), week 24 (± 7 days), then at least every 3 months (± 15 days)															

Q1C = every cycle; Q2C = Every second/other cycle; ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase; $BRAF^{V600}$ = v-raf murine sarcoma viral oncogene homolog B1 V600; qPCR = real-time quantitative polymerase chain reaction; HSV = herpes simplex virus; CT = computed tomography; PET = positron emission tomography; MRI = magnetic resonance imaging; HSV-1/2 = herpes simplex virus type 1/type 2; IgG = immunoglobulin G; IgM = immunoglobulin M; PFU = plaque-forming unit; WHO = World Health Organization; CNS = central nervous system

[a] Screening assessments to be performed within ≤ 28 days prior to enrollment unless otherwise indicated. During treatment, assessments and procedures can be performed within 3 days of the planned visit, unless otherwise indicated.

[b] Safety follow-up will be performed approximately 30 (+ 7) days and 60 (+ 7) days after the last dose of talimogene laherparepvec.

[c] All concomitant medications that are administered after the subject has signed the 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. Concomitant medications associated with serious adverse events will be collected through 60 (+ 7) days after the last dose of talimogene laherparepvec.
[d] 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.
[e] All serious adverse events that occur after the subject has signed the informed consent through 60 (+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.
[f] Physical examination as per standard of care.
[g] Vital signs (blood pressure, heart rate, and temperature) must be performed at screening; prior to talimogene laherparepvec administration on day 1 of cycles 1, 2, and 4, then every other cycle until end of treatment, and at the 30-day safety follow-up visit (+7 days).
[h] Urine or serum pregnancy test must be performed on females of childbearing potential within ≤ 3 days prior to enrollment. Urine or serum pregnancy test must also be performed on females of childbearing potential at the 30-day safety follow-up visit (+7 days).
[i] Blood samples for hematology will be collected at screening and within 3 days prior to talimogene laherparepvec administration on day 1 of cycles 1, 2, and 4, then every other cycle until end of treatment. 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 scheduled dose of study treatment. Blood sample will also be collected at the 30 (+7 days) safety follow-up visit (+7 days).
[j] Blood samples for chemistry will be collected at screening and within 3 days prior to talimogene laherparepvec administration on day 1 of cycles 1, 2, and 4, then every other cycle until end of treatment. 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 scheduled dose of study treatment. Blood sample will also be collected at the 30-day safety follow-up visit (+7 days).
[k] Formalin-fixed paraffin-embedded tumor tissue from either the primary tumor or a metastatic lesion (block or unstained tumor slides) and the associated pathology reports) must be submitted for BRAF ^{V600} mutation testing to either a local laboratory (if the test can be performed locally per standard of care) or to a central laboratory. Tumor sample BRAF^{V600} mutation testing should be submitted to the local site within 28 days of after enrollment. BRAF^{V600} tumor mutation status obtained prior to screening from a local laboratory will be acceptable. The local laboratory report supporting local BRAF^{V600} tumor testing results should be available at the site within 28 days after enrollment. In addition, tumor sample should be submitted within 28 days after enrollment to a central laboratory for archiving for other biomarker analyses.
[l] Blood and urine sample for qPCR testing will be performed at the following time points: Cycle 1: day 1 (prior to and approximately 1 hour [± 15 minutes], 4 hours [± 30 minutes], and 8 hours [± 1 hour] after talimogene laherparepvec administration), day 2 (24 [± 4] hours after talimogene laherparepvec administration), day 3 (48 [± 4] hours after talimogene laherparepvec administration), day 8 (± 2 days), and day 15 (± 2 days). Cycle 2: day 1 (prior to and approximately 1 hour [± 15 minutes], 4 hours [± 30 minutes], and 8 hours [± 1 hour] after talimogene laherparepvec administration), day 2 (24 [± 4] hours after talimogene laherparepvec administration), day 3 (48 [± 4] hours after talimogene laherparepvec administration), and day 8 (± 2 days). Cycle 3: day 1 (prior to talimogene laherparepvec administration) and day 8 (± 2 days). Cycle 4: day 1 (prior to talimogene laherparepvec administration). Blood and urine samples for qPCR testing will also be collected at the 30-day safety follow-up visit (+7 days).

[m] Swabs of oral mucosa: During treatment: Swabs of oral mucosa for qPCR testing and TCID50 assay will be collected at the following visits: cycle 1: day 1 (within 3-4 days prior to talimogene laherparepvec administration), day 8 (± 2 days), and day 15 (± 2 days); cycle 2: day 1 (within 3-4 days prior to talimogene laherparepvec administration) and day 8 (± 2 days); cycle 3: day 1 (within 3-4 days prior to talimogene laherparepvec administration), day 8 (± 2 days); cycle 4 day 1 (within 3-4 days of talimogene laherparepvec administration), cycle 5 day 1 (within 3-4 days of talimogene laherparepvec administration) and all subsequent cycles until end of treatment (except cycle 25 and cycle 50): day 1 of each cycle (within 3 days prior to talimogene laherparepvec administration); cycle 25 and cycle 50 (approximately 1 year and 2 years after start of treatment): day 1 (prior to talimogene laherparepvec administration) and day 8 (± 2 days). Swabs will also be collected at 30-day (+7) and 60-day (+7) safety follow-up visits **and weekly at home between day 30 and day 60 safety follow-up visits**. If qPCR testing is positive, then a TCID50 assay will be performed to evaluate whether live talimogene laherparepvec virus is detectable in the sample. Please refer to the Central Laboratory Manual for instructions regarding sample collection, storage, and shipment procedures.

[n] Swabs from the anogenital area for qPCR testing and TCID50 assay will be collected at the following visits: cycle 1: day 1 (within 3-4 days prior to talimogene laherparepvec administration), day 8 (± 2 days), and day 15 (± 2 days); cycle 2: day 1 (within 3-4 days prior to talimogene laherparepvec administration) and day 8 (± 2 days); cycle 3: day 1 (within 3 -4 days prior to talimogene laherparepvec administration) and day 8 (± 2 days); cycle 4 day 1 (within 3-4 days of talimogene laherparepvec administration), cycle 5 day 1 and beyond (within 3-4 days of talimogene laherparepvec administration), and all subsequent cycles until end of treatment (except cycle 25 and cycle 50): day 1 of each cycle (within 3 days prior to talimogene laherparepvec administration); cycle 25 and cycle 50 (approximately 1 year and 2 years after start of treatment): day 1 (prior to talimogene laherparepvec administration) and day 8 (± 2 days). Swabs will also be collected at 30-day (+7) and 60-day (+7) safety follow-up visits **and weekly at home between day 30 and day 60 safety follow-up visits**. If qPCR testing is positive, then a TCID50 assay will be performed to evaluate whether live talimogene laherparepvec virus is detectable in the sample. Please refer to the Central Laboratory Manual for instructions regarding sample collection, storage, and shipment procedures. Note: collection of swabs from anogenital area is optional for subjects enrolled into the study prior to the investigator obtaining IRB approval of amendment 1. Collection of swabs from the anogenital area for subjects injected any time during the study into a melanoma lesion <u>above the waist</u>, ie above the line that connects the tops of left and right iliac crests is optional for subjects enrolled into the study prior to the investigator obtaining IRB approval of amendment 2.

[o]. Swabs of the exterior of the occlusive dressing and the surface of injected lesions for qPCR testing and TCID50 assay. During treatment: Up to 3 occlusive dressings and 3 injected lesions will be selected at baseline (ie, on day 1 of cycle 1). The exterior of the selected occlusive dressing(s) and the surface of the selected injected lesion(s) will be swabbed starting on day 2 of cycle 1, at the following time points and only re-swabbed if the lesion is injected subsequently up to and including day 1 cycle 4: Cycle 1: day 2 (24 [± 4] hours after talimogene laherparepvec administration), day 3 (48 [± 4] hours after talimogene laherparepvec administration), day 8 (± 2 days), and day 15 (± 2 days). Cycle 2: day 1 (prior to talimogene laherparepvec administration), day 2 (24 [± 4] hours after talimogene laherparepvec administration), day 3 (48 [± 4] hours after talimogene laherparepvec administration), and day 8 (± 2 days). Cycle 3: day 1 (prior to talimogene laherparepvec administration) and day 8 (± 2 days). Cycle 4: day 1 (prior to talimogene laherparepvec administration). During safety follow-up: Swabs of the surface of up to 3 most recently injected lesion(s) (if a lesion is in CR, the place of the prior injection will be swabbed) will also be collected at the 30-day safety follow-up visit (+7 days), weekly at home between day-30 and day-60 safety follow-up visit, and at the 60-day safety follow-up visit (+7 days). At each time point only if qPCR testing is positive, then a TCID50 assay will be performed to evaluate whether the talimogene laherparepvec virus is detectable in the sample.

[p]. Swabs of any lesion of herpetic origin for qPCR testing 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 on the swab to evaluate whether the talimogene laherparepvec DNA is detectable in the sample.

[q] Blood samples for HSV serostatus will be collected on day 1 (within 3 days prior to talimogene laherparepvec administration) and day 15 of cycle 1 (for HSV-1/2 IgG and IgM antibody analyses), day 1 of cycle 2 (within 3 days prior to talimogene laherparepvec administration) (for HSV-1/2 IgG and IgM antibody analyses), day 1 of cycle 3, and cycle 4, then every other cycle until end of treatment (within 3 days prior to talimogene laherparepvec administration) (for HSV-1 IgG antibody analysis), and at the 30-day safety follow-up visit (+7 days) (for HSV-1 IgG antibody analysis).

[r] Blood samples for biomarker analyses will be collected on day 1 of cycle 1 and cycle 2 (within 3 days prior to study treatment administration).

[s] Tumor biopsy from at least one injected lesion and/or one uninjected lesion will be performed within 3 days prior to talimogene laherparepvec administration at day 1 of cycle 1 and cycle 3. Tumor biopsies will be collected from subjects enrolled at a limited number of sites.

[t] Reporting potential or known unintended exposure to talimogene laherparepvec: If a household member, caregiver, or healthcare provider who has had close contact with the subject is suspected to have been exposed to talimogene laherparepvec (eg, have or who have had signs or symptoms suspected to be herpetic origin or accidentally exposed to talimogene laherparepvec), report the potential or known unintended exposure to talimogene laherparepvec, suspected related signs or symptoms, and detection of talimogene laherparepvec DNA in a subject's household member, caregiver, or healthcare provider as specified in Section 9.4.
[u] Talimogene laherparepvec 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 first cycle of talimogene laherparepvec will be 21 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 10^6 PFU/mL. The second injection up to 4.0 mL of 10^8 PFU/mL should be administered 21 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.
[v] Investigator's clinical measurement of cutaneous, subcutaneous, or nodal tumor measurement by caliper and response assessment per a modification of WHO criteria. The screening measurement must be done within 28 days prior to enrollment and will be used as baseline. During treatment, the clinical tumor assessments will performed independent of treatment cycle at week 12 (± 1 week), week 24 (± 1 week), and then at least every 3 months (± 15 days) until signs of clinically relevant disease progression per the modified WHO criteria or end of treatment, whichever occurs first.
[w] Radiographic imaging (CT, PET/CT, MRI or US) of the chest, abdomen, and pelvis, and CT or MRI of the brain are required at screening, only if suspected symptoms or signs suggestive of CNS metastasis are present. Tumor assessments must also include all other sites of disease. The screening scans must be done within 28 days prior to enrollment and will be used as baseline. During treatment, radiographic imaging (CT, PET/CT, MRI, or US) of the abdomen, pelvis, and chest, along with tumor assessments of all other sites of disease, (and CT scan or MRI of the brain if a subject has symptoms or signs suggestive of CNS metastasis), will be performed independent of treatment cycle at week 12 (± 1 week), week 24 (± 1 week), and then at least every 3 months (± 15 days) until clinically relevant disease progression per the modified WHO criteria **beyond 6 months of treatment** or end of treatment, whichever occurs first.

Refer to the applicable supplemental laboratory manuals for detailed collection and handling laboratory samples.

7.2 General Study Procedures

A signed and dated IRB-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 otherwise indicated. It is recommended that dosing occur on the same day of the week (eg, if first dose is administered on Monday, all subsequent doses should be administered on a Monday), however a ± 3-day dosing and study procedure window is allowed.

The following laboratory analytes in Table 3 will be assessed at various times throughout the study:

Table 3. Laboratory Analytes

Chemistry	**Hematology**	**Biodistribution and Shedding**	**Biomarker**	**Other Labs**
Sodium Potassium Chloride Total protein Albumin Calcium Creatinine Total bilirubin Alkaline-phosphatase AST (SGOT) ALT (SGPT)	RBC Hemoglobin Hematocrit Platelets WBC Differential[a] • Neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes	qPCR for talimogene laherparepvec DNA TCID50 assay for talimogene laherparepvec virus	HSV-1 antibody Blood for biomarker analysis Archived tumor tissue for biomarker analysis Fresh Tumor biopsy for biomarker analysis[b]	Pregnancy LDH

[a] 3-part differential if 5-part unable to be performed.
[b] At limited number of sites.

The chemistry, hematology, and pregnancy tests are to be performed at a local laboratory and to be fully and routinely recorded on electronic CRFs (eCRFs). Missed tests that are not done must be reported as such on the eCRFs. The biodistribution and

biomarker tests will be performed at a central laboratory and tests results will not be reported on the eCRFs.

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., Section 7.1):

- confirmation that the Informed Consent Form has been signed
- demographic data including sex, date of birth, race, and ethnicity
- physical examination as per standard of care
- medical/surgical history
- vital signs (systolic/diastolic blood pressure, heart rate, temperature). Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign CRF. Record all measurements on the vital signs CRF. The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs CRF.
- determination of ECOG performance status (see 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), platelet
    - chemistry panel: sodium, potassium, chloride, total protein, albumin, calcium, creatinine, total bilirubin, alkaline phosphatase, AST, ALT
    - serum LDH
  - within ≤ 3 days prior to enrollment:
    - serum or urine pregnancy test for female subjects of childbearing potential.
- clinical tumor assessments, including clinical measurement of cutaneous, subcutaneous, or nodal tumor measurement by caliper to be used as baseline assessment.
- radiographic tumor imaging (including CT scan, positron emission tomography [PET]/CT scan, MRI, or ultrasound) of the chest, abdomen, pelvis and all other sites of disease, and CT scan or MRI of the brain only if symptoms or signs suggestive of CNS metastasis are present); to be used as baseline imaging.
- recording of serious adverse event that occur after subject signs informed consent. Serious adverse events will be reported to Amgen within 24 hours following the investigator's knowledge of the event.
- documentation of concomitant medications

- review of inclusion and exclusion criteria
- registration in ETO system (refer to Section 5)

7.2.2 Treatment

Treatment begins when the first dose of protocol treatment 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. Section 7.1):

- Vital signs (systolic/diastolic blood pressure, heart rate, temperature) at day 1 of cycles 1, 2, and 4, then every other cycle until end of treatment. Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign CRF. Record all measurements on the vital signs CRF. The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs CRF.
- 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 unable to be performed), RBC, platelet
    - day 1 of cycles 1, 2, and 4, then every other cycle until end of study treatment
  - chemistry panel: sodium, potassium, chloride, total protein, albumin, calcium, creatinine, total bilirubin, alkaline phosphatase, AST, ALT
    - day 1 of cycles 1, 2, and 4, then every other cycle until end of study treatment
- Central laboratory assessments:
  - blood and urine samples for qPCR testing:
    - cycle 1: day 1 (prior to and approximately 1 hour [± 15 minutes], 4 hours [± 30 minutes], and 8 hours [± 1 hour] after talimogene laherparepvec administration), day 2 (approximately 24 [± 4] hours after talimogene laherparepvec administration), day 3 (approximately 48 [± 4] hours after talimogene laherparepvec administration), day 8 (± 2 days), and day 15 (± 2 days)
    - cycle 2: day 1 (prior to and approximately 1 hour [± 15 minutes], 4 hours [± 30 minutes], and 8 hours [± 1 hour] after talimogene laherparepvec administration), day 2 (approximately 24 [± 4] hours after talimogene laherparepvec administration), day 3 (approximately 48 [± 4] hours after talimogene laherparepvec administration), and day 8 (± 2 days)

- cycle 3: day 1 (prior to talimogene laherparepvec administration) and day 8 (± 2 days)
- cycle 4: day 1 (prior to talimogene laherparepvec administration)

- Swabs from the exterior of the occlusive dressing and the surface of injected lesion for qPCR and TCID50 assay testing. Up to 3 injected lesions will be selected at baseline (ie, on day 1 of cycle 1). The exterior of the selected occlusive dressing(s) and the surface of the selected injected lesion(s) will be swabbed starting on day 2 of cycle 1 at time points described below and only re-swabbed if lesion is injected subsequently up to and including day 1 cycle 4 (refer to the Central Laboratory Manual for additional instructions regarding sample collection and management):
  - cycle 1: day 2 (approximately 24 [± 4] hours after talimogene laherparepvec administration), day 3 (approximately 48 [± 4] hours after talimogene laherparepvec administration), day 8 (± 2 days), and day 15 (± 2 days)
  - cycle 2: day 1 (prior to talimogene laherparepvec administration), day 2 (approximately 24 [± 4] hours after talimogene laherparepvec administration), day 3 (approximately 48 [± 4] hours after talimogene laherparepvec administration), and day 8 (± 2 days)
  - cycle 3: day 1 (prior to talimogene laherparepvec administration) and day 8 (± 2 days)
  - cycle 4: day 1 (prior to talimogene laherparepvec administration)
  - At each time point the outside of the occlusive dressing will be swabbed. The dressing will be removed and the surface of the lesions will be swabbed. Initially, a qPCR analysis will be performed on the swab sample to evaluate whether the talimogene laherparepvec DNA is detectable outside of the occlusive dressing and/or on the surface of the injected lesion:
    - If result of the qPCR testing is negative, TCID50 assay testing is not required.
    - If the result of the qPCR testing is positive, then a TCID50 assay will be performed on the swab sample to measure viral infectivity.
- Swabs of oral mucosa for qPCR and TCID50 assay testing:
  - cycle 1: day 1 (within 3 to 4 days prior to talimogene laherparepvec administration), day 8 (± 2 days), and day 15 (± 2 days)
  - cycle 2: day 1 (within 3 to 4 days prior to talimogene laherparepvec administration) and day 8 (± 2 days)
  - cycle 3: day 1 (within 3 to 4 days prior to talimogene laherparepvec administration) and day 8 (± 2 days)
  - cycle 4 day 1 (within 3 to 4 days prior to talimogene laherparepvec administration)
  - cycle 5 day 1 (within 3-4 days of talimogene laherparepvec administration) and all subsequent cycles until end of treatment (except cycle 25 and cycle 50): day 1 of each cycle (within 3 days prior to talimogene laherparepvec administration).
  - cycle 25 and cycle 50 (approximately 1 year and 2 years after start of treatment): day 1 (prior to talimogene laherparepvec administration) and day 8 (± 2 days)

- Swabs from the anogenital area for qPCR and TCID50 assay testing anogenital:
  - Note: collection of swabs from anogenital area is optional for subjects enrolled into the study prior to the investigator obtaining IRB approval of amendment 1. Collection of swabs from the anogenital area for subjects injected any time during the study into a melanoma lesion above the waist, ie above the line that connects the tops of left and right iliac crests is optional for subjects enrolled into the study prior to the investigator obtaining IRB approval of amendment 2.
  - cycle 1: day 1 (within 3 to 4 days prior to talimogene laherparepvec administration), day 8 (± 2 days), and day 15 (± 2 days)
  - cycle 2: day 1 (within 3 to 4 days prior to talimogene laherparepvec administration) and day 8 (± 2 days)
  - cycle 3: day 1 (within 3 to 4 days prior to talimogene laherparepvec administration) and day 8 (± 2 days)
  - cycle 4 day 1 (within 3 to 4 days prior to talimogene laherparepvec administration)
  - cycle 5 day 1 (within 3-4 days of talimogene laherparepvec administration) and all subsequent cycles until end of treatment (except cycle 25 and cycle 50): day 1 of each cycle (within 3 days prior to talimogene laherparepvec administration).
  - cycle 25 and cycle 50 (approximately 1 year and 2 years after start of treatment): day 1 (prior to talimogene laherparepvec administration) and day 8 (± 2 days)
  - At each of the above swab collection timepoints, initially, a qPCR analysis will be performed on the swab sample to evaluate whether the talimogene laherparepvec DNA is detectable in the sample:
    - If result of the qPCR testing is negative, TCID50 assay testing is not required.
    - If the result of the qPCR testing is positive, then a TCID50 assay will be performed on the swab sample to measure viral infectivity.
- Swab of cold sore, 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.
- Blood sample for HSV antibody serostatus:
  - day 1 (within 3 days prior to talimogene laherparepvec administration) and day 15 (± 3 days) of cycle 1 for determination of both herpes simplex virus type 1/type (HSV-1/2) immunoglobulin G (IgG) and immunoglobulin M (IgM) antibody serostatus
  - day 1 of cycle 2 (within 3 days prior to talimogene laherparepvec administration) for determination of both HSV-1/2 IgG and IgM antibody serostatus

  - day 1 of cycle 3 and cycle 4, then every other cycle until end of treatment (within 3 days prior to talimogene laherparepvec administration) for determination of HSV-1 IgG antibody serostatus only
- Blood samples for biomarker analysis:
  - day 1 of cycle 1 and cycle 2
- Tumor biopsy from at least one injected lesion and/or one uninjected lesion within 3 days prior to talimogene laherparepvec administration at day 1 of cycle 1 and day 1 of cycle 3. Tumor biopsy will be collected from subjects enrolled at limited number of sites. The tumor biopsy samples will be used to study the relationship between the immune response induced by talimogene laherparepvec and clinical response or resistance to talimogene laherparepvec. The immune and cancer cells in the biopsy may be analyzed to identify RNA transcripts and/or proteins whose levels change with treatment, to evaluate changes in the number and/or type of immune cells infiltrating the tumor during treatment, and to assess tumor specific mutations or epigenetic changes. Refer to Laboratory Manual for tumor biopsy procedures.

- Archived tumor tissue for $BRAF^{V600}$ mutation testing and biomarker analyses:
  - $BRAF^{V600}$ mutation testing for may be obtained in a number of ways as listed below:
    - Previously Known $BRAF^{V600}$ Tumor Status: $BRAF^{V600}$ tumor status result, obtained prior to screening for this study, from a local laboratory will be acceptable. The local laboratory report supporting the local $BRAF^{V600}$ tumor testing result should be available at the site within 28 days after enrollment.
    - Previously Unknown $BRAF^{V600}$ 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 during within 28 days after enrollment.
- 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.
- Clinical tumor assessments must include clinical measurement of cutaneous, subcutaneous, or nodal tumor measurement by caliper to be performed independent of treatment cycle at week 12 (± 7 days), week 24 (± 7 days), and then at least every 3 months (± 15 days) until clinically relevant disease progression per modified WHO response criteria (Appendix D) **beyond 6 months of treatment** or end of treatment for other reasons, whichever occurs first.
- Radiographic tumor imaging assessments 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. Imaging to be performed independent of treatment cycle at week 12 (± 7 days), week 24 (± 7 days), and then at least every 3 months (± 15 days) until clinically relevant disease progression per modified WHO response criteria (Appendix D) **beyond 6 months of treatment** or end of treatment for other reasons, whichever occurs first.

- Tumor response will be assessed using the modified WHO response criteria (Appendix D) at week 12 (± 7 days), week 24 (± 7 days), and then at least every 3 months (± 15 days) until clinically relevant disease progression per modified WHO criteria (Appendix D) **beyond 6 months of treatment** or end of treatment for other reasons, whichever occurs first.
- 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.
- Administration of talimogene laherparepvec treatment at day 1 of each cycle. (refer to Section 6.2.1.1 for dosage, administration, and schedule)

7.2.3 Safety Follow-up

7.2.3.1 30-Day Safety Follow-up Visit

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

- Physical examination as per standard of care
- Vital signs (systolic/diastolic blood pressure, heart rate, temperature). Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign CRF. Record all measurements on the vital signs CRF. The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs CRF.
- Determination of ECOG performance status (see Appendix E)
- Local laboratory assessments:
  - Hematology panel: hemoglobin, hematocrit, WBC with 5-part differential (3-part differential if 5-part unable to be performed), RBC, platelet
  - 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:
  - Blood and urine samples for qPCR analysis
  - Swabs of the surface of up to 3 most recently injected lesion(s) for qPCR and TCID50 assay testing (if a lesion is in CR, the place of the **prior** injection will be swabbed):
    - Initially, a qPCR analysis will be performed on the swab to evaluate whether the talimogene laherparepvec DNA is detectable on the surface of the injected lesion:

- If result of the qPCR testing is negative, TCID50 assay testing is not required.
- If the result of the qPCR testing is positive, then a TCID50 assay will be performed on the swab to measure viral infectivity.

- Swabs of oral mucosa and anogenital area for qPCR and TCID50 assay testing.
  - Initially, a qPCR analysis will be performed on the swab to evaluate whether the talimogene laherparepvec DNA is detectable on the surface of the injected lesion:
    - If result of the qPCR testing is negative, TCID50 assay testing is not required.
    - If the result of the qPCR testing is positive, then a TCID50 assay will be performed on the swab to measure viral infectivity.
- Note: collection of swabs from the anogenital area is optional for subjects enrolled into the study prior to the investigator obtaining IRB approval of amendment 1. Collection of swabs from the anogenital area for subjects injected any time during the study into a melanoma lesion above the waist, ie above the line that connects the tops of left and right iliac crests is optional for subjects enrolled into the study prior to the investigator obtaining IRB approval of amendment 2.
- Swabs of cold sore, vesicles and other lesions suspected to be herpetic in origin (if any) for qPCR:
  - 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 antibody serostatus
  - Determination of HSV-1 IgG antibody serostatus only.

- Recording of adverse event
- 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

7.2.3.2 Procedures Between 30-Day and 60-Day Safety Follow-up Visits

- **Central laboratory assessments:**

  The following samples will be collected daily by the subject at home between 30 (+7) days and 60 (+7) days after the last dose of talimogene laherparepvec starting approximately 1 day after the 30-day safety follow-up visit:

  - Swabs of oral mucosa and anogenital area for qPCR testing:
    - Samples will be collected daily at home by the subject starting 1 day after the 30-day safety follow-up visit (+7 days) until 1 day before the 60-day safety follow-up visit (+7 days). Please refer to the Central Laboratory Manual for instructions regarding sample collection, storage, and shipment procedures.

- Note: collection of swabs from anogenital area is optional for subjects enrolled into the study prior to the investigator obtaining IRB approval of amendment 1. Collection of swabs from the anogenital area for subjects injected any time during the study into a melanoma lesion above the waist, ie above the line that connects the tops of left and right iliac crests is optional for subjects enrolled into the study prior to the investigator obtaining IRB approval of amendment 2.

Once per week, the following samples will collected by a trained healthcare staff person at the subject's home between 30 (+7) days and 60 (+7) days after the last dose of talimogene laherparepvec starting approximately 7 days after the 30-day safety follow-up visit:

- Swabs of the surface of up to 3 most recently injected lesion(s) for qPCR (if a lesion is in CR, the place of the prior injection will be swabbed):

- 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 associated with serious adverse events.

7.2.3.3 60-Day Safety Follow-up Visit

The following procedures will be performed approximately 60 (+7) days after the last dose of talimogene laherparepvec:

- Central laboratory assessments:
  - Swabs from of the surface of up to 3 most recently injected lesion(s) for qPCR (if a lesion is in CR, the place of the prior injection will be swabbed):
  - Swabs of oral mucosa and anogenital area for qPCR
    - Note: collection of swabs from anogenital area is optional for subjects enrolled into the study prior to the investigator obtaining IRB approval of amendment 1. Collection of swabs from the anogenital area for subjects injected any time during the study into a melanoma lesion above the waist, ie above the line that connects the tops of left and right iliac crests is optional for subjects enrolled into the study prior to the investigator obtaining IRB approval of amendment 2.
  - Swabs of cold sore, vesicles and other lesions suspected to be herpetic in origin (if any) for qPCR:
    - 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.
- 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 associated with serious adverse events.

7.2.4 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 DNA in a subject's household member, caregiver, or healthcare provider as specified Section 9.4.

7.2.5 Long-term Follow-up

All subjects who permanently discontinue study for any reason other than death or withdrawal of full consent and who provide consent must be followed for survival under an ongoing separate registry protocol that is in place for the long-term follow-up of subjects treated with talimogene laherparepvec in clinical trials **(Study 20120139)**. The registry protocol will also monitor for late and long-term adverse events thought to be potentially related to talimogene laherparepvec **and anti-cancer therapy for melanoma**.

7.3 Biomarker Development

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

Amgen will attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to talimogene laherparepvec. Several such tests will be applied to both tumor and blood samples in order to identify markers that associate with clinical benefit of talimogene laherparepvec treatment. Examples of such tests include analyzing archival tumor samples to identify differences in the number, type, or activation state of immune cells within the tumors prior to treatment that correlate with later clinical response. 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.

Blood samples (both cells and plasma) will be analyzed for changes in the immune system before and during treatment that correlate with clinical response. Examples include measuring antibody responses to melanoma antigens, functional T cell

responses to melanoma antigens, and the number, type and activation state of immune regulatory cells.

On study biopsies will be collected to characterize the mechanism of action of talimogene laherparepvec. These samples of both injected and uninjected lesions are critical for identifying the changes in infiltrating immune cells that occur following talimogene laherparepvec treatment that are responsible for clinical benefit.

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, Section 7.1) and as described in Sections 7.2.1 and 7.2.2.

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 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, Section 7.1) and the Screening Procedures (Section 7.2.1).

The tumor block is to be carefully selected by a pathologist or a skilled experienced histology associate to include generous tumor tissue using the Pathology Report as a guide. In lieu of a block, approximately 20 unstained sections on charged slides from the same block can be submitted. Refer to Laboratory Manual for tumor specific instructions on slide preparation. Analyses of tumor specific mutations or epigenetic changes may be performed (eg, somatic mutations) on tumor tissues.

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 therapy 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, urine, or tumor samples collected according to the Schedule of Assessments (Table 2, Section 7.1) 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 benefit the subject directly or to alter the treatment course, the results of biodistribution of talimogene laherparepvec in the blood and urine, shedding of talimogene laherparepvec from oral mucosa and in swab from the anogenital area, HSV antibody serostatus, pharmacogenetic, 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, urine, 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 (eg, 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 or protocol-required procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product 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 (eg, in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records).

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapy 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 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) 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 protocol-required investigational product or procedural assessments include any of the following:

- subject request
- safety concern (eg, due to an adverse event)
- ineligibility determined requiring treatment discontinuation
- protocol deviation requiring treatment discontinuation
- non-compliance
- requirement for alternative therapy
- pregnancy
- death
- lost to follow-up
- decision by sponsor (other than subject request, safety concern, lost to follow-up)
- clinically relevant disease progression per modified WHO response criteria (Appendix C),
- other protocol-specified criteria (See Section 6.2.1.2)

8.3.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are as follows:

- 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 (eg, 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 (eg, 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 and required end of study assessments.

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 (eg, overnight stay).

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a 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 first dose of talimogene laherparepvec through 30 (+7) days after the last dose of talimogene laherparepvec) are reported using the applicable CRF (eg, Adverse Event Summary).

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 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 the 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 talimogene laherparepvec?

The investigator must assess whether the adverse event is possibly related to any study-mandated activity (eg, administration of investigational product, and/or procedure [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 (eg, administration of investigational product, 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.

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 60 (+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 CRF.

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

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 in compliance with all reporting requirements according to local regulations and Good Clinical Practice (GCP).

The investigator is to notify the appropriate IRB 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 talimogene laherparepvec 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's 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).

If a lactation case occurs while the female subject is taking talimogene laherparepvec report the lactation case to Amgen as specified below.

In addition to reporting a lactation case during the study, investigators should **report** 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's **Global Patient Safety** within 24 hours of the investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix C).

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 60 (+7) days after the last dose of talimogene laherparepvec.

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

Prevalence of detectable talimogene laherparepvec DNA: Proportions of subjects with detectable talimogene laherparepvec DNA in the blood and urine any time after the administration of talimogene laherparepvec within the first 3 cycles.

10.1.1.2 Secondary Endpoints

- Incidence of clearance of talimogene laherparepvec DNA: Incidence of clearing talimogene laherparepvec DNA from the blood and urine after receiving talimogene laherparepvec.
- Rate of talimogene laherparepvec DNA detection and viral detection on the exterior of the occlusive dressing during treatment: Defined for each subject who has occlusive dressing swab sample, the proportion of testing samples exhibiting

detection of talimogene laherparepvec DNA and detection of talimogene laherparepvec virus from the exterior of the occlusive dressing swabs out of total number of samples collected.

- Subject incidence of talimogene laherparepvec DNA and viral detection on the exterior of the occlusive dressing during treatment: Defined as among subjects who have provided samples, the proportion of subjects having detectable talimogene laherparepvec DNA and that for detectable talimogene laherparepvec virus on the exterior of the occlusive dressing.
- Rate of talimogene laherparepvec DNA detection and viral detection from the surface of injected lesions during treatment: Defined for each subject who has injected lesion swab sample, the proportion of testing samples exhibiting detection of talimogene laherparepvec DNA and detection of talimogene laherparepvec virus from the injected lesion swabs out of total number of samples collected.
- Subject incidence of talimogene laherparepvec DNA and viral detection from the surface of injected lesions during treatment: Defined as among subjects who have provided samples, the proportion of subjects having detectable talimogene laherparepvec DNA and that for detectable talimogene laherparepvec virus in the injected lesions.
- Rate of talimogene laherparepvec DNA detection and viral detection in oral mucosa swabs during treatment: Defined for each subject who has oral mucosa swab sample during treatment, the proportion of testing samples exhibiting detection of talimogene laherparepvec DNA and detection of talimogene laherparepvec virus from the oral mucosa swabs out of total number of samples collected during treatment.
- Subject incidence of talimogene laherparepvec DNA detection and viral detection in oral mucosa swabs during treatment: Defined as among subjects who have provided samples, the proportion of subjects having detectable talimogene laherparepvec DNA and that for detectable talimogene laherparepvec virus in oral mucosa swabs during treatment.
- Rate of talimogene laherparepvec DNA detection and viral detection in anogenital swabs from the anogenital area during treatment: Defined for each subject who has anogenital swab sample during treatment, the proportion of testing samples exhibiting detection of talimogene laherparepvec DNA and detection of talimogene laherparepvec virus from the anogenital swabs from the anogenital area out of total number of samples collected.
- Subject incidence of talimogene laherparepvec DNA and viral detection in anogenital swabs from the anogenital area during treatment: Defined as among subjects who have provided samples, the proportion of subjects having detectable talimogene laherparepvec DNA and that for detectable talimogene laherparepvec virus in anogenital swabs from the anogenital area during treatment.
- Rate of talimogene laherparepvec DNA detection in oral mucosa swabs after **the** end of treatment: Defined for each subject who has oral mucosa swab sample collected after end of treatment, the proportion of testing samples exhibiting detection of talimogene laherparepvec DNA from the oral mucosa swabs out of total number of samples collected.
- Subject incidence of talimogene laherparepvec DNA and viral detection in oral mucosa after the end of treatment: Defined as among subjects who have provided samples, the proportion of subjects having detectable talimogene laherparepvec

DNA and that for detectable talimogene laherparepvec virus in oral mucosa swabs after end of treatment.

- Rate of talimogene laherparepvec DNA detection and viral detection in anogenital swabs from the anogenital area after the end of treatment: Defined for each subject who has anogenital swab sample collected after end of treatment, the proportion of testing samples exhibiting detection of talimogene laherparepvec DNA from the anogenital swabs from the anogenital area out of total number of samples collected.
- Subject incidence of talimogene laherparepvec DNA and viral detection in anogenital swabs from the anogenital area after the end of treatment: Defined as among subjects who have provided samples, the proportion of subjects having detectable talimogene laherparepvec DNA and that for detectable talimogene laherparepvec virus in anogenital swabs from the anogenital area after end the of treatment.
- Incidence of talimogene laherparepvec DNA detection in lesions suspected to be herpetic in origin: Incidence of detection of talimogene laherparepvec DNA in lesions suspected to be herpetic in origin out of all swab samples collected from these lesions.
- Best overall response rate (BORR): Best overall response of complete response (CR), PR, SD, and progressive disease (PD) per modified WHO response criteria after subjects receiving protocol specified therapy. CR and PR do not require a confirmation.
- Objective response rate (ORR): Complete response (CR) or partial response (PR) rate per modified WHO criteria where CR and PR do not require a subsequent confirmation.
- Duration of response (DOR): (calculated only for those subjects with an objective response) time from first objective response (CR or PR) to disease progression per the modified WHO criteria or death, whichever occurs earlier.
- Durable response rate (DRR): defined as CR or PR for a duration of 6 months or longer.
- 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, and clinically significant laboratory changes.

10.1.1.3 Exploratory Endpoints

- Identification of potential blood and tumor biomarkers (eg, proteins and RNA transcripts), which predict clinical outcomes to talimogene laherparepvec
- Correlation between infiltrating immune cells in fresh tumor biopsy samples induced by talimogene laherparepvec and clinical response or resistance to talimogene laherparepvec

10.1.2 Analysis Sets

Blood/Urine Evaluable Analysis Set: Subjects who are enrolled, receive at least one dose of talimogene laherparepvec, and have at least one post dose blood and/or urine sample collected. The analysis set is used for examining biodistribution of talimogene laherparepvec.

Blood/Urine Clearance Analysis Set: Subjects who are enrolled, receive at least one dose of talimogene laherparepvec, and have at least 2 post dose blood and/or urine samples collected within the same dosing cycle. In addition, subjects included in the Blood/Urine Clearance Set must have at least 1 positive talimogene laherparepvec DNA sample and at least 1 subsequent sample at any time during the cycle (including the sample collected prior to the next dose of investigational product, if applicable) in order to evaluate clearance of a positive result. A subject will be defined as having cleared talimogene laherparepvec if a negative blood and/or urine sample is obtained following a prior positive test and if there are no subsequent positive tests. The Blood/Urine Clearance Analysis Set will be also used to determine the clearance of talimogene laherparepvec DNA in the blood and urine over time.

Exterior of Occlusive Dressing Evaluable Analysis Set: Subjects who are enrolled, receive at least one dose of talimogene laherparepvec, and have at least one swab collected from the exterior of the occlusive dressing. This analysis set is used to examine the detection of talimogene laherparepvec DNA and virus in the exterior of the occlusive dressing.

Injected Lesion Evaluable Analysis Set: Subjects who are enrolled, receive at least one dose of talimogene laherparepvec, and have at least one injected lesion swab collected. This analysis set is used to examine the detection of talimogene laherparepvec DNA and virus from the surface of injected lesions.

Oral Mucosa Evaluable Analysis Set: Subjects who are enrolled, receive at least one dose of talimogene laherparepvec, and have at least one oral mucosa swab collected during treatment. This analysis set is used to examine the detection of talimogene laherparepvec DNA and virus in the oral mucosa during treatment.

Swab from The Anogenital Area Evaluable Analysis Set: Subjects who are enrolled, received at least one dose of talimogene laherparepvec, and have at least 1 swab from the anogenital area collected during treatment. This analysis set is used to examine the detection of talimogene laherparepvec DNA and virus in the swab from the anogenital area during treatment.

Post Treatment Oral Mucosa Evaluable Analysis Set: Subjects who are enrolled, receive at least one dose of talimogene laherparepvec, and have at least one oral mucosa swab collected after end of treatment. This analysis set is used to examine the

detection of talimogene laherparepvec DNA and virus in the oral mucosa after end of treatment.

Post Treatment Swab From the Anogenital Area Evaluable Analysis Set: Subjects who are enrolled, receive at least one dose of talimogene laherparepvec, and have at least one swab from the anogenital area collected after end of treatment. This analysis set is used to examine the detection of talimogene laherparepvec DNA and virus in the anogenital swab after end of treatment.

Suspicious Lesion Swab Analysis Set: Subjects who are enrolled, receive at least one dose of talimogene laherparepvec, and have at least one swab sample collected from lesions suspicious to be herpetic in origin during the study. This analysis set is used to examine the detection of talimogene laherparepvec DNA in lesions suspicious to be herpetic in origin.

Safety Analysis Set: Subjects who are enrolled and receive at least one dose of talimogene laherparepvec will be included in the Safety Analysis Set. The Safety Analysis Set will be used for analyzing BORR, ORR, and safety endpoints such as clinically significant laboratory changes or adverse events.

10.1.3 Covariates and Subgroups

The following covariates may be used to examine the biodistribution and shedding of talimogene laherparepvec in subgroup analyses:

- age at enrollment (< 50, ≥ 50; < 65, ≥ 65; < 75, ≥ 75)
- sex (female, male)
- disease stages (stage IIIB and stage IIIC, stage IVM1a, stage IVM1b and stage IVM1c)
- baseline HSV serostatus (seropositive, seronegative)

10.2 Sample Size Considerations

This is an estimation study. The primary endpoint is the incidence of subjects exhibiting talimogene laherparepvec DNA in the blood and urine, respectively.

The **expected** exact 95% CIs of the binomial proportion **given 50** subjects **for** true incidence rate**s from 40% to 95%** are provided in Table 4.

Table 4. Expected 95% Exact Confidence Intervals by Proportion of Detectable Talimogene Laherparepvec DNA in Blood and Urine During the First 3 Treatment Cycles From a Sample Size of 50 Subjects

Proportion (p)	Expected 95% Exact Confidence Interval
40%	**(27%, 55%)**
45%	**(31%, 60%)**
50%	**(36%, 64%)**
55%	**(40%, 69%)**
60%	**(45%, 73%)**
65%	**(50%, 78%)**
70%	**(56%, 82%)**
75%	**(61%, 86%)**
80%	**(66%, 90%)**
85%	**(72%, 93%)**
90%	**(78%, 96%)**
95%	**(85%, 99%)**

p = proportion of subjects exhibiting detectable talimogene laherparepvec DNA

Given a sample size of **50** subjects, the probability of observing at least 1 subject with an event of detectable talimogene laherparepvec DNA in the sample ranges from **0.72** to **1.00** with a true event probability (p_a) ranges from 0.025 to 0.15 (Table 5).

Table 5. Probability of Observing at Least 1 Subject With an Event With a True Event Probability (p_a) by Sample Size

	Sample Size					
p_a	**60**	**55**	**50**	**40**	**30**	**20**
0.025	**0.78**	**0.75**	**0.72**	**0.64**	**0.53**	**0.40**
0.050	**0.95**	**0.94**	**0.92**	**0.87**	**0.79**	**0.64**
0.075	**0.99**	**0.99**	**0.98**	**0.96**	**0.90**	**0.79**
0.100	**1.00**	**1.00**	**0.99**	**0.99**	**0.96**	**0.88**
0.125	**1.00**	**1.00**	**1.00**	**0.99**	**0.98**	**0.93**
0.150	**1.00**	**1.00**	**1.00**	**1.00**	**0.99**	**0.96**

In addition, Table 6 provides **the expected 95% CIs of the binomial proportion** of subjects with shedding event(s) **for true incidence rates from 0% to 15% for sample sizes from 20 to 60:**

Table 6. Expected 95% Exact Confidence Intervals by Proportion of Detectable Talimogene Laherparepvec DNA in Swabs by Sample Size

	Sample Size					
p_a	60	55	50	40	30	20
0	(0.00, 0.06)	(0.00, 0.06)	(0.00, 0.07)	(0.00, 0.09)	(0.00, 0.12)	(0,00,0.17)
0.025	(<0.01, 0.10)	(<0.01, 0.11)	(<0.01, 0.11)	(<0.01, 0.13)	(<0.01, 0.16)	(<0.01, 0.21)
0.050	(0.01, 0.14)	(0.01, 0.14)	(0.01,0.15)	(0.01, 0.17)	(0.01, 0.19)	(0.01, 0.24)
0.075	(0.03, 0.17)	(0.02, 0.18)	(0.02, 0.18)	(0.02, 0.20)	(0.02, 0.23)	(0.01, 0.28)
0.100	(0.04, 0.20)	(0.04, 0.21)	(0.04, 0.22)	(0.03, 0.23)	(0.03, 0.26)	(0.02, 0.31)
0.125	(0.06, 0.23)	(0.05, 0.24)	(0.05, 0.25)	(0.04, 0.27)	(0.04, 0.29)	(0.03, 0.34)
0.150	(0.07, 0.26)	(0.07, 0.27)	(0.07, 0.28)	(0.06, 0.30)	(0.05, 0.32)	(0.04, 0.37)

The final number of subjects in the study will depend on enrollment of a minimal number of approximately 20 subjects evaluable for the estimation of detection of talimogene laherparepvec DNA in any analysis of on treatment set of swabs as specified in Section 10.1.2. Since analysis of swabs of anogenital area for subjects injected below the waistline was introduced in the protocol amendment 1 when approximately 10 subjects were estimated to be enrolled, the minimal number of subjects to be enrolled in the study is approximately 50, taking into consideration a 50% probability that newly enrolled subjects will have an injected lesion below the waistline. The sample size may be increased to a maximum of approximately 60 subjects to allow enrollment of approximately 20 subjects evaluable for the estimation of detection of talimogene laherparepvec DNA in the analysis set of swabs from the anogenital area and to account for possible incomplete collection of anogenital swab data in approximately 10 subjects.

10.3 Planned Analyses

10.3.1 Interim Analyses

No efficacy or safety interim analysis or stopping rules are planned for this study. However, ad hoc analyses may be conducted before the planned primary analysis if interim data is required for submission to regulatory authorities.

10.3.2 Primary Analysis

The primary analysis will be triggered once all enrolled subjects have had a chance to complete their **cycle 4 day 1 blood and urine** sample collection for the qPCR assay. A clinical study report (CSR) will be written based on the results of the primary analysis.

10.3.3 Final Analysis

A final analysis will be performed after all enrolled subjects have had a chance to complete their 60-day safety follow up visit. The CSR will be amended to include updated primary and key secondary endpoints, and safety data at the study conclusion. The exploratory endpoint of describing factors contributing to the detection of talimogene laherparepvec DNA may be included in the CSR amendment. However, exploratory biomarker analyses other than HSV serostatus will be included in a separate biomarker report.

10.4 Planned Methods of Analysis

10.4.1 General Considerations

In principle, mean, standard deviation, median, first and third quartiles, minimum and maximum will be calculated for continuous variables; frequency and percent will be calculated for binary and categorical variables. Analyses of the efficacy and safety endpoints will be based on the Safety Analysis Set unless otherwise specified.

10.4.2 Primary Endpoint

The primary endpoint is the prevalence of subjects with detectable talimogene laherparepvec DNA per qPCR in the blood and urine any time after the administration of talimogene laherparepvec within the first 3 cycles The analysis of the primary endpoint will be based on the Blood/Urine Evaluable Analysis Set. Proportions of subjects at each time point that meets the criteria of detectable DNA will be calculated. The point-wise exact 95% CIs for binomial proportions using the F-distribution (Leemis and Trivedi, et al, 1996) from SAS® PROC FREQ procedure with the Binomial option will also be calculated. Analysis of the primary endpoint will be based on available cases. That is, subjects who do not have blood and urine sample collected at the respective time points will be excluded from the analysis for that time point.

10.4.3 Secondary Endpoint(s)

Incidence of clearance of talimogene laherparepvec DNA:

The proportion of subjects with undetectable talimogene laherparepvec DNA per qPCR at cycles 1, 2, and 3 following a positive qPCR testing in each cycle will be presented. The exact 95% CI for the binomial proportions using F-distributions will be calculated. Analysis of clearance of talimogene laherparepvec will include subjects in the Blood/Urine Clearance Analysis Set.

Incidence of clearance at day 8 of cycles 1, 2, and 3 will be repeated for subjects with HSV seropositive and –seronegative at baseline. The difference in clearance rate at day 8 for cycles 1, 2, and 3 will be provided. The corresponding 95% CI will be based on the Wilson's score method with continuity correction (Newcombe, 1998).

Subject incidence of talimogene laherparepvec DNA detection and viral detection on the exterior of occlusive dressing:

The overall and by time points proportions of subjects with positive qPCR testing results in the swab from the exterior of occlusive dressing will be calculated. The exact 95% CIs will also be calculated using the F-distribution. Analysis of this endpoint will be based on the Exterior of Occlusive Dressing Evaluable Analysis Set.

Rate of talimogene laherparepvec DNA detection and viral detection on the exterior of occlusive dressing:

Summary statistics will be presented. A similar analysis will be performed for detectable talimogene laherparepvec virus in exterior of occlusive dressing per TCID50 assay. Analysis of this endpoint will be based on the Exterior of Occlusive Dressing Evaluable Analysis Set.

Subject incidence of talimogene laherparepvec DNA detection and viral detection from the surface of injected lesions and all subject incidence endpoints pertaining to DNA and viral detection in various swab samples:

Analysis will be similar to that described for the endpoint of subject incidence of talimogene laherparepvec DNA detection and viral detection on the exterior of occlusive dressing using the respective analysis set.

Rate of talimogene laherparepvec DNA detection and viral detection from the surface of injected lesions and all rate endpoints pertaining to DNA and viral detection in various swab samples:

Analysis will be similar to that described for the endpoint of rate of talimogene laherparepvec DNA and viral detection on the exterior of occlusive dressing using the respective analysis set.

Incidence of talimogene laherparepvec DNA detection in lesions suspected to be herpetic in origin:

The number of detectable talimogene laherparepvec DNA per qPCR in swabs collected from lesions suspected to be herpetic in origin divided by all specimens collected from

lesions will be calculated. To qualify for the numerator and the denominator, only new lesions or a recurrence of a lesion that has clinically resolved will be included. The exact 95% CI of the event incidence will be calculated based on the F-distribution. Analysis of rate of talimogene laherparepvec DNA detection in lesions suspected to herpetic in origin will be based on the Suspicious Lesion Swab Analysis Set.

Best overall response rate (BORR):

Best overall tumor response per modified WHO response criteria over the duration of study will be presented. The response categories include CR, PR, SD, and PD where CR and PR do not require a confirmation and SD must be at least for 12 weeks. Subjects with no tumor evaluation after initiating their study therapy will be categorized in the "missing" category. Response (CR or PR) observed postsurgical resections or subsequent anticancer therapies will be censored at the time of tumor resection or initiation of a subsequent anticancer therapy. Analysis of BORR will be based on the Safety Analysis Set.

Objective response rate (ORR) and Durable response rate (DRR):

ORR and DRR will be analyzed as a binary variable. The exact 95% CI of the ORR will be calculated based on the F-distribution. Analysis of ORR will be based on the Safety Analysis Set.

Duration of response (DOR):

DOR will be analyzed using the Kaplan-Meier method and will be analyzed for responders only. Subjects who have not ended their response will be censored at the last tumor assessment.

10.4.4 Safety Endpoints

Adverse events will be coded with the most recent version of Medical Dictionary for Regulatory Activities and will be grouped by system organ class and preferred term within system organ class. Event severity will be graded using CTCAE version 3. Subject incidence rates of treatment-emergent and treatment-related adverse events (including all adverse events, grade ≥ 3 adverse events, serious adverse events, fatal adverse events, adverse events of interest as detailed in a separate document, and adverse events requiring permanent discontinuation of study drug) after initiation of the study therapy through 30-day safety follow-up visit will be summarized. In addition, subject incidence rates of serious adverse events from the 30-day safety follow-up visit

through the 60-day safety follow-up visit will be summarized. Clinically significant laboratory changes will be summarized with descriptive statistics.

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

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 subject 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

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IRB 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 for all subsequent protocol amendments and changes to the informed consent document. The investigator is to notify the IRB 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 approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB 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) GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB 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 CSR 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 must be informed of all amendments and give approval. The investigator **must** send a copy of the approval letter from the IRB 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 in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen investigational product by an extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen investigational product(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 CRFs will be included on the Amgen Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical

and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

In this study, the ETO system captures the following data points and these are considered source data: patient identification.

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

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

Elements to include the following:

- subject files containing completed CRFs, 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 and Amgen
- investigational product-related correspondence including Proof of Receipts, Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), and Final Investigational Product Reconciliation Statement, as applicable.

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

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

12.3 Study Monitoring and Data Collection

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

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

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

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

Data capture for this study is planned to be electronic:

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

Amgen (or designee) will perform self-evident corrections to obvious data errors in the clinical trial database, as documented in the Study Specific Self Evident Corrections Plan. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (eg, same results sent twice with the same date with different 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, 2010), which states the following:

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

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

12.7 Compensation

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

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14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

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

Appendix B. Sample Serious Adverse Event Report 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.

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 (eg, 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 if:
- 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, designee must be identified on the Delegation of Authority form.*

FORM-056006 eSAE Contingency Reporting Form *Version 3.0 Effective Date 04-Feb-2013*

Page 1 of 2

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 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 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 6). 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.*

AMGEN **Study # 20120324** Talimogene Laherparepvec	**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 (eg, 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/complete all that apply):**

☐ An event that applies to a specialty CRF page titled _____ (eg, 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 (eg, Rave) has either not begun or has ended for this study. I am submitting (check all that apply):**

☐ Screening event (as defined by the protocol)
- ☐ This is a new event report
- ☐ This is follow-up information for a previously reported event

OR

☐ Event after access to the EDC system (eg, 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*

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

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Date of Birth Day Month Year	Sex ☐F ☐M	Race	If applicable, provide End of Study date

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

3. 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 **If diagnosis is unknown, enter Signs / Symptoms** **When Final Diagnosis is known, enter as Adverse Event** *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	Check only if event occurred before first dose of IP	**Enter Serious Criteria code** *(see codes below)*	**Relationship** Is there a reasonable possibility that the event may have been caused by IP?		**Relationship** Is there a reasonable possibility that the event may have been caused by an Amgen device?			**Outcome of Event** Resolved Not resolved Fatal Unknown	Check only if event is related to study procedure eg, biopsy
					No✓	Yes✓	No✓	Yes✓	If yes, what device?		

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

If you temporarily cannot access the EDC system (eg, Rave), sign below and submit ONLY this page to the number noted in the header above Section 1.

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 *Version 3.0 Effective Date 04-FEB-2013*

Page 1 of 3

AMGEN Study # 20120324 Talimogene Laherparepvec	**Electronic Serious Adverse Event (eSAE) Contingency Reporting Form** **For Restricted Use**

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

Site Number	Subject ID Number

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

Date Admitted Day Month Year	Date Discharged Day Month Year

5. Was IP administered prior to this event? ☐No ☐Yes, If yes, please complete all of Section 5

IMP: _____ ☐ (✓) Blinded ☐ (✓) Open Label	Initial Start Date Day Month Year	Prior to, or at time of Event Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld

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

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

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

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

Date Day Month Year	Test Unit											

AMGEN Study # 20120324 Talimogene Laherparepvec	**Electronic Serious Adverse Event (eSAE) Contingency Reporting Form** **For Restricted Use**

Site Number | Subject ID Number

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

Date (Day Month Year)	Additional Tests	Results	Units

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

Signature of Investigator or Designee -	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

US: +888 814 8653

1. Case Administrative Information

Protocol/Study Number: 20120324

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

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (_____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject DOB:** mm_____ / dd_____/ yyyy_____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

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

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

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

5. Pregnancy Information

Pregnant female's LMP mm_____ / dd_____/ yyyy_____ ☐ Unknown

Estimated date of delivery mm_____ / dd_____/ yyyy_____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm_____ / dd_____/ yyyy_____

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

If yes, provide date of delivery: mm _____/ dd_____/ yyyy_____

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

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

Effective Date: March 27, 2011 Page 1 of 1

AMGEN® Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX# US: +888 814 8653

1. Case Administrative Information

Protocol/Study Number: 20120324

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

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (_____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Date of Birth:** mm_____ / dd_____/ yyyy_____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

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

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

****

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

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

Appendix 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 can be accurately measured in at least 2 dimensions the longest diameter of which is ≥ 10 mm as assessed using calipers (eg, superficial cutaneous melanoma lesion). (Note: When a lesion can be evaluated by both, clinical examination and imaging, radiographic imaging evaluations should be **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 scan is based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be the greater of either at least 10 mm or twice the slice thickness. MRI is acceptable to assess disease extent if used 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 to 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.

Measureable 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 tumors longest diameter and the diameter perpendicular to that.

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

Definitions of Measurable and Nonmeasurable:

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 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 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 "Index Lesions":

All baseline evaluations should be performed as close as to the 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 individually 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 1, Table 2, and Table 3.

Table 1. Definition of Index Lesion Tumor Response Including New Lesions

Complete Response (CR):	Complete disappearance of all both 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.
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 tumors have appeared, the sum of products of the perpendicular diameters of these must have reduced by 50% or more from when first documented.
Disease Progression (PD):	A > 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. **There are 2 types of PD defined in this protocol:** **Non-clinically relevant disease progression (PDn):** 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 will be allowed to continue study treatment. **Clinically relevant disease progression (PDr):** 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.
Stable Disease (SD):	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.
Unable to Evaluate (UE):	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.
Not Done (ND)	Radiographic image or clinical measurement were not performed at this time point to evaluate the index lesions

Table 2. Definition of Nonindex Lesion Tumor Response

Complete Response (CR):	Disappearance of all nonindex lesions.
Incomplete Response/Stable Disease (SD):	Persistence of one or more nonindex lesions.
Disease Progression (PD):	Unequivocal appearance of one or more nonindex lesions. There are 2 types of PD defined in this protocol: Nonclinically relevant disease progression (PDn): 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. Clinically relevant disease progression (PDr): 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.
Unable to Evaluate (UE):	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.
Not Applicable (NA)	No nonindex lesions were identified at baseline.
Not Done (ND)	Radiographic image or clinical measurement were not performed at this time point to evaluate the nonindex lesions.

Table 3. Matrix for Determining the Overall Response at Each Assessment Point

Index Lesion Response Including New Lesions	Nonindex Lesion Response	Overall Response
CR	CR	CR
	SD	PR
	PDn	PDn
	PDr	PDr
	NA	CR
	UE/ND	UE
PR	CR/SD	PR
	PDn	PDn
	PDr	PDr
	NA	PR
	UE/ND	UE
SD	CR	SD
	SD	SD
	PDn	PDn
	PDr	PDr
	NA	SD
	UE/ND	UE
PDn	CR/SD/PDn/NA/UE/ND	PDn
	PDr	PDr
PDr	Any	PDr
UE/ND	CR/SD/ NA/UE/ND	UE
	PDn	PDn
	PDr	PDr

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 relevant 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

Grade	Description
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, ie, light housework or office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about > 50% of waking hours.
3	Capable of only limited self-care, confined to a bed or chair > 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Amendment 3

Protocol Title: A Phase 2, Multicenter, Single-arm Trial to Evaluate the Biodistribution and Shedding of Talimogene Laherparepvec in Subjects With Unresected, Stage IIIB to IVM1c Melanoma

Amgen Protocol Number (Talimogene Laherparepvec) 20120324

Amendment 3 Date: 18 August 2015

Rationale:

This document provides the rationale and detailed list of changes for Amendment 3, dated 18 August 2015, from protocol amendment 2, dated 06 April 2015.

The purpose of the amendment is to:

- Provide additional explanation for increasing number of subjects to approximately 50-60
- Correct the timing of the primary analysis
- Provide additional guidance on measurements of splitting, coalescing lesions and lesions that in aggregate have total diameter of at least 10 mm at baseline

Description of Changes:

Section: Global; Header date

Replace:

Date: 06 April 2015

With:

Date: 18 August 2015

Section: Title page

Add:

Amendment 3 Date: 18 August 2015

Section: Investigator's Agreement

Paragraph 1; line 3

Replace:

06 April 2015

With:

18 August 2015

Section: Protocol Synopsis, Study Design

Paragraph 1; line 3

Replace:

This is a phase 2, multicenter, and single-arm study to investigate the biodistribution and shedding of talimogene laherparepvec in subjects with unresected, stage IIIB to IVM1c melanoma. Between 50 to 60 subjects will be enrolled in this study.

With:

This is a phase 2, multicenter, and single-arm study to investigate the biodistribution and shedding of talimogene laherparepvec in subjects with unresected, stage IIIB to IVM1c melanoma. **Approximately** 50 to 60 subjects will be enrolled in this study.

Paragraph 3

Replace:

Subjects will be followed for safety approximately 30 (+ 7) days and 60 (+ 7) days after the last dose of talimogene laherparepvec, respectively. Thereafter, subjects will be followed under an ongoing separate registry protocol for the long-term survival follow-up of subjects treated with talimogene laherparepvec in clinical trials. The registry protocol will also monitor for late and long-term adverse events thought to be potentially related to talimogene laherparepvec.

With:

Subjects will be followed for safety approximately 30 (+ 7) days and 60 (+ 7) days after the last dose of talimogene laherparepvec, respectively. Thereafter, subjects will be followed under an ongoing separate registry protocol for the long-term survival follow-up of subjects treated with talimogene laherparepvec in clinical trials **(Study 20120139)**. The registry protocol will also monitor for late and long-term adverse events thought to be potentially related to talimogene laherparepvec **and anti-cancer therapy for melanoma**.

Section: Protocol Synopsis, Sample Size

Line 1

Replace:

Between 50 to 60 subjects will enroll in this study

With:

Approximately 50 to 60 subjects will enroll in this study

Section: Protocol Synopsis, Key Exclusion Criteria

Paragraph 1; line 10

Replace:

Subject who has active herpetic skin lesions or prior complications of HSV-1 infection (eg, herpetic keratitis or encephalitis), and/or requires intermittent or chronic systemic (intravenous or oral) treatment with an antiherpetic drug (eg, acyclovir), other than intermittent topical use will also be excuded.

With:

Subject who has active herpetic skin lesions or prior complications of HSV-1 infection (eg, herpetic keratitis or encephalitis), and/or requires intermittent or chronic systemic (intravenous or oral) treatment with an antiherpetic drug (eg, acyclovir), other than intermittent topical use will also be **excluded**.

Section: Protocol Synopsis, Statistical Considerations

Paragraph 1; line 2

Replace:

The primary analysis will be triggered once all enrolled subjects have had a chance to complete their 60 day follow up visit sample collection for the qPCR assay.

With:

The primary analysis will be triggered once all enrolled subjects have had a chance to complete their **cycle 4 day 1 blood and urine** sample collection for the qPCR assay.

Section: Protocol Synopsis, Statistical Considerations

Paragraph 6

Add:

A final analysis will be performed after all enrolled subjects have had a chance to complete their 60-day safety follow up visit.

Section: 3.1, Study Design

Paragraph 1; line 3

Replace:

Between 50 to 60 subjects will be enrolled in this study.

With:

Approximately 50 to 60 subjects will be enrolled in this study.

Add:

The final number of subjects in the study (with the minimal number of approximately 50 and the maximal number of approximately 60 subjects) will depend on enrollment of approximately 20 subjects evaluable for the estimation of

detection of talimogene laherparepvec DNA in any set of swabs (ie, swabs from the surface of injected lesions, exterior of the occlusive dressing, oral mucosa, or anogenital area). For a full description of determination of the final number of subjects in the study, please refer to Section 10.2.

Section: 3.1, Study Design

Paragraph 5; bullet 2

Replace:

During safety follow-up only the surface of up to 3 most recently injected lesion(s) will be swabbed starting on day-30 (+ 7) safety follow-up visit at time points designated in Section 7.2.3 (if a lesion is in CR, the place of the prior injection will be swabbed). At each time point the outside of the occlusive dressing will be swabbed. The dressing will be removed and the surface of the lesion will be swabbed.

With:

During safety follow-up only the surface of up to 3 most recently injected lesion(s) will be swabbed starting on day-30 (+ 7) safety follow-up visit at time points designated in Section 7.2.3 (if a lesion is in CR, the place of the prior injection will be swabbed).

Section: 3.3, Number of Subjects

Paragraph 2; line 1

Replace:

Between 50 to 60 subjects will be enrolled in this study.

With:

Approximately 50 to 60 subjects will be enrolled in this study.

Section: 3.4, Replacement of Subjects

Paragraph 1; line 4

Replace:

Subjects who withdraw from treatment before the first dose of talimogene laherparepvec or have received the first dose talimogene laherparepvec but have not provided blood and urine samples 1 hour after cycle 1 dosing and at 8 hours or beyond may be replaced

in order to obtain approximately 30 subjects evaluable for the estimation of the biodistribution of talimogene laherparepvec in the blood and urine.

With:

Subjects who withdraw from treatment before the first dose of talimogene laherparepvec or have received the first dose talimogene laherparepvec but have not provided blood and urine samples 1 hour after cycle 1 dosing and at 8 hours or beyond may be replaced in order to obtain approximately **50** subjects evaluable for the estimation of the biodistribution of talimogene laherparepvec in the blood and urine.

Section: 3.4, Replacement of Subjects

Paragraph 3

Delete:

Refer to Section 10.2 for sample size considerations for additional information.

~~Additionally, at least 20 subjects evaluable for the estimation of talimogene laherparepvec DNA and viral detection in swabs (oral swabs, swabs from the anogenital area, swabs from injected lesions, or swabs from exterior of occlusive dressing, or any swab collected during the safety follow up period) will be required.~~

~~Evaluable subjects for the estimation of talimogene laherparepvec DNA and viral detection in swabs collected during the treatment (oral swabs, swabs from anogenital area, swabs from injected lesions, or swabs from exterior of occlusive dressing) are defined as those who have received the first dose of talimogene laherparepvec and have swabs collected at cycle 1 and at least once beyond cycle 1. Evaluable subjects for the estimation of talimogene laherparepvec DNA and viral detection in swabs collected during the safety follow up period are defined as those who have received the first dose of talimogene laherparepvec and have swabs (oral swabs, swabs from anogenital area, or swabs from injected lesions) collected at least once during the safety follow up period.~~

Add:

The final number of subjects needed to be enrolled in the study (with the minimal number of approximately 50 and the maximal number of approximately 60 subjects) will depend on enrollment of approximately 20 subjects evaluable for the estimation of detection of talimogene laherparepvec DNA in any set of swabs (ie, swabs from oral mucosa, swabs from the anogenital area, swabs from injected

lesions, or swabs from exterior of occlusive dressing). For a full description of determination of the final number of subjects in the study, please refer to Section 10.2.

Section: 3.5.1, Study Duration for Subjects

Paragraph 3; line 3 and 5

Replace:

The registry protocol will also monitor for long-term adverse events thought to be potentially related to talimogene laherparepvec.

With:

The registry protocol **(Study 20120139)** will also monitor for long-term adverse events thought to be potentially related to talimogene laherparepvec **and use of anti-cancer therapy for melanoma**.

Section: 6.2.1, Amgen Investigational Product Talimogene Laherparepvec

Paragraph 1; line 6

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. The supply for 10^6 PFU/mL concentration will be packaged separately from the supply for 10^8 PFU/mL concentration.

With:

Each vial contains a minimum of 1.0 mL talimogene laherparepvec at either 10^6 PFU/mL or 10^8 PFU/mL concentrations. The supply for 10^6 PFU/mL concentration will be packaged separately from the supply for 10^8 PFU/mL concentration. **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 8; line 4

Replace:

Subjects will be treated with talimogene laherparepvec until CR, all injectable tumors have disappeared, clinically relevant (resulting in clinical deterioration or requiring change of therapy) disease progression per the modified WHO response criteria (Appendix D), or intolerance of study treatment, whichever occurs first.

With:

Subjects will be treated with talimogene laherparepvec until CR, all injectable tumors have disappeared, clinically relevant (resulting in clinical deterioration or requiring change of therapy) disease progression per the modified WHO response criteria (Appendix D) **beyond 6 months of treatment**, or intolerance of study treatment, whichever occurs first.

Section: 7, Schedule of Assessments

Table 2; Central Laboratory Section; rows 4 and 5

Replace:

Table 2. Schedule of Assessments

Schedule of Assessments																
	Screening[1]	Treatment Period[2]												Follow-up Period		
Cycle		1	1	1	1	1	2	2	2	2	3	3	Cycle 4	Cycle 5 and Subsequent Cycles	Safety[3] Follow-up		
Day		1	2	3	8	15	1	2	3	8	1	8	1	1	30 (+/-)	30 to 60	60 (+/-)
GENERAL & SAFETY ASSESSMENTS																	
Informed Consent & Review of Eligibility Criteria	X																
Medical/Surgical History & Demographics	X																
Concomitant Medications[5]	X	→	→	→	→	→	→	→	→	→	→	→	→	→			X
Adverse Events[3]		X	→	→	→	→	→	→	→	→	→	→	→	→	X		
Serious Adverse Events[4]	X	→	→	→	→	→	→	→	→	→	→	→	→	→			X
Physical Exam[6]	X														X		
Vital Signs[7]	X	X					X						Q2C		X		
ECOG Performance Status	X														X		
LOCAL LABORATORY ASSESSMENTS																	
Urine or Serum Pregnancy Test[8]	X														X		
Hematology[9]	X	X					X						Q2C		X		
Chemistry[9]	X	X					X						Q2C		X		
Serum LDH	X																
Archived Tumor Tissue for BRAF[V600]		X															
CENTRAL LABORATORY ASSESSMENTS																	
Blood and Urine for qPCR[10]		X	X	X	X	X	X	X	X	X	X	X	X		X		
Swab of Oral Mucosa for qPCR and TCID50[10]		X			X	X	X			X	X	X	X	X	X	X	X
Anogenital Swab for qPCR and TCID50[10]		X			X	X	X			X	X	X	X	X	X	X	X
Swab of Exterior of Occlusive Dressing for qPCR and TCID50[10]			X	X	X	X	X	X	X	X	X	X	X		X		X
Swab of Surface of Injected Lesion for qPCR and TCID50[10]			X	X	X	X	X	X	X	X	X	X	X				

Page 1 of 2

Footnote defined on the next page of the table

With:

Table 2. Schedule of Assessments

Schedule of Assessments																
	Screening[a]	Treatment Period[a]												Follow-up Period		
Cycle		1	1	1	1	1	2	2	2	2	3	3	Cycle 4	Cycle 5 and Subsequent Cycles	Safety[b] Follow-up		
Day		1	2	3	8	15	1	2	3	8	1	8	1	1	30 (+/-)	30 to 60	60 (+/-)
GENERAL & SAFETY ASSESSMENTS																	
Informed Consent & Review of Eligibility Criteria	X																
Medical/Surgical History & Demographics	X																
Concomitant Medications[c]	X	→	→	→	→	→	→	→	→	→	→	→	→	→			X
Adverse Events[d]		X	→	→	→	→	→	→	→	→	→	→	→	→	X		
Serious Adverse Events[e]	X	→	→	→	→	→	→	→	→	→	→	→	→	→			X
Physical Exam[f]	X														X		
Vital Signs[g]	X	X					X						Q2C		X		
ECOG Performance Status	X														X		
LOCAL LABORATORY ASSESSMENTS																	
Urine or Serum Pregnancy Test[h]	X														X		
Hematology[i]	X	X					X						Q2C		X		
Chemistry[j]	X	X					X						Q2C		X		
Serum LDH	X																
Archived Tumor Tissue for BRAF[V600]		X															
CENTRAL LABORATORY ASSESSMENTS																	
Blood and Urine for qPCR[k]		X	X	X	X	X	X	X	X	X	X	X	X		X		
Swab of Oral Mucosa for qPCR and TCID50[m]		X			X	X	X			X	X	X	X	X	X	X	X
Anogenital Swab for qPCR and TCID50[n]		X			X	X	X			X	X	X	X	X	X	X	X
Swab of Exterior of Occlusive Dressing for qPCR and TCID50[o]			X	X	X	X	X	X	X	X	X	X	X				
Swab of Surface of Injected Lesion for qPCR and TCID50[o]			X	X	X	X	X	X	X	X	X	X	X		X		X

Page 1 of 2

Footnote defined on the next page of the table

Section: 7, Schedule of Assessments

Table 2; Footnote m

Replace:

Swabs will also be collected at 30-day (+7) and 60-day (+7) safety follow-up visits.

With:

Swabs will also be collected at 30-day (+7) and 60-day (+7) safety follow-up visits **and weekly at home between day 30 and day 60 safety follow-up visits.**

Section: 7, Schedule of Assessments

Table 2; Footnote n

Replace:

Swabs will also be collected at 30-day (+7) and 60-day (+7) safety follow-up visits.

With:

Swabs will also be collected at 30-day (+7) and 60-day (+7) safety follow-up visits **and weekly at home between day 30 and day 60 safety follow-up visits.**

Section: 7, Schedule of Assessments

Table 2; Footnote v

Replace:

During treatment, the clinical tumor assessments will performed independent of treatment cycle at week 12 (± 1 week), week 24 (± 1 week), and then at least every 3 months (± 15 days) until signs of clinically relevant disease progression per the modified WHO criteria or end of treatment, whichever occurs first.

With:

During treatment, the clinical tumor assessments will performed independent of treatment cycle at week 12 (± 1 week), week 24 (± 1 week), and then at least every 3 months (± 15 days) until signs of clinically relevant disease progression per the modified WHO criteria **beyond 6 months of treatment** or end of treatment, whichever occurs first.

Section: 7, Schedule of Assessments

Table 2; Footnote w

Replace:

During treatment, radiographic imaging (CT, PET/CT, MRI, or US) of the abdomen, pelvis, and chest, along with tumor assessments of all other sites of disease, (and CT scan or MRI of the brain if a subject has symptoms or signs suggestive of CNS metastasis), will be performed independent of treatment cycle at week 12 (± 1 week), week 24 (± 1 week), and then at least every 3 months (± 15 days) until clinically relevant disease progression per the modified WHO criteria, or end of treatment, whichever occurs first.

With:

During treatment, radiographic imaging (CT, PET/CT, MRI, or US) of the abdomen, pelvis, and chest, along with tumor assessments of all other sites of disease, (and CT scan or MRI of the brain if a subject has symptoms or signs suggestive of CNS metastasis), will be performed independent of treatment cycle at week 12 (± 1 week), week 24 (± 1 week), and then at least every 3 months (± 15 days) until clinically relevant disease progression per the modified WHO criteria **beyond 6 months of treatment** or end of treatment, whichever occurs first.

Section: 7.2, General Study Procedures

Table 3; Biomarker column, row 1

Replace:

Table 3. Laboratory Analytes

Chemistry	**Hematology**	**Biodistribution and Shedding**	**Biomarker**	**Other Labs**
Sodium Potassium Chloride Total protein Albumin Calcium Creatinine Total bilirubin Alkaline-phosphatase AST (SGOT) ALT (SGPT)	RBC Hemoglobin Hematocrit Platelets WBC Differential[a] • Neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes	qPCR for talimogene laherparepvec DNA TCID50 assay for talimogene laherparepvec virus	HSV-1 antibody Blood for biomarker analysis Archived tumor tissue for biomarker analysis Fresh Tumor biopsy for biomarker analysis[b]	Pregnancy LDH

[a] 3-part differential if 5-part unable to be performed.
[b] At limited number of sites.

With:

Table 3. Laboratory Analytes

Chemistry	**Hematology**	**Biodistribution and Shedding**	**Biomarker**	**Other Labs**
Sodium Potassium Chloride Total protein Albumin Calcium Creatinine Total bilirubin Alkaline-phosphatase AST (SGOT) ALT (SGPT)	RBC Hemoglobin Hematocrit Platelets WBC Differential[a] • Neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes	qPCR for talimogene laherparepvec DNA TCID50 assay for talimogene laherparepvec virus	HSV-1**/2** antibody Blood for biomarker analysis Archived tumor tissue for biomarker analysis Fresh Tumor biopsy for biomarker analysis[b]	Pregnancy LDH

[a] 3-part differential if 5-part unable to be performed.
[b] At limited number of sites.

Section: 7.2.2, Treatment

Bullet 8; sub-bullet 3; line 3

Replace:

- day 1 of cycle 3 and cycle 4, then every other cycle until end of treatment (within 3 days prior to talimogene laherparepvec administration) for determination of HSV-1 IgG antibody serostatus only

With:

- day 1 of cycle 3 and cycle 4, then every other cycle until end of treatment (within 3 days prior to talimogene laherparepvec administration) for determination of HSV-1**/2** IgG antibody serostatus only

Section: 7.2.2, Treatment

Bullet 13

Replace:

- Clinical tumor assessments must include clinical measurement of cutaneous, subcutaneous, or nodal tumor measurement by caliper to be performed independent of treatment cycle at week 12 (± 7 days), week 24 (± 7 days), and then at least every 3 months (± 15 days) until clinically relevant disease progression per modified WHO response criteria (Appendix D), or end of treatment for other reasons, whichever occurs first.

With:

- Clinical tumor assessments must include clinical measurement of cutaneous, subcutaneous, or nodal tumor measurement by caliper to be performed independent of treatment cycle at week 12 (± 7 days), week 24 (± 7 days), and then at least every 3 months (± 15 days) until clinically relevant disease progression per modified WHO response criteria (Appendix D) **beyond 6 months of treatment** or end of treatment for other reasons, whichever occurs first.

Section: 7.2.2, Treatment

Bullet 14

Replace:

- Radiographic tumor imaging assessments 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. Imaging to be performed independent of treatment cycle at week 12 (± 7 days), week 24 (± 7 days), and then at least every 3 months (± 15 days) until clinically relevant disease progression per

modified WHO response criteria (Appendix D) or end of treatment for other reasons, whichever occurs first.

With:

- Radiographic tumor imaging assessments 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. Imaging to be performed independent of treatment cycle at week 12 (± 7 days), week 24 (± 7 days), and then at least every 3 months (± 15 days) until clinically relevant disease progression per modified WHO response criteria (Appendix D) **beyond 6 months of treatment** or end of treatment for other reasons, whichever occurs first.

Section: 7.2.2, Treatment

Bullet 15

Replace:

- Tumor response will be assessed using the modified WHO response criteria (Appendix D) at week 12 (± 7 days), week 24 (± 7 days), and then at least every 3 months (± 15 days) until clinically relevant disease progression per modified WHO criteria (Appendix D) or end of treatment for other reasons, whichever occurs first.

With:

- Tumor response will be assessed using the modified WHO response criteria (Appendix D) at week 12 (± 7 days), week 24 (± 7 days), and then at least every 3 months (± 15 days) until clinically relevant disease progression per modified WHO criteria (Appendix D) **beyond 6 months of treatment** or end of treatment for other reasons, whichever occurs first.

Section: 7.2.5, Long-term Follow-up

Paragraph 1; line 4 and 6

Replace:

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

With:

All subjects who permanently discontinue study for any reason other than death or withdrawal of full consent and who provide consent must be followed for survival under an ongoing separate registry protocol that is in place for the long-term follow-up of subjects treated with talimogene laherparepvec in clinical trials **(Study 20120139)**. The registry protocol will also monitor for late and long-term adverse events thought to be potentially related to talimogene laherparepvec **and anti-cancer therapy for melanoma**.

Section: 7.2.3.1, 30 Day Safety Follow-up Visit

Bullet 10; sub-bullet 1

Replace:

- Blood sample for HSV antibody serostatus
  - Determination of HSV-1 IgG antibody serostatus only.

With:

- Blood sample for HSV antibody serostatus
  - Determination of HSV-1**/2** IgG antibody serostatus only.

Section: 8.3.1, Reasons for Removal From Treatment

Bullet 11

Replace:

- clinically relevant disease progression per modified WHO response criteria (Appendix D),

With:

- clinically relevant disease progression per modified WHO response criteria (Appendix D),

Section: 9.3, Pregnancy and Lactation Reporting

Paragraph 2; line 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.

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.

Section: 9.3, Pregnancy and Lactation Reporting

Paragraph 3; line 1

Replace:

The pregnancy should be reported to Amgen's global Pregnancy Surveillance Program 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 Pregnancy Surveillance Program will seek to follow the pregnant woman throughout her pregnancy and her baby up to 12 months after birth.

With:

The pregnancy should be reported to Amgen's 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; line 1

Replace:

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.

With:

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

Section: 9.3, Pregnancy and Lactation Reporting

Paragraph 6; line 1

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's **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 2; line 9

Replace:

If the exposed individual is reporting sign or symptoms suspected to be related to talimogene laherparepvec exposure, the exposed individual may be asked to have a swab taken to evaluate for the presence of talimogene laherparepvec DNA in the lesion by qPCR testing.

With:

If the exposed individual is reporting sign or symptoms suspected to be related to talimogene laherparepvec exposure, the exposed individual may be asked to have a swab taken to evaluate for the presence of talimogene laherparepvec DNA in the lesion by qPCR testing**, within 3 days of the symptoms or signs occurring**.

Section: 10.1.3, Covariates and Subgroups

Paragraph 1; bullet 4

Replace:

- baseline HSV-1 serostatus (seropositive, seronegative)

With:

- baseline HSV serostatus (seropositive, seronegative)

Section: 10.2, Sample Size Considerations

Paragraph 2

Replace:

The exact 95% CIs of the binomial proportion from approximately 30 subjects based on various assumptions of the true incidence rate are provided in Table 4.

With:

The **expected** exact 95% CIs of the binomial proportion **given 50** subjects **for** true incidence rate**s from 40% to 95%** are provided in Table 4.

Section: 10.2, Sample Size Considerations

Table 4

Replace:

Table 4. Expected 95% Exact Confidence Intervals by Proportion of Detectable Talimogene Laherparepvec DNA in Blood and Urine During the First 3 Treatment Cycles From a Sample Size of 30 Subjects

Proportion (p)	Expected 95% Exact Confidence Interval
40%	**(23%, 59%)**
45%	**(27%, 64%)**
50%	**(32%, 68%)**
55%	**(36%, 73%)**
60%	**(41%, 77%)**
65%	**(46%, 81%)**
70%	**(51%, 85%)**
75%	**(56%, 89%)**
80%	**(62%, 92%)**
85%	**(68%, 95%)**
90%	**(74%, 97%)**
95%	**(81%, 99%)**

With:

Table 4. Expected 95% Exact Confidence Intervals by Proportion of Detectable Talimogene Laherparepvec DNA in Blood and Urine During the First 3 Treatment Cycles From a Sample Size of 50 Subjects

Proportion (p)	Expected 95% Exact Confidence Interval
40%	**(27%, 55%)**
45%	**(31%, 60%)**
50%	**(36%, 64%)**
55%	**(40%, 69%)**
60%	**(45%, 73%)**
65%	**(50%, 78%)**
70%	**(56%, 82%)**
75%	**(61%, 86%)**
80%	**(66%, 90%)**
85%	**(72%, 93%)**
90%	**(78%, 96%)**
95%	**(85%, 99%)**

Section: 10.2, Sample Size Considerations

Paragraph 3

Replace:

In addition, given a sample size of 30 subjects, the probability of observing at least 1 subject with an event of detectable talimogene laherparepvec DNA in the sample ranges from 0.53 to 0.99 with a true event probability (p_a) ranges from 0.025 to 0.15 (Table 5).

With:

Given a sample size of **50** subjects, the probability of observing at least 1 subject with an event of detectable talimogene laherparepvec DNA in the sample ranges from 0.**72** to **1.00** with a true event probability (p_a) ranges from 0.025 to 0.15 (Table 5).

Section: 10.2, Sample Size Considerations

Table 5

Replace:

Table 5. Probability of Observing at Least 1 Subject With an Event With a True Event Probability (p_a) by Sample Size

	Sample Size			
p_a	40	35	30	20
0.025	0.64	0.59	0.53	0.40
0.050	0.87	0.89	0.79	0.64
0.075	0.96	0.93	0.90	0.79
0.100	0.99	0.97	0.96	0.88
0.125	0.99	0.99	0.98	0.93
0.150	0.99	0.99	0.99	0.96

With:

Table 5. Probability of Observing at Least 1 Subject With an Event With a True Event Probability (p_a) by Sample Size

	Sample Size					
p_a	**60**	**55**	**50**	**40**	**30**	**20**
0.025	**0.78**	**0.75**	**0.72**	**0.64**	**0.53**	**0.40**
0.050	**0.95**	**0.94**	**0.92**	**0.87**	**0.79**	**0.64**
0.075	**0.99**	**0.99**	**0.98**	**0.96**	**0.90**	**0.79**
0.100	**1.00**	**1.00**	**0.99**	**0.99**	**0.96**	**0.88**
0.125	**1.00**	**1.00**	**1.00**	**0.99**	**0.98**	**0.93**
0.150	**1.00**	**1.00**	**1.00**	**1.00**	**0.99**	**0.96**

Section: 10.2, Sample Size Considerations

Paragraph 4

Replace:

The sample size may be increased to maximum of **40** subjects from preliminary results. Table 6 provides estimated proportion of subjects with shedding event(s) and the corresponding exact 95% Cis.

With:

In addition, Table 6 provides **the expected 95% CIs of the binomial proportion** of subjects with shedding event(s) **for true incidence rates from 0% to 15% for sample sizes from 20 to 60.**

Section: 10.2, Sample Size Considerations

Table 6

Replace:

Table 6. Expected 95% Exact Confidence Intervals by Proportion of Detectable Talimogene Laherparepvec DNA in Swabs by Sample Size

Proportion (p)	N=40	N=35	N=30	N=20
0	(0.000, 0.09)	(0.000, 0.10)	(0.000, 0.12)	(0.000, 0.17)
0.025	(0.003, 0.13)	(0.003, 0.14)	(0.002, 0.16)	(0.002, 0.21)
0.050	(<0.01, 0.17)	(<0.01, 0.18)	(<0.01, 0.19)	(<0.01, 0.24)
0.075	(0.02, 0.20)	(0.02, 0.21)	(0.02, 0.23)	(0.01, 0.28)
0.100	(0.03, 0.23)	(0.03, 0.25)	(0.03, 0.26)	(0.02, 0.31)
0.125	(0.04, 0.27)	(0.04, 0.28)	(0.04, 0.29)	(0.03, 0.34)
0.150	(0.06, 0.30)	(0.06, 0.31)	(0.05, 0.33)	(0.04, 0.37)

With:

Table 6. Expected 95% Exact Confidence Intervals by Proportion of Detectable Talimogene Laherparepvec DNA in Swabs by Sample Size

	Sample Size					
p_a	**60**	**55**	**50**	**40**	**30**	**20**
0	**(0.00, 0.06)**	**(0.00, 0.06)**	**(0.00, 0.07)**	**(0.00, 0.09)**	**(0.00, 0.12)**	**(0,00,0.17)**
0.025	**(<0.01, 0.10)**	**(<0.01, 0.11)**	**(<0.01, 0.11)**	**(<0.01, 0.13)**	**(<0.01, 0.16)**	**(<0.01, 0.21)**
0.050	**(0.01, 0.14)**	**(0.01, 0.14)**	**(0.01,0.15)**	**(0.01, 0.17)**	**(0.01, 0.19)**	**(0.01, 0.24)**
0.075	**(0.03, 0.17)**	**(0.02, 0.18)**	**(0.02, 0.18)**	**(0.02, 0.20)**	**(0.02, 0.23)**	**(0.01, 0.28)**
0.100	**(0.04, 0.20)**	**(0.04, 0.21)**	**(0.04, 0.22)**	**(0.03, 0.23)**	**(0.03, 0.26)**	**(0.02, 0.31)**
0.125	**(0.06, 0.23)**	**(0.05, 0.24)**	**(0.05, 0.25)**	**(0.04, 0.27)**	**(0.04, 0.29)**	**(0.03, 0.34)**
0.150	**(0.07, 0.26)**	**(0.07, 0.27)**	**(0.07, 0.28)**	**(0.06, 0.30)**	**(0.05, 0.32)**	**(0.04, 0.37)**

Section: 10.2, Sample Size Considerations

Paragraph 5

Add:

The final number of subjects in the study will depend on enrollment of a minimal number of approximately 20 subjects evaluable for the estimation of detection of talimogene laherparepvec DNA in any analysis of on treatment set of swabs as specified in Section 10.1.2. Since analysis of swabs of anogenital area for subjects injected below the waistline was introduced in the protocol amendment 1 when approximately 10 subjects were estimated to be enrolled, the minimal number of subjects to be enrolled in the study is approximately 50, taking into consideration a 50% probability that newly enrolled subjects will have an injected lesion below the waistline. The sample size may be increased to a maximum of approximately 60 subjects to allow enrollment of approximately 20 subjects evaluable for the estimation of detection of talimogene laherparepvec DNA in the analysis set of swabs from the anogenital area and to account for possible incomplete collection of anogenital swab data in approximately 10 subjects.

Section: 10.3.2, Primary Analysis

Replace:

The primary analysis will be triggered once all enrolled subjects have had a chance to complete their 60 day follow up visit sample collection for the qPCR assay. A clinical study report (CSR) will be written based on the results of the primary analysis.

With:

The primary analysis will be triggered once all enrolled subjects have had a chance to complete their **cycle 4 day 1 blood and urine** sample collection for the qPCR assay. A clinical study report (CSR) will be written based on the results of the primary analysis.

Section: 10.4.3, Secondary Endpoint(s)

Paragraph 2; line 2

Replace:

Incidence of clearance at day 8 of cycles 1, 2, and 3 will be repeated for subjects with HSV-1 seropositive and –seronegative at baseline.

With:

Incidence of clearance at day 8 of cycles 1, 2, and 3 will be repeated for subjects with HSV seropositive and –seronegative at baseline.

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

Paragraph 2; line 9

Replace:

(Note: When a lesion can be evaluated by both, clinical examination and imaging, radiographic imaging evaluations should be undertaken since it is more objective).

With:

(Note: When a lesion can be evaluated by both, clinical examination and imaging, radiographic imaging evaluations should be **preferred** since it is more objective).

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

Paragraph 12; Coalescing or splitting lesions section

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 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).

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

Paragraph 16; Measureable Tumor Assessment/Burden section

Add:

If subject has multiple small superficial melanoma lesions at baseline (< 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 individually 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.

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

Table 1; row 2

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 tumors have appeared, the sum of products of the perpendicular diameters of these must have reduced by 50% or more from when first documented. Any residual cutaneous or subcutaneous index lesion 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 tumors have appeared, the sum of products of the perpendicular diameters of these must have reduced by 50% or more from when first documented.