

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

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

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

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

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

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

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

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Name of Investigator

Date (DD Month YYYY)

Protocol Synopsis

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

Study Phase: 2

Indication: Unresected stage IIIB to IVM1c melanoma

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

Secondary Objective(s):

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

Exploratory Objective(s):

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

Hypotheses:

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

Primary Endpoint:

Correlation between baseline intratumoral CD8+ cell density and objective response rate

Secondary Endpoint(s):

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

Exploratory Endpoint(s):

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

Study Design:

This is a phase 2, multicenter, open-label, single-arm study to evaluate biomarkers in subjects with unresected stage IIIB to IVM1c melanoma who are treated with talimogene laherparepvec.

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

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

Blood and tumor tissue samples will be collected at timepoints outlined in the Schedule of Assessments ([Table 2](#)). Tumor biopsies (**taken from accessible cutaneous, subcutaneous or nodal lesions**) will be performed on an uninjected lesion on day 1 of week 1, on a different uninjected lesion at week 6 (if available), and at disease progression **that results in treatment discontinuation from the lesion responsible for progression** as outlined in [Section 7.2.2](#).

Samples will be analyzed to explore if intratumoral CD8+ cell density at baseline and its change during treatment is correlated with the objective response rate in subjects with unresected stage IIIB-IVM1c melanoma treated with talimogene laherparepvec.

For a full description of the study design, please refer to [Section 3.1](#).

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

Summary of Subject Eligibility Criteria:

Key Inclusion Criteria:

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

Key Exclusion Criteria:

Subject must not have clinically active cerebral metastases, greater than 3 visceral metastases (this does not include lung or nodal metastases associated with visceral organs), or any bone metastases, primary ocular or mucosal melanoma, history or evidence of symptomatic autoimmune **disease (such as** pneumonitis, glomerulonephritis, vasculitis, or other) **or history of autoimmune disease that required systemic treatment (ie, use of corticosteroids, immunosuppressive drugs or biological agents used for treatment of autoimmune diseases) in past 2 months prior to enrollment. Replacement therapy (eg, thyroxine for hypothyroidism, insulin for diabetes mellitus) is not considered a form of systemic treatment for autoimmune disease.** Subject must not have evidence of clinically significant immunosuppression or active herpetic skin lesions or prior complications of HSV-1 infection (eg, herpetic keratitis or encephalitis) and must not require intermittent or chronic systemic treatment with an antiherpetic drug (eg, acyclovir), other than intermittent topical use. Subjects known to have acute or chronic active hepatitis B, hepatitis C, or human immunodeficiency virus

infection will also be excluded. Subjects must not have been treated previously with talimogene laherparepvec.

For a full list of eligibility criteria, please refer to [Section 4](#).

Investigational Product Dosage and Administration:

Talimogene laherparepvec will be administered by intralesional injection into injectable cutaneous, subcutaneous, and nodal lesions with or without image ultrasound guidance. Talimogene laherparepvec must not be administered into visceral organ metastases. The initial dose of talimogene laherparepvec is up to 4.0 mL of 10^6 PFU/mL. Subsequent doses of talimogene laherparepvec are up to 4.0 mL of 10^8 PFU/mL. The second dose up to 4.0 mL of 10^8 PFU/mL should be administered 21 (+5) days after the initial dose (ie, no sooner than day 22, but should not be delayed more than 5 days after the day 21 time point). Subsequent doses up to 4.0 mL of 10^8 PFU/mL should be given every 14 (\pm 3) days.

Procedures:

Screening:

The following will be performed during the screening period:

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

Treatment:

The following will be performed during the treatment period:

- vital signs
- **physical examination**
- **ECOG Performance Status assessment**
- local laboratory tests
 - hematology panel
 - chemistry panel
- archived tumor tissue for *BRAF*^{V600E/K} mutation testing and biomarker analyses
- central laboratory tests
 - swabs of cold sore, vesicles and other lesions suspected to be herpetic origin (if any) for qPCR analysis of talimogene laherparepvec DNA
 - blood samples for herpes simplex virus (HSV) serostatus

- blood samples for biomarker analysis
- tumor biopsies for biomarker analyses
- radiographic tumor imaging, clinical tumor assessment, and tumor response assessment
- photographs of **all** visible cutaneous and subcutaneous tumor lesions (select sites only) **always within 3 days of the treatment visit starting from the first treatment visit**
- recording of concomitant medications, adverse events, and serious adverse events at each visit
- administration of talimogene laherparepvec at day 1 of each **treatment** cycle

Safety Follow-Up Visit:

The following will be performed during the safety follow-up visit:

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

Long-term Follow-up/End of Study:

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

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

After the long term follow-up period of this study has ended, subjects who end the study for any reason other than death or withdrawal of full consent will be followed for survival under an ongoing separate registry protocol (Study 20120139) that is in place for the long-term follow-up of all subjects treated with talimogene laherparepvec in clinical trials. The registry protocol will also monitor for late and long-term adverse events thought to be potentially related to talimogene laherparepvec **and use of anti-cancer therapies for melanoma**.

Reporting Exposure to Talimogene Laherparepvec:

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

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

Statistical Considerations:

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

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

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

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

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

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

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

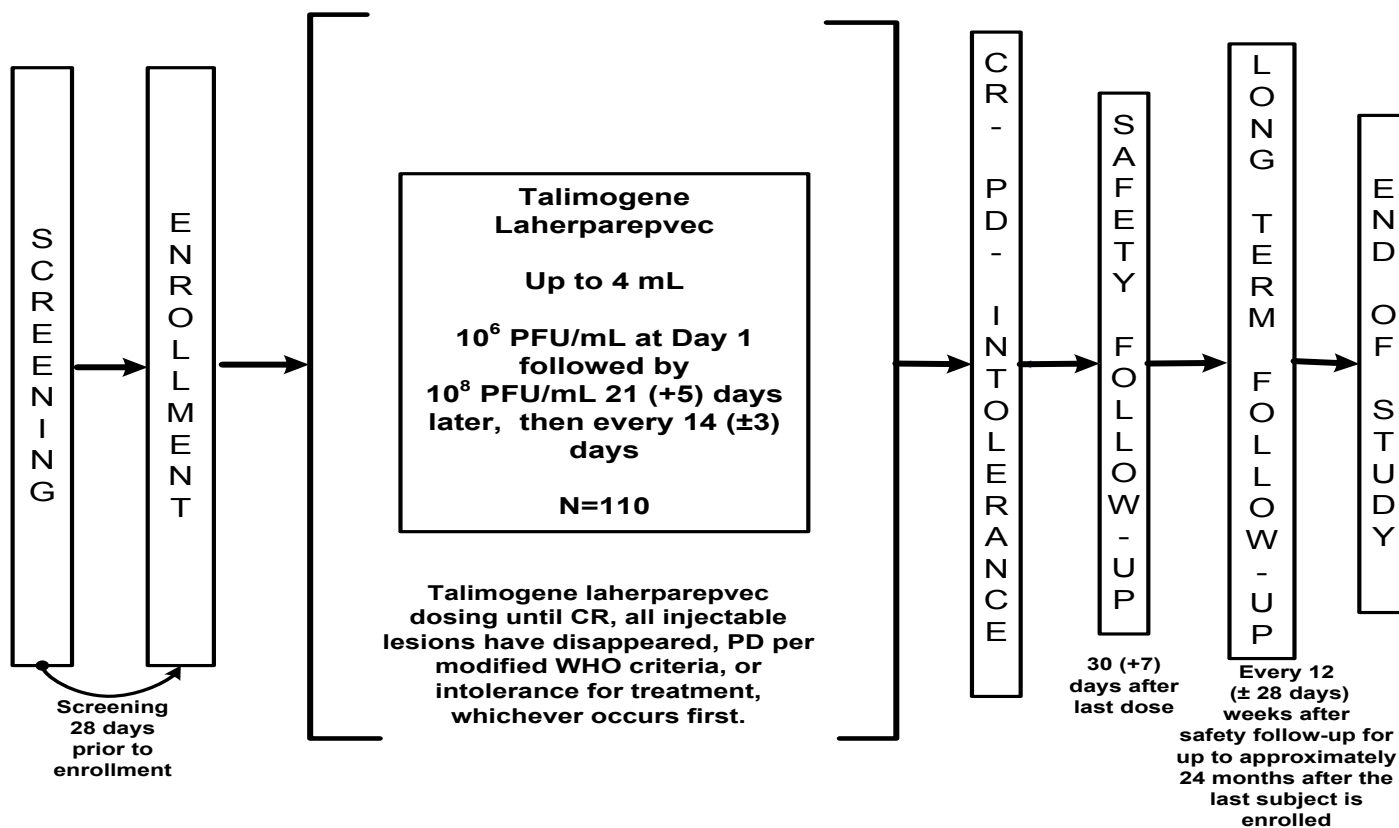
For further details on the statistical analysis, please refer to [Section 10](#).

Sponsor: Amgen Inc.

Data Element Standards
Version(s)/Date(s):

Version 4.0, 31 October 2013

Study Design and Treatment Schema



Study Glossary

Abbreviation or Term	Definition/Explanation
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BRAF, BRAF ^{V600} , BRAF ^{V600E/K}	v-raf murine sarcoma viral oncogene homolog B1, BRAF V600 mutation, BRAF V600E/K mutations
CI	confidence interval
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
CZ	Crystal Zenith
DOR	duration of response
DRR	durable response rate
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 long-term follow-up, or dies, whichever is earlier
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 talimogene laherparepvec and has had the opportunity to complete the safety follow-up visit or the long term follow-up visit, whichever occurs later
End of Treatment	defined as the last dose of the protocol-specified treatment plus 30 days after the last dose
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.
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GM-CSF	granulocyte macrophage colony-stimulating factor
HLA	human leukocyte antigen
HR	hazard ratio
HSV, HSV-1, HSV-2	herpes simplex virus, herpes simplex virus type 1, herpes simplex virus type 2

Abbreviation or Term	Definition/Explanation
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IgG	immunoglobulin G
IgM	immunoglobulin M
INR	international normalization ratio
IPIM	Investigational Product Instruction Manual
IRB	institutional review board
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NA	not applicable
ND	not done
NPV	negative predictive value
ORR	objective response rate
OS	overall survival
PD	disease progression
PDn	nonclinically relevant disease progression
PD _r	clinically relevant disease progression
PET	positron emission tomography
PFU	plaque-forming unit
PPV	positive predictive value
PR	partial response
PSP	Pregnancy Surveillance Program
PT	prothrombin time
PTT	partial thromboplastin time
QC	every cycle
qPCR	real-time polymerase chain reaction
Q4C	every fourth cycle
RBC	red blood cells
ROC	receiver operating characteristic
SAE(s)	serious adverse event(s)
SOC	system organ class

Abbreviation or Term	Definition/Explanation
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.
Study Day 1	defined as the first day that protocol-specified investigational product is administered to the subject
TTF	time to treatment failure
ULN	upper limit of normal
USA	United States of America
WBC	white blood cells
WHO	World Health Organization

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1. OBJECTIVES

1.1 Primary

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

1.2 Secondary

The secondary objectives are as follows:

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

1.3 Exploratory

The exploratory objectives are as follows:

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

2. BACKGROUND AND RATIONALE

2.1 Melanoma

Cutaneous melanoma is the fifth most common cancer in men and the seventh most common cancer in women in the United States of America (USA), with an estimated **73,870** new cases and **9,940** deaths expected in 2015 ([Siegel et al, 2015](#)). In Europe, the annual incidence of melanoma is somewhat lower than that in the USA, with a crude rate of approximately 14 per 100,000 as compared to 20 per 100,000 in the USA, but is the sixth most common cancer among women ([Ferlay et al, 2013](#); [Siegel et al, 2014](#)). In Europe as a whole, approximately 100,442 new cases were diagnosed in 2012 ([Ferlay et al, 2013](#)). The incidence of melanoma is increasing rapidly worldwide, with a 270% increase in the USA between 1973 and 2002. This increase is the most rapid of any cancer with the exception of lung cancer in women ([Jemal et al, 2006](#); [Ries et al, 2000](#)).

Melanoma that has spread to multiple regional nodal sites (stage III) is infrequently curable with standard therapy. For those with multiple or clinically detectable nodal metastases or in-transit/satellite lesions (stages 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 low, ranging from 20% for stage M1a disease (skin, subcutaneous or nodes only), 5% to 10% for stage M1b disease (lung only), and < 5% for stage M1c disease (other visceral lesions or high serum lactate dehydrogenase [LDH]); median survival is 12 months for stages M1a and M1b disease and 4 to 6 months for stage M1c disease (O'Day and Boasberg, 2006; Tannous et al, 2005).

Until recently, traditional nonsurgical therapies for unresectable or advanced melanoma in adults included chemotherapy (dacarbazine, temozolomide, or other agents either alone or in combination), or interleukin-2. Although some regimens produced objective responses, they were usually short-lived (Anderson et al, 1995; Chapman et al, 1999; Wagner et al, 2000; Middleton et al, 2000). Response rates for interleukin-2 ranged from 10% to 20% (Rosenberg et al, 1994; Sparano et al, 1993; Atkins et al, 1999), with a small proportion achieving prolonged response, but its administration requires close patient monitoring in specialized facilities with well-trained staff based on the notable toxicity profile associated with its administration.

Recently, the Food and Drug Administration (FDA), European Commission, and other regulatory agencies have approved 6 novel therapies for advanced melanoma: an immune stimulatory agent, ipilimumab (Yervoy[®], 2015), pembrolizumab (Keytruda[®], 2015) and nivolumab (Opdivo[®], 2015) and 3 agents for use in patients with *BRAF* mutant melanoma, a v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) inhibitor, vemurafenib (Zelboraf[®], 2015), the *BRAF* inhibitor dabrafenib (Tafinlar[™], 2013) and the *MEK* inhibitor trametinib (Mekinist[™], 2014). The studies upon which approvals for ipilimumab and vemurafenib were based demonstrated improved survival compared to control treatments. The pivotal study of ipilimumab showed an overall survival (OS) improvement in subjects with human leukocyte antigen (HLA)-A2*0201 genotype previously treated metastatic melanoma as compared with a gp100 peptide vaccine (Hodi et al, 2010; Yervoy[®] 2015). The median overall survival (OS) was 10.0 months in the group that received ipilimumab in combination with the gp100 peptide vaccine and 6.4 months in the group that received gp100 peptide vaccine alone (hazard ratio

[HR] = 0.68, $p < 0.001$) ([Hodi et al, 2010](#)). Approximately 8% more patients survived 2 years in the ipilimumab arm than in the control arm (21.6% vs 13.7%). The objective response rate was 5.7% vs 1.5%, respectively ($p = 0.04$). Similar results were reported for another study conducted in previously untreated subjects with metastatic melanoma who received ipilimumab and dacarbazine vs placebo and dacarbazine ([Robert et al, 2011](#)).

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

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

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

Pembrolizumab, is a monoclonal antibody that targets PD-1 protein, improved PFS and OS versus ipilimumab in subjects with advanced melanoma. Six-month progression-free rates were 47% and 46%, for pembrolizumab administered every 2 and 3 weeks, versus 27% for ipilimumab (HR 0.58; $P < 0.001$ for both

pembrolizumab regimens versus ipilimumab). Twelve-months OS rates were 74%, 68%, and 58%, respectively (HR 0.63, P=0.0005 for pembrolizumab every 2 weeks and 0.69, P=0.004 for pembrolizumab every 3 weeks) ([Robert et al, 2015](#))

While the approval of these newer agents represents a clear milestone in the treatment of advanced melanoma, limitations still exist. The two-year overall survival following ipilimumab remains only approximately 20%, and the drug is associated with severe and potentially fatal immunological adverse effects ([Hodi et al, 2010](#)). **Although not as common and severe as with ipilimumab, a wide range of immune related toxicities has been reported with permbrlizumab and nivolumab, which include pneumonitis, hepatitis, colitis, nephritis, thyroid dysfunction and others** ([Larkin et al, 2015](#); [Robert et al, 2015](#); [Weber et al, 2015](#)). Vemurafenib, dabrafenib, and trametinib are indicated only in patients with *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[®], 2015](#); [Tafinlar[™], 2013](#)). Additionally, grade 2 or higher dermatologic reactions including rash, pruritus, and hyperkeratosis are common with both agents. Trametinib is associated with cuneiform dermatitis, peripheral edema, hypertension, decreased cardiac ejection fraction, and ocular events ([Mekinist[™], 2014](#)). Thus, the need remains for additional treatment options for patients with advanced melanoma (including those with regional and/or distant metastases).

Biomarkers of melanoma prognosis and treatment effect and toxicity have been increasingly well studied in the past few years. *BRAF* mutations have been identified that predict for response to *BRAF* inhibitors ([Hoeflich et al, 2009](#)). Immunologic-based biomarkers are likely to be important for immunotherapies, including talimogene laherparepvec. Many tumors, including melanoma, are heavily infiltrated by inflammatory and lymphoid cells which can be used as prognostic and predictive biomarkers and a variety of “immunoscores” have been employed in attempts to capture the maximal prognostic value of intratumoral immune cells ([Galon et al, 2012](#)). These immunoscores are generally algorithms that combine the number of one or more types of immune cells observed in the tumor with information on the localization of the immune cells within the tumor (eg, proximity to blood vessels, invasive margin). The most commonly used immunoscore is based on the density of cytotoxic CD8+ T-lymphocytes

in the center and in the invasive margins of tumor ([Mlecnik et al, 2011](#)). The prognostic value of immunoscores composed of a combination of immunohistochemical staining densities for both intratumoral CD3+ / CD8+ T cells, combined with the location of the cells either in the invasive margin or central tumor, has been well documented in colon cancer and was shown to have a prognostic significance superior to that of the AJCC TNM classification system ([Galon et al, 2006](#), [Galon et al, 2012](#)). An international effort is underway to qualify an immunoscore as a predictive and prognostic biomarker for other cancers ([Galon et al, 2014](#)).

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

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

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

In addition, we will also explore the possibility that altered viral replication might affect response. Deletion of the ICP34.5 gene is one of the means by which talimogene laherparepvec was engineered to limit replication to tumor cells. ICP34.5 normally

interferes with the PKR (double-stranded RNA activated protein kinase) pathway which cells activate to protect themselves from viral infection. This PKR pathway is typically inactivated in tumors, but the degree of residual PKR signaling in tumor cells may influence replication of talimogene laherparepvec. Analysis of mutations in the PKR pathway and possibly other tumor cell pathways will be performed in this study in order to explore whether these mutations may affect response to treatment.

2.2 Talimogene Laherparepvec Investigational Product Background

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

Additionally, the virus contains the coding sequence for human GM-CSF, a pleiotropic cytokine involved in the stimulation of cellular immune responses by promoting the generation of dendritic cells from blood monocytes ([Demir et al, 2003](#); [Lonial, 2004](#); [Conti and Gessani, 2008](#)). Dendritic cells have the capacity to capture antigens, migrate in response to chemotactic stimuli, and induce proliferative responses and Th1 cytokine production in CD4+ and CD8+ T-lymphocytes ([Hart, 1997](#); [Steinman, 2001](#); [Ikeda et al, 2004](#); [Paul, 2007](#)). These Th1-type cytokines have the capacity to produce proinflammatory responses, eradicate tumors, and perpetuate autoimmune responses ([Nishimura et al, 2000](#); [Ikeda et al, 2004](#); [Knutson and Disis, 2005](#)).

Clinical data currently available has provided evidence of talimogene laherparepvec's efficacy in patients with regionally and distantly metastatic melanoma ([Talimogene Laherparepvec Investigator's Brochure](#)). In particular, a high rate of complete response (CR) was achieved (16% in the phase 2 study with talimogene laherparepvec in stage IIIC to IV melanoma) ([Senzer et al, 2009](#); [Talimogene Laherparepvec Investigator's Brochure](#)). Moreover, responses were observed in both injected and uninjected sites, including visceral sites. Responses were seen most often in earlier stage disease, including stage IIIB/C and stage IVM1a, and in disease with lower visceral burden.

In the open-label, randomized, phase 3 study of talimogene laherparepvec versus subcutaneously administered GM-CSF in stages IIIB, IIIC, and IV unresectable melanoma, talimogene laherparepvec or GM-CSF was administered until CR, clinically significant disease progression, intolerable side effects, 12 months of therapy without an objective response, or withdrawal of consent (Study 20110263; OPTiM). The primary endpoint of the study is durable response rate, defined as the rate of subjects with an objective response by central review (CR or partial response [PR]) lasting continuously for 6 months and starting any time within 12 months of initiating therapy.

Primary analysis of the OPTiM Study showed a statistically significant difference between the rate of durable response among subjects treated with talimogene laherparepvec (16%; 95% CI: 12%, 21%) versus those treated with GM-CSF (2%; 95% CI: 0%, 5%) (p -value < 0.0001). **Overall response rate was also improved from 6% with GM-CSF to 26% with talimogene laherparepvec (P < 0.0001, descriptive). Similarly, 11% of patients had a CR in the talimogene laherparepvec arm vs. < 1% in the GM-CSF arm. In the event-driven primary OS analysis (secondary endpoint), median OS with talimogene laherparepvec treatment was 23.3 months compared with 18.9 months with GM-CSF treatment (HR, 0.79 [95% CI, 0.62–1.00]; P = 0.051) (Andtbacka et al, 2015). At the final planned analysis of OS which happened when last enrolled subject completed 3 years of follow-up, median OS was 23.3 months in the talimogene laherparepvec arm and 18.9 months in the GM-CSF arm (HR, 0.79; 95% CI, 0.62–1.00; P =0.049), (descriptive) (Andtbacka et al, 2015).**

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

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

2.3 Rationale

The purpose of the study is to explore the correlation between baseline intratumoral CD8+ cell density and objective response rate (ORR) in subjects with unresected stage IIIB to IVM1c melanoma. In addition, the study is planned to inform on the mechanism (s) of systemic action of talimogene laherparepvec on distant metastatic tumors and to identify candidate biomarkers which may predict treatment outcome. Biopsy samples will be used to investigate the relationship between intratumoral CD8+ cell density and response to treatment. Leaving one lesion uninjected during the treatment for biopsy at week 6 is critical for defining the proposed locally-initiated systemic anti-tumor immune response of talimogene laherparepvec. One hypothesis is that tumors with significant number of infiltrating CD8+ T cells will be more likely to respond to an immunotherapy with talimogene laherparepvec. Additionally, we hypothesize that talimogene laherparepvec treatment increases the number of tumor antigen specific T cells and further that subjects with higher levels of tumor antigen specific T cells will have greater response to treatment. In addition to examining the association, if any, between tumor infiltrating T cells prior to treatment and clinical response to treatment, a number of other biomarkers will be assessed to determine any association with response. CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

2.4 Clinical Hypotheses

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

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a phase 2, multicenter, open-label, single-arm study to evaluate biomarkers in subjects with unresected stage IIIB to IVM1c melanoma who are treated with talimogene

laherparepvec. Subjects with unresected stage IIIB to IVM1c melanoma who meet the eligibility criteria outlined in [Section 4](#) will be considered for participation in this study.

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

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

Blood and tumor tissue samples will be collected at timepoints outlined in the Schedule of Assessments ([Table 2](#)). Tumor biopsies will be performed **from** an uninjected lesion on day 1 of week 1, **from** a different uninjected lesion at week 6 (if available), and **from the lesion responsible for progression at the time of disease progression that results in treatment discontinuation** as outlined in [Section 7.2.2](#). Samples will be analyzed to explore if intratumoral CD8+ cell density at baseline and its change during

treatment is correlated with the objective response rate in subjects with unresected stage IIIB-IVM1c melanoma treated with talimogene laherparepvec.

The overall study design is described by a [study schema](#) at the end of the protocol synopsis section.

The study endpoints are defined in [Section 10.1.1](#).

3.2 Number of Sites

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

3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as “subjects”. Approximately 110 subjects will be enrolled in the study. Refer to [Section 10.2](#) for sample size considerations.

3.4 Replacement of Subjects

Subjects who are withdrawn or removed from treatment or from the study will not be replaced.

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

The subject enrollment period is planned for approximately 17 months.

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

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

3.5.2 End of Study

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

End of Trial: the time when the last subject is assessed or receives an intervention for evaluation in the study. The end of study will occur **24 months after the last subject has been enrolled or** when the last subject discontinues talimogene laherparepvec and has had the opportunity to complete the safety follow-up visit, whichever occurs later.

4. SUBJECT ELIGIBILITY

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

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see [Section 11.1](#)).

4.1 Inclusion and Exclusion Criteria

4.1.1 Inclusion Criteria

- 101 Subject has provided informed consent prior to initiation of any study-specific activities/procedures
- 102 Male or female age ≥ 18 years at the time of informed consent
- 103 Histologically confirmed diagnosis of melanoma
- 104 Subject with stage IIIB to IVM1c melanoma for whom surgery is not recommended
- 105 Subject who is treatment naïve **or had received prior treatment** for melanoma. **Any systemic treatment for melanoma must have been completed at least 28 days prior to enrollment**

- 106 Candidate for intralesional therapy (ie, disease is appropriate for direct injection or through the use of ultrasound guidance) defined as one of the following:
- at least 1 injectable cutaneous, subcutaneous, or nodal melanoma lesion ≥ 10 mm in longest diameter, or
 - multiple injectable melanoma lesions that in aggregate have a longest diameter of ≥ 10 mm
- 107 Measurable disease defined as one or more of the following:
- at least 1 melanoma lesion that can be accurately and serially measured in at least 2 dimensions and for which the greatest diameter is ≥ 10 mm as measured by contrast-enhanced or spiral computed tomography (CT) scan, magnetic resonance imaging (MRI), or ultrasound for nodal/soft tissue disease (including lymph nodes)
 - at least 1 ≥ 10 mm superficial cutaneous or subcutaneous melanoma lesion as measured by calipers
 - multiple superficial melanoma lesions which in aggregate have a total diameter of ≥ 10 mm
- 108 Serum lactate dehydrogenase (LDH) levels ≤ 1.5 X upper limit of normal (ULN) within 28 days prior to enrollment
- 109 Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (see [Appendix E](#))
- 110 Adequate organ function determined within 28 days prior to enrollment, defined as follows:
- absolute neutrophil count $\geq 1500/\text{mm}^3$
 - platelet count $\geq 75,000/\text{mm}^3$
 - 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
 - prothrombin time (PT) ≤ 1.5 x ULN (or international normalization ratio [INR] ≤ 1.3)*
 - partial thromboplastin time (PTT) ≤ 1.5 x ULN*
- * Prolongation in INR, PT, and PTT when the result is from therapeutic anticoagulation treatment are permitted for subjects whose injectable lesions are cutaneous and/or subcutaneous such that direct pressure could be applied in the event of excessive bleeding.

4.1.2 Exclusion Criteria

- 201 Clinically active cerebral metastases. Subjects with up to 3 cerebral metastases may be enrolled, provided that all lesions have been adequately treated with stereotactic radiation therapy (including Gamma Knife) or **resection**, with no evidence of progression and have not required steroids for at least two months prior to enrollment.
- 202 Greater than 3 visceral metastases (this does not include lung metastases or nodal metastases associated with visceral organs). For subjects with ≤ 3 visceral metastases, no lesion > 3 cm and liver lesions must be stable for at least 1 month prior to enrollment.
- 203 Bone metastases
- 204 Primary ocular or mucosal melanoma
- 205 History or evidence of symptomatic autoimmune **disease (such as pneumonitis, glomerulonephritis, vasculitis, or other), or history of autoimmune disease that required systemic treatment (ie, use of corticosteroids, immunosuppressive drugs or biological agents used for treatment of autoimmune diseases) in past 2 months prior to enrollment. Replacement therapy (eg, thyroxine for hypothyroidism, insulin for diabetes mellitus) is not considered a form of systemic treatment for autoimmune disease.**
- 206 Evidence of clinically significant immunosuppression such as the following:
- primary immunodeficiency state such as Severe Combined Immunodeficiency Disease
 - concurrent opportunistic infection
 - receiving systemic immunosuppressive therapy (> 2 weeks), including oral steroid doses > 10 mg/day of prednisone or equivalent **during the 2 months prior to enrollment**
- 207 Active herpetic skin lesions or prior complications of HSV-1 infection (eg, herpetic keratitis or encephalitis)
- 208 Requires intermittent or chronic systemic (intravenous or oral) treatment with an antiherpetic drug (eg, acyclovir), other than intermittent topical use
- 209 Previous treatment with talimogene laherparepvec
- 211 Currently receiving treatment with another investigational device or drug study, or less than 28 days since ending treatment with another investigational device or drug study(s)
- 212 Other investigational procedures while participating in this study are excluded
- 213 Known to have acute or chronic active hepatitis B infection
- 214 Known to have acute or chronic active hepatitis C infection
- 215 Known to have human immunodeficiency virus infection
- 216 History of other malignancy within the past 3 years with the following exceptions:
- malignancy treated with curative intent and with no known active disease present for ≥ 3 years before enrollment and felt to be at low risk for recurrence by the treating physician
 - adequately treated non-melanoma skin cancer without evidence of disease

- adequately treated cervical carcinoma in situ without evidence of disease
 - adequately treated breast ductal carcinoma in situ without evidence of disease
 - prostatic intraepithelial neoplasia without evidence of prostate cancer
 - adequately treated urothelial papillary noninvasive carcinoma or carcinoma in situ
- 217 Subject has known sensitivity to any of the products or components to be administered during dosing
- 218 Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures to the best of the subject's and investigator's knowledge
- 219 History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen medical monitor, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion
- 220 Subject previously has entered this study
- 221 Female subject is pregnant or breast-feeding, or planning to become pregnant during study treatment and through 3 months after the last dose of talimogene laherparepvec
- 222 Female subject of childbearing potential who is unwilling to use acceptable method(s) of effective contraception during study treatment and through 3 months after the last dose of talimogene laherparepvec
- Note: Women not of childbearing potential are defined as: Any female who is post-menopausal (age \geq 55 years with cessation of menses for 12 or more months or $<$ than 55 years with postmenopausal status confirmed by follicle-stimulating hormone [FSH] in the postmenopausal range), or who have had a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy.
- Note: Acceptable methods of effective contraception are defined in the informed consent form. Where required by local laws and regulations, additional country-specific requirements are outlined in a country-specific protocol supplement at the end of the [Appendix Section](#) of the protocol.
- 223 **Sexually active subjects and their partners unwilling to use male or female latex condom to avoid potential viral transmission during sexual contact while on treatment and within 30 days after treatment with talimogene laherparepvec.**

5. SUBJECT ENROLLMENT

Before subjects may be entered into the study, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see [Section 11](#)). All subjects must personally sign and date the informed consent form before commencement of study-specific activities/procedures (ie, non-standard of care procedures).

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

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

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

6. TREATMENT PROCEDURES

6.1 Classification of Product

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

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

6.2 Investigational Product

6.2.1 Amgen Investigational Product Talimogene Laherparepvec

Talimogene laherparepvec will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures. Talimogene laherparepvec is supplied as a sterile frozen liquid in a single-use 2-cc Crystal Zenith (CZ resin) vial with a gray Fluorotec®-coated chlorobutyl elastomer stopper, aluminum

seal, and polypropylene cap. Each vial contains a minimum of 1.0 mL talimogene laherparepvec at either 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 healthcare professional. Subjects should be assessed clinically for adverse events/toxicity prior to each dose using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 ([Appendix A](#)). Complete blood count with differential and chemistry panels including liver function laboratory tests (**such as** ALT, AST, and total bilirubin) should be obtained according to the Schedule of Assessments (see [Table 2](#)) and the results should be checked before scheduled **doses as per the requirements described in the Schedule of Assessments**. Dosing will occur only if these test values are acceptable, per [Section 6.2.1.2](#).

Talimogene laherparepvec will be administered by intralesional injection only into injectable cutaneous, subcutaneous, and nodal tumors, with or without image ultrasound guidance. Talimogene laherparepvec must not be administered into visceral organ metastases. The initial dose of talimogene laherparepvec is up to 4.0 mL of 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 (+ 5) days. Subsequent cycles of talimogene laherparepvec will be 14 (\pm 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 (+ 5) days after the initial injection (ie, no sooner than day 22 but should not be delayed more than 5 days after the 21-day time point). Subsequent injections up to 4.0 mL of 10^8 PFU/mL should be given every 14 (\pm 3) days.

The maximum volume of talimogene laherparepvec administered at any dose is 4.0 mL for any individual lesion. The maximum dose in any treatment is 4.0 mL. Investigators are encouraged to use the maximum amount whenever lesions allow. Dose reduction for adverse events is not allowed. However, if in the course of administration of talimogene laherparepvec the subject cannot tolerate the full dose due to an

injection-related adverse event such as pain, the total volume given should be recorded, and the reason for intolerance should be documented as an adverse event.

The recommended volume of talimogene laherparepvec to be injected into the tumor(s) is dependent on the size of the tumor(s) and should be determined according to the injection volume guideline in [Table 1](#). The tumor size assessment should be done by clinical exam using ruler or caliper for cutaneous and palpable and protruding subcutaneous and nodal lesions, or by measurements under ultrasound of deep-seated subcutaneous and nodal lesions.

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

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

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

- any new injectable tumor that has appeared since the last injection
- by tumor size, beginning with the largest tumor
- any previously uninjectable tumor(s) that is now injectable, including the previously uninjected lesion(s) after the biopsy at week 6 if now injectable

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

A subject will be treated with talimogene laherparepvec until the subject has achieved a CR, all injectable tumors have disappeared, clinically significant (resulting in clinical deterioration or requiring change of therapy) disease progression beyond 6 months of treatment, per modified World Health Organization (WHO) response criteria ([Appendix D](#)), or intolerance of study treatment, whichever occurs first. Due to the mechanism of action, subjects may experience growth in existing tumors or the appearance of new tumors prior to maximal clinical benefit of talimogene laherparepvec. Therefore, dosing should be continued for at least 6 months from the time of initial dose, provided that the subject has no evidence of clinically significant deterioration of health status requiring discontinuation of treatment with talimogene laherparepvec and is able to tolerate the treatment.

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

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

Dose reductions of talimogene laherparepvec are not permitted, other than with respect to a reduction in the volume injected due to a disease response.

If a subject experiences any of the following treatment-related toxicities, talimogene laherparepvec administration should be delayed until the toxicity has resolved to at least CTCAE grade 1 or has returned to baseline:

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

Subjects who are receiving talimogene laherparepvec may not receive systemic antiherpetic drugs (eg, acyclovir, valacyclovir, famciclovir), but **may receive a topically administered antiherpetic drug more than 20 cm from a talimogene laherparepvec injection site. If a subject requires treatment with systemic antiherpetic drugs (eg, acyclovir, valacyclovir, famciclovir) talimogene laherparepvec should be withheld and the investigator or designee should notify the Amgen medical monitor as soon as possible. Subject may be allowed to continue treatment after discussion between the Amgen medical monitor and the investigator to determine the appropriateness of treatment resumption.**

Dosing should be permanently discontinued if, in the opinion of the investigator, the subject develops clinical evidence of any systemic herpes infection (such as encephalitis or disseminated infection).

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

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

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

If talimogene laherparepvec dosing is delayed by more than 4 weeks from the date of the planned dose (ie, approximately 6 weeks from the previous dose) due to the occurrence of an adverse event that is considered related to talimogene laherparepvec, the subject must be permanently withdrawn from talimogene laherparepvec treatment.

If talimogene laherparepvec dosing is delayed by more than 4 weeks from the date of the planned dose (ie, approximately 6 weeks from the previous dose) for reasons other than treatment-related toxicity, the case must be reviewed by the Amgen medical monitor in conjunction with the investigator to determine if the subject can resume talimogene laherparepvec therapy.

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

- The subject, for any reason, requires treatment with another anticancer therapeutic agent for treatment of the study disease (other than the exceptions noted in [Section 6.5](#)). In this case, discontinuation from the treatment occurs immediately upon introduction of the new agent.
- Clinically relevant disease progression beyond 6 months of treatment occurs as defined per the modified WHO response criteria ([Appendix D](#)).
- A grade 2 or greater immune-mediated adverse event (with the exception of vitiligo) or allergic reactions attributed to talimogene laherparepvec that would require a dose delay of greater than 4 weeks from the date of the planned dose (ie, approximately 6 weeks from the previous dose).

Note: immune-mediated glomerulonephritis, vasculitis, and pneumonitis and exacerbation of psoriasis have been observed in subjects receiving talimogene laherparepvec in clinical trials. Most of these subjects had a history of other autoimmune disease and/or prior treatment with agents that offered plausible

alternative etiologies, however, immune-mediated adverse events can potentially involve any organ system.

- Any other talimogene laherparepvec-related non-hematologic or hematologic toxicities grade 3 or greater occur that, in the opinion of the investigator, would require a dose delay of greater than 4 weeks from the date of the planned dose (ie, approximately 6 weeks from the previous dose).
- The subject develops clinical evidence of any systemic herpes infection (such as encephalitis or disseminated infection).
- A female subject becomes pregnant or fails to use acceptable method(s) of effective contraception (for those subjects who are able to conceive) **including but not limited to male or female latex condom to avoid potential viral transmission during sexual contact.**
- A female subject breast feeds while on study treatment.
- Concurrent medical illness that, in the judgment of the investigator, would make continued treatment with talimogene laherparepvec dangerous for the subject.

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

6.3 Other Protocol-required Therapies

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

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

6.4 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in [Section 6.8](#).

All prescription and nonprescription concomitant medication administered up to 28 days prior to enrollment, on an ongoing basis **after** enrollment, as well as changes in such concomitant medication, and any new concomitant medication taken while the subject is on study, should be recorded on the appropriate case report form (CRF) until 30 days (+ 7 days) after the last dose of talimogene laherparepvec. The therapy name, indication, dose, unit, frequency, start date, and stop date will be collected.

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

6.5 Other Treatment Procedures

Treatment with talimogene laherparepvec may result in the reduction of tumor burden such that surgical resection of previously unresected lesion becomes possible.

Investigators may choose to resect lesions which become suitable for resection to render the subject free of macroscopic disease. Additionally, biopsies will be taken of cutaneous, subcutaneous or **nodal** lesions for tumor analysis during study. In the event of a complete response, residual **visible** cutaneous or subcutaneous index lesions must be documented by representative biopsy to not contain viable tumor. If a subject undergoes resection of the lesion in the event other than CR, the investigator or designee should notify the sponsor medical monitor as soon as possible and the procedure should be recorded in the source document and eCRF. In these instances, if the response of other lesions is at least PR (if other lesions remain), the response should be designated PR with the date of surgery as the date of response. If no residual disease remains following surgery, this should also be noted in the eCRF, the response definition again being PR **with the date of surgery as the date of response. If no viable melanoma was found in the surgical specimen and all other tumor lesions resolved completely (if were present), the response definition will be CR with the date of surgery as the date of response.**

Local palliative radiation treatment for relief of various symptoms including, but not limited to, bleeding or pain associated with the underlying disease will be permitted at any time during the study. Subjects with local symptoms suggestive of disease progression should be evaluated for tumor response per modified WHO response criteria (see [Appendix D](#)) prior to the administration of palliative radiotherapy. If a subject undergoes local radiation, the investigator or designee should notify the sponsor medical monitor as soon as possible and the treatment should be recorded in the source document and eCRF.

If a subject demonstrates evidence of recurrent or new central nervous system (CNS) metastases, talimogene laherparepvec should be withheld and the investigator or designee should notify the Amgen medical monitor as soon as possible. Subjects may be allowed to remain on protocol after discussion between the Amgen medical monitor and the investigator to determine the appropriateness of treatment resumption provided

CNS lesions can be treated with stereotactic radiotherapy (including GammaKnife) or **resection** and if there is no change in the baseline ECOG performance status. Subjects may be allowed to reinitiate talimogene laherparepvec following treatment of CNS metastases while receiving dexamethasone or a similar corticosteroid at no more than 1.5 mg dexamethasone (or 10 mg prednisone **or equivalent**) per day. If higher doses of a steroid are used, talimogene laherparepvec must be held until that dose level is reached during the period of steroid tapering.

6.6 Medical Devices

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

6.7 Product Complaints

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

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

6.8 Excluded Treatments and/or Procedures During Study Period

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

- other investigational agents or procedures
- concurrent experimental or approved anti-tumor therapies other than study drug and radiation therapy required for palliation (as noted in [Section 6.5](#))
- chronic oral or systemic steroid medication use at a dose of >10 mg/day of prednisone or equivalent (with the exception of treatment for adverse events [see [Section 6.2.1.2](#)] and CNS metastases [see [Section 6.5](#)]). Steroids with low systemic absorption [eg, triamcinolone hexacetonide] injected into a joint space is allowed)
- antiherpetic drugs (eg, acyclovir), other than if topically administered > 20 cm from a talimogene laherparepvec injection site. **If a subject requires treatment with a systemic antiherpetic drugs (eg, acyclovir, valacyclovir, famciclovir) talimogene laherparepvec should be withheld and the investigator or designee should notify the Amgen medical monitor as soon as possible. Subject may be allowed to continue treatment after discussion between the Amgen medical monitor and the investigator to determine the appropriateness of treatment resumption.**

- Subjects must not schedule any elective surgeries during the treatment period and for at least 30 days after the last administration of study drug. If a subject undergoes any unexpected surgery during the course of the study, study treatment must be withheld and the investigator or designee should notify the sponsor medical monitor as soon as possible. A subject may be allowed to resume study drug if both the investigator and sponsor medical monitor agree to restart study therapy.

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

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

7. STUDY PROCEDURES

7.1 Schedule of Assessments

The schedule of assessments for the study is summarized in [Table 2](#)

Table 2. Schedule of Assessments

	Screening ^a	Treatment Period ^b									Follow-up Period	
Cycle ⁱ	≤ 28 days	1	2	3	4	5	6	7	8	Cycle 8 and Beyond ⁱ	Safety ^c	Survival ^d
Day		1	1	1	1	1	1	1	1	1	30 (+7) Days	Every 12 (±28 days) Weeks
GENERAL & SAFETY ASSESSMENTS												
Informed Consent	X											
Review of Medical/Surgical History	X											
Review of Eligibility Criteria	X											
Concomitant Medications ^e	X											
Adverse and Serious Adverse Events ^f	X											
Adverse Events Thought to Be Related to Talimogene Laherparepvec ^f		X										X
Physical Exam ^g	X	X					X			Q6C	X	
Vital Signs ^h	X	X	X		X		X		X	Q2C	X	
ECOG Performance Status ^w	X	X					X			Q6C	X	
Survival Assessment												X
Anti-cancer therapy for melanoma ^x											X	X
LOCAL LABORATORY ASSESSMENTS												
Urine or Serum Pregnancy Test ^t	X										X	
Hematology ^j	X	X	X	X				X		Q4C	X	
Chemistry ^k	X	X	X	X				X		Q4C	X	
Serum LDH	X											
PT (or INR) and PTT	X											
CENTRAL LABORATORY ASSESSMENTS												
Archived Tumor Tissue for Biomarker Analysis and BRAF ^{V600E/K} ^l		Within 28 days after enrollment										
Swab of Herpetic Lesion for qPCR ^m		Within 3 days of occurrence of suspected lesion of herpetic origin									X	X
Blood for HSV Serostatus ⁿ		Within 3 days prior to dose at day 1 of week 1, week 6, and week 12										

Table 2. Schedule of Assessments

	Screening ^a	Treatment Period ^b									Follow-up Period	
Cycle ^t	≤ 28 days	1	2	3	4	5	6	7	8	Cycle 8 and Beyond	Safety ^c	Survival ^d
Day		1	1	1	1	1	1	1	1	1	30 (+7) Days	12 (±28 days) Weeks
Blood for Biomarker Analysis ^o		Within 3 days prior to dose at day 1 of week 1, week 6, week 12, week 24										
Tumor Biopsy for Biomarker Analysis ^p		Within 5 days prior to dose at day 1 of week 1, within 7 days prior to dose at week 6 and <i>within 7 days after the documentation of</i> disease progression followed by treatment discontinuation										
TUMOR/RESPONSE ASSESSMENTS												
Clinical Tumor Assessments ^q	X	Day 1 of week 12 and then every 12 weeks until PD or start of new anticancer therapy									X	X
Radiological Tumor Assessments ^r	X	Day 1 of week 12 and then every 12 weeks until PD or start of new anticancer therapy									X	X
Photographs of all Visible Tumor Lesions ^s (Select Sites Only)		X	X		X		X		X	Q2C		
DOSING												
Talimogene Laherparepvec Administration ^t		X	X	X	X	X	X	X	X	QC		
REPORTING EXPOSURE TO TALIMOGENE LAHERPAREPVEC												
Exposure of Household member, Healthcare provider, or close contact ^u		X										
REPORTING PREGNANCY/LACTATION												
Reporting of Pregnancy or Lactation ^v		X										

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^a Screening assessments to be performed within 28 days prior to enrollment, unless otherwise indicated.

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

^c Safety follow-up will be performed 30 (+7) days after the last dose of talimogene laherparepvec.

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

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

- ^f All nonserious adverse events (**related or not related to talimogene laherparepvec**) that occur after **the first dose** through 30 (+7) days after the last administration of talimogene laherparepvec will be recorded in the case report form. **In addition, all adverse events deemed by the investigator to be potentially related to talimogene laherparepvec will be recorded in the case report form through the survival follow-up.** Adverse events should be assessed on an ongoing basis and recorded at each subject visit. All serious adverse events that occur after the subject has signed the informed consent through 30 (+7) days after the last administration of talimogene laherparepvec will be reported to Amgen and recorded in the case report form. Serious adverse events must be reported to Amgen within 24 hours of discovery.
- ^g Physical examination as per standard of care.
- ^h Vital signs (blood pressure, heart rate, and temperature) must be performed at screening, prior to talimogene laherparepvec administration on day 1 of cycle 1, 2, and 4, then every other cycle (Q2C) until end of treatment, and at the safety follow-up visit.
- ⁱ Urine or serum pregnancy test must be performed on females of childbearing potential within 3 days prior to enrollment and at the safety follow-up visit. Note: Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as defined in a country-specific protocol supplement at the end of the [Appendix Section](#) of the protocol as required per local laws and regulations.
- ^j Blood samples for hematology will be collected at screening, within 3 days prior to talimogene laherparepvec administration on day 1 of cycles 1, 2, and 3, then every 4th cycle (Q4C) until end of treatment, and at the safety follow-up visit. Results must be reviewed prior to scheduled dose of study treatment.
- ^k Blood samples for chemistry will be collected at screening, within 3 days prior to talimogene laherparepvec administration on day 1 of cycles 1, 2, and 3, then every 4th cycle (Q4C) until end of treatment, and at the safety follow-up visit. Results must be reviewed prior to scheduled dose of study treatment.
- ^l Archived formalin-fixed paraffin-embedded tumor tissue (block or unstained tumor slide) from either the primary tumor or a metastatic lesion, and the associated pathology reports should be submitted to the central laboratory within 28 days after enrollment for biomarker analyses. *BRAF*^{V600E/K} mutation status may be obtained in a number of ways. For previously Known *BRAF*^{V600E/K} Tumor Status, *BRAF*^{V600E/K} tumor status result, obtained from a local laboratory prior to screening for this study will be acceptable. For previously Unknown *BRAF*^{V600E/K} Tumor Status, archived formalin-fixed paraffin-embedded tumor tissue (block or unstained tumor slide) from either the primary tumor or a metastatic lesion should be analyzed at a local laboratory or submitted to the central laboratory within 28 days after enrollment.
- ^m Swabs of any lesion suspected to be herpetic in origin will be collected as follows: Subject should return to clinic within 3 days of the occurrence of reportable lesion suspected to be herpetic in origin, such as cold sores or vesicles. The lesion should be evaluated by the investigator and swabbed if **herpetic** infection is suspected. A qPCR analysis will be performed at a central lab on the swab to evaluate whether the talimogene laherparepvec DNA is detectable in the sample.
- ⁿ Blood sample for HSV serostatus will be collected (within 3 days prior to talimogene laherparepvec administration) at day 1 of week 1 [**Cycle 1**], week 6 [**Cycle 3**], and week 12 [**Cycle 6**].
- ^o Blood sample for biomarker analysis will be collected (within 3 days prior to talimogene laherparepvec administration) at day 1 of week 1 [**Cycle 1**], week 6 [**Cycle 3**], week 12 [**Cycle 6**], and week 24 [**Cycle 12**].
- ^p Tumor biopsy **from cutaneous, subcutaneous or nodal lesions** for biomarker analysis **should not be collected prior to the subject being enrolled. Tumor biopsy should be collected** (within 5 days prior to **first** talimogene laherparepvec administration) from one lesion at day 1 of week 1 [**Cycle 1**] and, if there are ≥ 2 lesions at baseline and one is left uninjected as described in [Section 6.2.1.1](#), from an uninjected lesion **within 7 days prior to dose** at day 1 of week 6 [**Cycle 3**]. Also **within 7 days after documentation of disease progression followed by treatment discontinuation** from the **available cutaneous, subcutaneous or nodal** lesion responsible for PD **and easily accessible for biopsy with or without ultrasound guidance**. Note: uninjected lesion biopsied at day 1 of week 6 [**Cycle 3**] must be different lesion from the lesion biopsied at day 1 of week 1 [**Cycle 1**].
- ^q Investigator's clinical measurement of cutaneous, subcutaneous, or nodal tumor by caliper at screening, day 1 of week 12 (± 1 week) [**Cycle 6**] and then every 12 weeks (± 1 week), or more frequently if clinically indicated, until clinically relevant disease progression beyond 6 months of treatment (per modified WHO response criteria, [Appendix D](#)) or until the start of a new anticancer therapy. The screening measurement must be done within 28 days prior to enrollment and will be used as baseline. If subject discontinues talimogene laherparepvec for reason other than disease progression or death, clinical tumor measurements are to be performed at safety follow-up visit (if not performed within previous 4 weeks [+ 1 week]) and every 12 weeks (±1week) during the long term follow-up period until clinically relevant disease progression beyond 6 months of treatment (per modified WHO response criteria, [Appendix D](#)) or until the start of a new anticancer therapy.

- ^r Radiographic imaging (CT, PET/CT, MRI, or US) of the chest, abdomen, and pelvis, and all other sites of disease, and CT scan or MRI of brain (only if symptoms or signs suggestive of CNS metastasis are present) at screening, day 1 of week 12 (± 1 week) [**Cycle 6**] and then every 12 weeks (± 1 week), or more frequently if clinically indicated, until clinically relevant disease progression beyond 6 months of treatment (per modified WHO response criteria, [Appendix D](#) or until the start of a new anticancer therapy. The screening assessment must be done within 28 days prior to enrollment and will be used as baseline. If subject discontinues talimogene laherparepvec for reason other than disease progression or death, radiographic imaging is to be performed at safety follow-up visit (if not performed within previous 4 weeks [± 1 week]) and every 12 weeks (± 1 week) during the long term follow-up period until clinically relevant disease progression beyond 6 months of treatment (per modified WHO response criteria, [Appendix D](#)) or until the start of a new anticancer therapy.
- ^s At select sites only, photographs of **all** visible cutaneous and subcutaneous tumor lesions at **Cycle 1, Cycle 2, and every second subsequent cycle** until end of treatment (**always within 3 days prior to investigational product administration**). See [Section 7.2.6](#)
- ^t The first cycle of talimogene laherparepvec will be 21 (+ 5) days. Subsequent cycles of talimogene laherparepvec will be 14 (± 3) days (QC). On day 1 of cycle 1, the first dose of talimogene laherparepvec will be up to 4.0 mL of 10^6 PFU/mL. The second injection up to 4.0 mL of 10^8 PFU/mL should be administered 21 (+ 5) days after the initial injection (ie, no sooner than day 22 but should not be delayed more than 5 days after the 21-day time point). Subsequent injections up to 4.0 mL of 10^8 PFU/mL should be given every 14 (± 3) days. Subjects will be treated with talimogene laherparepvec until the subject has achieved a complete response, all injectable tumors have disappeared, clinically significant (resulting in clinical deterioration or requiring change of therapy) disease progression beyond 6 months of treatment, per modified WHO response criteria ([Appendix D](#)), or intolerance of study treatment, whichever occurs first.
- ^u Reporting potential or known unintended exposure to talimogene laherparepvec: If a household member, caregiver, or healthcare provider who has had close contact with the subject is suspected to have been exposed to talimogene laherparepvec (eg, have or who have had signs or symptoms suspected to be herpetic origin or accidentally exposed to talimogene laherparepvec), report the potential or known unintended exposure to talimogene laherparepvec, suspected related signs or symptoms, and detection of talimogene laherparepvec in a subject's household member, caregiver, or healthcare provider as specified in [Section 9.4](#)
- ^v Reporting of pregnancy or lactation: If a pregnancy occurs in a female subject, or female partner of a male subject, or a lactation case occurs while the subject is taking talimogene laherparepvec, the case must be reported to Amgen **Global Patient Safety** through 3 months after the last dose of talimogene laherparepvec as specified in [Section 9.3](#)
- ^w **ECOG Performance Status will be assessed at screening, day 1 of Cycle 1, then every 12 weeks (ie, every sixth cycle) alongside the tumor response assessments until the end of tumor response assessments per study protocol.**
- ^x **Anti-cancer therapy may include any systemic, regional, and local therapies for melanoma disease.**

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

7.2 General Study Procedures

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

During treatment, assessments and procedures can be performed within 3 days of the planned visit **unless specified otherwise**. It is recommended that dosing occur on the same day of the week (eg, if first dose is administered on Monday, all subsequent doses should be administered on a Monday), however a \pm 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

<u>Chemistry</u>	<u>Hematology</u>	<u>Biomarkers</u>	<u>Other Labs</u>
Sodium	RBC	HSV Serostatus	Pregnancy
Potassium	Hemoglobin	Blood for	LDH
Chloride	Hematocrit	biomarker	qPCR for
Total protein	Platelets	analysis	talimogene
Albumin	WBC	Archived tumor	laherparepvec DNA
Calcium	Differential ^a	tissue for	PT (or INR), PTT
Creatinine	• Bands/Neutrophils	biomarker	
Total bilirubin	• Eosinophils	analysis	
Alkaline phosphatase	• Basophils	Tumor biopsy for	
AST (SGOT)	• Lymphocytes	biomarker	
ALT (SGPT)	• Monocytes	analysis	

^a 3-part differential if 5-part is unable to be performed

The chemistry, hematology, PT(or INR), PTT and pregnancy tests are to be performed at a local laboratory and test results are to be fully and routinely recorded on the electronic CRFs (eCRFs). Missed tests that are not done must be reported as such on the eCRFs **and should not be completed as unscheduled tests between cycles**.

The real-time **quantitative** polymerase chain reaction (qPCR) and biomarker/**antibody** tests will be performed at a central laboratory and tests results will not be reported on the eCRFs.

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

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

7.2.1 Screening and Enrollment

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

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

- Documentation of concomitant medications
- Reporting of serious adverse events (SAEs) that occur after subject signs informed consent form. SAEs will be reported to Amgen within 24 hours following the investigator's knowledge of the event
- Registration in Electronic Trial Operation (ETO) system (see [Section 5](#))

7.2.2 Treatment

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

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

- Vital signs (eg, systolic/diastolic blood pressure, heart rate, and temperature) at day 1 of cycles 1, 2, and 4, then every other cycle until end of study treatment
- **Determination of ECOG Performance Status at day 1 of Cycle 1, and then every 12 weeks (ie, every sixth cycle) in parallel with tumor response assessment and until the end of tumor assessment per study protocol ([Appendix E](#))**
- **Physical exams as per standard of care at day 1 of Cycle 1, and then every 12 weeks (ie, every sixth cycle) until the end of study treatment**
- Local laboratory assessments: Screening laboratory values may be used for day 1 cycle 1 assessment if completed within 3 days of study treatment initiation. On treatment tests can be performed within 3 days of the planned visit. Results must be reviewed prior to the administration of study treatment.
 - hematology panel: hemoglobin, hematocrit, WBC with 5-part differential (3-part differential if 5-part is unable to be performed), RBC, platelets
 - day 1 of cycles 1, 2, and 3, then every fourth (4th) cycle until end of study treatment
 - chemistry panel: sodium, potassium, chloride, total protein, albumin, calcium, creatinine, total bilirubin, alkaline phosphatase, AST, ALT
 - day 1 of cycles 1, 2, and 3, then every fourth (4th) cycle until end of study treatment
 - Note: Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as defined in a country-specific protocol supplement at the end of the [Appendix Section](#) of the protocol as required per local laws and regulations.
- Central laboratory assessments:
 - Archived formalin-fixed paraffin-embedded tumor tissue (block or unstained tumor slide) from either the primary tumor or a metastatic lesion, and the associated pathology reports, must be submitted to the central laboratory within 28 days after enrollment for biomarker analyses

- $BRAF^{V600E/K}$ mutation testing/status may be obtained in a number of ways as listed below:
 - o previously known $BRAF^{V600E/K}$ tumor status: $BRAF^{V600E/K}$ tumor status result, obtained from a local laboratory prior to screening for this study will be acceptable and should be available within 28 days after enrollment
 - o previously unknown $BRAF^{V600E/K}$ tumor status: Archived formalin-fixed paraffin-embedded tumor tissue (block or unstained tumor slide) from either the primary tumor or a metastatic lesion (as described above) will be analyzed at a local laboratory or submitted to the central laboratory within 28 days after enrollment for $BRAF^{V600E/K}$ tumor status determination
- swabs of cold sores, vesicles, and other lesions suspected to be herpetic in origin (if any) for qPCR testing:
 - o subject should return to clinic within 3 days of the occurrence of a reportable lesion suspected to be herpetic in origin, such as cold sores or vesicles. The lesion should be evaluated by the investigator and swabbed if **herpetic** infection is suspected. A qPCR analysis will be performed on the swab sample to evaluate whether the talimogene laherparepvec DNA is detectable in the sample.
- blood sample for HSV serostatus (within 3 days prior to talimogene laherparepvec administration) at day 1 of week 1, week 6, and week 12.
- blood sample for biomarker analysis (within 3 days prior to talimogene laherparepvec administration) at day 1 of week 1, week 6, week 12 and week 24. Note: Lymphocyte subsets will be measured by flow cytometric determination CCI
- **all tumor biopsies in the study should be performed from easily accessible with or without ultrasound guidance cutaneous, subcutaneous or nodal lesions.** Tumor biopsy for biomarker analysis **should not be collected prior to the subject being enrolled. Tumor biopsy should be collected** (within 5 days prior to **first** talimogene laherparepvec administration) from one lesion at day 1 of week 1 and, if there are ≥ 2 lesions at baseline and one is left uninjected as described in [Section 6.2.1.1](#), from an uninjected lesion **within 7 days prior to talimogene laherparepvec injection** at day 1 of week 6. Also **within 7 days after documentation of** disease progression (PDn or PDr) **that resulted in treatment discontinuation**, from the **available and easily accessible for biopsy with or without ultrasound guidance cutaneous, subcutaneous or nodal** lesion responsible for **progression**

Note: uninjected lesion biopsied at day 1 of week 6 must be a different lesion from the lesion biopsied at day 1 of week 1
- Radiographic tumor imaging assessments at day 1 of week 12 (± 1 week) and then every 12 (± 1 week) weeks, or more frequently if clinically indicated, until clinically relevant disease progression beyond 6 months of treatment, per modified WHO response criteria [Appendix D](#)), or until the start of a new anticancer treatment
 - radiographic imaging must include CT scan, PET/CT, MRI, or ultrasound (**if applicable**) of the chest, abdomen, and pelvis and all other sites of disease. In addition, CT scan or MRI of the brain will only be performed if symptoms or signs suggestive of CNS metastasis are present. The imaging modality selected

(eg, CT or MRI) should remain constant **throughout the study** for any individual subject.

- Clinical tumor assessments (clinical measurement of cutaneous, subcutaneous, or nodal tumor measurement by caliper) at day 1 of week 12 (± 1 week) and then every 12 (± 1 week) weeks or more frequently if clinically indicated, until clinically relevant disease progression beyond 6 months of treatment, per modified WHO response criteria ([Appendix D](#)), or until the start of a new anticancer therapy
- Tumor response assessments at day 1 of week 12 (± 1 week) and then every 12 (± 1 week) weeks or more frequently if clinically indicated, until clinically relevant disease progression beyond 6 months of treatment, per modified WHO response criteria ([Appendix D](#)), or until the start of a new anticancer therapy
- Photographs of **all** visible cutaneous and subcutaneous tumor lesions **at day 1 Cycle 1, day 1 Cycle 2, and day 1 of every second subsequent cycle** until end of tumor response assessment per protocol, always within 3 days prior to investigational product administration. (Select Sites Only: see [Section 7.2.6](#))
- Recording of adverse events at each visit
- Recording of serious adverse events at each visit. Serious adverse events will be reported to Amgen within 24 hours following the investigator's knowledge of the event
- Documentation of concomitant medications at each visit
- Reporting pregnancy in a female subject or a female partner of a male subject while the subject is taking talimogene laherparepvec treatment and through 3 months after end of treatment ([Section 9.3](#))
- Reporting lactation case in a female subject while the subject is taking talimogene laherparepvec treatment and through 3 months after end of treatment ([Section 9.3](#))
- Administration of talimogene laherparepvec treatment at day 1 of each cycle ([Section 6.2.1.1](#))

7.2.3 Safety Follow-up Visit

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

- Physical examination as per standard of care
- Vital signs (eg, systolic/diastolic blood pressure, heart rate, and temperature)
- Determination of ECOG Performance Status **alongside the tumor response assessments until the end of tumor response assessments per study protocol** ([Appendix E](#))
- Local laboratory assessments:
 - hematology panel: hemoglobin, hematocrit, WBC with 5-part differential (3-part differential if 5-part is unable to be performed), RBC, platelets
 - chemistry panel: sodium, potassium, chloride, total protein, albumin, calcium, creatinine, total bilirubin, alkaline phosphatase, AST, ALT
 - serum or urine pregnancy test for female subjects of childbearing potential

- Central laboratory assessments:
 - swabs of cold sores, vesicles, and other lesions suspected to be herpetic in origin (if any) for qPCR testing:
 - subject should return to clinic within 3 days of the occurrence of a reportable lesion suspected to be herpetic in origin such as cold sores or vesicles. The lesion should be evaluated by the investigator and swabbed if HSV infection is suspected. A qPCR analysis will be performed on the swab sample to evaluate whether the talimogene laherparepvec DNA is detectable in the sample.
- Radiographic tumor imaging, clinical tumor assessments, and tumor response assessments, will be performed as documented in [Section 7.2.2](#) until documented clinically relevant disease progression beyond 6 months of treatment, per modified WHO response criteria ([Appendix D](#)), or until the start of a new anticancer therapy. (Only if subject has discontinued study treatment for reason other than disease progression or death and if not performed within 4 weeks [+1 week] of the safety visit.)
- Recording of adverse events
- Recording of serious adverse events. SAEs will be reported to Amgen within 24 hours following the investigator's knowledge of the event.
- Documentation of concomitant medications

7.2.4 Long-term Follow-up/End of Study

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

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

After the long term follow-up period of this study has ended, subjects who end the study for any reason other than death or withdrawal of full consent will be followed for survival

under an ongoing separate registry protocol (Study 20120139) that is in place for the long-term follow-up of all subjects treated with talimogene laherparepvec in clinical trials. The registry protocol will also monitor for late and long-term adverse events thought to be potentially related to talimogene laherparepvec **and use of anti-cancer therapies for melanoma.**

7.2.5 Reporting Exposure to Talimogene Laherparepvec

If a household member, caregiver, or healthcare provider who have had close contact with the subject is suspected to have been exposed to talimogene laherparepvec (eg, have or who have had signs or symptoms suspected to be herpetic in origin or accidentally exposed to talimogene laherparepvec), report the potential or known unintended exposure to talimogene laherparepvec, suspected related signs or symptoms, and detection of talimogene laherparepvec in a subject's household member, caregiver, or healthcare provider as specified [Section 9.4](#).

7.2.6 Optional Photography Substudy (Select Sites Only)

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

7.3 Biomarker Development

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic

intervention. In oncology, there is particular interest in the molecular changes underlying the oncogenic processes that may identify cancer subtypes, stage of disease, assess the amount of tumor growth, or predict disease progression, metastasis, and responses to investigational product.

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

7.3.1 Blood Samples

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

Blood samples (both cells and plasma) will be analyzed for changes in the immune system before and during treatment that correlate with clinical response. Tumor antigen specific cytotoxic T cells will be enumerated in blood samples CCI [REDACTED]

Changes in circulating immune cells will be characterized by flow cytometry to enumerate the number of immune cell subsets CCI [REDACTED]

T cell subsets will also be characterized for activation markers CCI [REDACTED]

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

7.3.2 Tumor Tissue Samples

Archived Tumor Tissue Sample:

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

The tumor block is to be carefully selected by a pathologist or a skilled experienced histology associate to include generous tumor tissue using the Pathology Report as a guide. In the event that multiple tumor blocks with generous tumor tissue are available, the most recent block should be submitted. In lieu of a block, approximately 20 unstained sections on charged slides from the same block can be submitted.

Analyses of tumor specific mutations or epigenetic changes may be performed (eg somatic mutations) on tumor tissues.

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

Tumor Biopsy Samples:

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

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

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

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

7.4 Pharmacogenetic Studies

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

7.5 Sample Storage and Destruction

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

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

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

Since the evaluations are not expected to be available in time to benefit the subject directly or to alter the treatment course, the results of qPCR testing from swabs of cold sores, vesicles, and other lesions suspected to be herpetic in origin will not be provided unless requested by the investigator or the subject. Results may not be available until the end of the study. Results of biomarker development or other exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

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

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as appropriate (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 and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments ([Table 2](#)) and collection of data, including endpoints and adverse events. The investigator must document the change to the Schedule of Assessments ([Table 2](#)) and the level of follow-up that is agreed to by the subject (eg, in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records).

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

8.2 Investigator or Sponsor Decision to Withdraw or Terminate Subjects' Participation Prior to Study Completion

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

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

8.3 Reasons for Removal From Treatment or Study

8.3.1 Reasons for Removal From Treatment

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

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

8.3.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

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

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Adverse Events

9.1.1 Definition of Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment.

The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition (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.

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

The investigator must assign the following adverse event attributes:

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

The adverse event grading scale used will be the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. The grading scale used in this study is described in [Appendix A](#). The investigator must assess whether the adverse event is possibly related to talimogene laherparepvec. This relationship is indicated by a “yes” or “no” response to the question: Is there a reasonable possibility that the event may have been caused by administration of investigational product?

The investigator must assess whether the adverse event is possibly related to any study-mandated activity and/or procedure (eg, including any screening procedures). This relationship is indicated by a “yes” or “no” response to the question: “Is there a reasonable possibility that the event may have been caused by a study activity and/or procedure”?

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject’s baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator’s judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment

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

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

9.2.2 Reporting Procedures for Serious Adverse Events

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

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

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

The investigator must assess whether the serious adverse event is possibly related to talimogene laherparepvec. This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by the investigational product"?

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

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

New information relating to a previously reported serious adverse event must be submitted to Amgen. All new information for serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. The investigator may be asked to provide additional follow-up information, which may include a discharge summary or extracts from the medical record. Information provided about the serious adverse event must be consistent with that recorded on the applicable CRF (eg, Adverse Event Summary eCRF).

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

Amgen will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and IRBs/IECs in compliance with all reporting requirements according to local regulations and Good Clinical Practice (GCP).

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

9.3 Pregnancy and Lactation Reporting

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

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

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

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

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

9.4 Reporting of Exposure to Talimogene Laherparepvec

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

Any potential or known unintended exposure should be reported to Amgen within 24 hours of the investigator's knowledge of the event of exposure. Amgen will seek to follow-up with the exposed individual, if necessary, to collect more information about the exposed individual contact with clinical trial subject, signs and/or symptoms related to the exposure, medical history, and/or outcome of the exposure. If the exposed individual is reporting signs or symptoms suspected to be related to talimogene laherparepvec exposure, the exposed individual may be asked to have a swab taken to evaluate for the presence of talimogene laherparepvec in the lesion, **within 3 days of the symptoms or signs occurring.**

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

10.1.1.1 Primary Endpoint

- Correlation between baseline intratumoral CD8+ cell density and objective response rate (ORR)

10.1.1.2 Secondary Endpoints

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

10.1.1.3 Exploratory Endpoints

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

10.1.2 Analysis Sets

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

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

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

10.1.3 Covariates and Subgroups

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

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

10.2 Sample Size Considerations

All analyses will be descriptive with no formal hypothesis testing. The sample size was selected based on practical considerations. The primary objective of the study is to assess whether baseline intratumoral CD8+ cell density is correlated with the likelihood of response to talimogene laherparepvec. Analyses for the objective will focus on whether the response rate varies with baseline intratumoral CD8+ cell density. The functional manner in which the response rate may vary with the biomarker is unknown, therefore multiple functional relationships may be examined. It is assumed that 100 subjects (approximately 91% of the enrolled) will have an evaluable baseline intratumoral CD8+ cell density. The adequacy of the sample size was evaluated for one of several possible analyses that evaluates whether the response rate is positively correlated with a high baseline intratumoral CD8+ cell density where a low and high biomarker is defined as a value below versus at or above the sample median, respectively. A one-sided Fisher's Exact test will be performed at a 5% nominal level to explore the hypothesis that the response rate is equal regardless of baseline intratumoral CD8+ cell density. The overall ORR is assumed to be 26.4%. The power for the test will depend on the true response rates in the biomarker subgroups. Assuming the true response rate is 13.2% in the biomarker low subgroup, and 39.6% in the biomarker high subgroup, the power will be 88% to detect a positive association.

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

Table 4. Expected 95% Confidence Intervals by Various True ORRs

Subjects enrolled (N)	True	Expected 95% CI (width)
110	20%	13% - 29% (16%)
	30%	22% - 39% (18%)
	40%	31% - 50% (19%)
	50%	40% - 60% (19%)

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

10.3 Planned Analyses

10.3.1 Interim Analyses

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

10.3.2 Primary Analysis

The clinical study report (CSR) will be written based on the results of the primary analysis. The main goals of the primary analysis are to evaluate the ORR and correlation of baseline intratumoral CD8+ cell density and the likelihood of response to talimogene laherparepvec, in addition to the correlation between changes in intratumoral CD8+ cell density during treatment and objective response. The timing of the primary analysis will be when all subjects have had the opportunity to complete 12 months of treatment of talimogene laherparepvec.

10.3.3 Final Analysis

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

10.4 Planned Methods of Analysis

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

The efficacy analysis will be conducted using the safety analysis set as well unless otherwise specified. The ORR will be estimated with the associated 95% CI.

Descriptive statistics for DRR, time to treatment failure and OS will be provided. In addition, DOR and changes in tumor burden for responders will also be summarized.

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

10.4.1 Primary Endpoint

The primary endpoint of the study is the correlation between baseline intratumoral CD8+ cell density and objective response rate (ORR). The correlation of intratumoral

CD8+ cell density and other biomarkers with ORR will be evaluated as described in [Section 10.4](#) for ORR and DRR.

10.4.2 Secondary Endpoint (s)

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

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

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

10.4.3 Safety Endpoints

Subject incidence rates of treatment-emergent adverse events (including all adverse events, grade ≥ 3 adverse events, serious adverse events, adverse events of interest and events requiring the discontinuation of study drug, and local effects on the tumor [ie, pain, inflammation and ulceration]) will be summarized. Medical Dictionary for Regulatory Activities (MedDRA) will be used to code adverse events to a system organ class (SOC) and a preferred term within the SOC. The CTCAE version 3.0 will be used to grade severity of adverse events. In addition clinically significant laboratory changes

and clinically significant changes in vital signs will be summarized with descriptive statistics. Summary statistics will also be provided for concomitant medications, dose delay, study drug discontinuation, overall exposure, and changes in ECOG performance status. Tables and/or narratives of deaths after initiation of the study through 30 days since the last dose of talimogene laherparepvec will be provided.

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

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

10.4.4 Exploratory Endpoints

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

10.5 Handling of Missing and Incomplete Data

Partial or missing dates of adverse events and concomitant medications will be imputed. Adverse events with missing severity and/or possible relationship to talimogene laherparepvec will be included in the all adverse events analyses, except by severity grade and treatment-related. Every effort will be made to obtain complete dates for deaths. Details of the imputation algorithms will be specified in the study-specific statistical analysis plan.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

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

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any

protocol-specific screening procedures or any investigational product(s) is/are administered.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

11.2 Institutional Review Board/Independent Ethics Committee

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

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

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

11.3 Subject Confidentiality

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

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

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

11.4 Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multi-center studies, the coordinating investigator. The coordinating investigator, identified by Amgen, will be any or all of the following:

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

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

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

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

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

12.2 Study Documentation and Archive

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

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

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

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

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

Elements to include the following:

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

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

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

12.3 Study Monitoring and Data Collection

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

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

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

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

Data capture for this study is planned to be electronic:

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

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

12.4 Investigator Responsibilities for Data Collection

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

12.5 Language

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

12.6 Publication Policy

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

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors Guidelines).

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

12.7 Compensation

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

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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

Amgen Study # 20120325 Talimogene laherparepvec	Electronic Adverse Event Contingency Report Form For Restricted Use
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Reason for reporting this event via fax The Clinical Trial Database (eg. Rave): <input type="checkbox"/> Is not available due to internet outage at my site <input type="checkbox"/> Is not yet available for this study <input type="checkbox"/> Has been closed for this study [If the protocol provides instructions to submit certain types of events ONLY to Amgen Safety and not to the Clinical Trial Database, state that reason below and remove these instructions. If no protocol-specific reasons, remove these instructions and the following bullet.] Protocol specific reason(s): <input type="checkbox"/> <<Note protocol instruction/reason here and change text from italics to standard.>> <<For completion by Amgen prior to providing to sites: SELECT OR TYPE IN A FAX#>>										
1. SITE INFORMATION										
Site Number		Investigator				Country				
Reporter				Phone Number ()		Fax Number ()				
2. SUBJECT INFORMATION										
Subject ID Number		Age at event onset		Sex <input type="checkbox"/> F <input type="checkbox"/> 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. ADVERSE EVENT										
Provide the date the Investigator became aware of this information: Day ____ Month ____ Year ____										
Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report 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 IPidrug under study Is event serious? <input type="checkbox"/> Yes <input type="checkbox"/> No		Relationship Is there a reasonable possibility that the Event may have been caused by IPidrug under study or an Amgen device used to administer the IPidrug under study? If serious, enter Serious Criteria code (see codes below) No/ Yes/ No/ Yes/ No/ Yes/ No/ Yes/	
									Outcome of Event -Resolved -Not resolved -Fatal -Unknown Check only if event is related to study procedure eg, biopsy	
Serious Criteria: 01 Fatal 02 Immediately life-threatening			03 Required/prolonged hospitalization 04 Persistent or significant disability/incapacity			05 Congenital anomaly / birth defect 06 Other medically important serious event				
4. Was subject hospitalized or was a hospitalization prolonged due this event? <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, please complete all of Section 4										
Date Admitted Day Month Year					Date Discharged Day Month Year					

Amgen Study # 20120325 Talimogene laherparepvec	Electronic Adverse Event Contingency Report Form For Restricted Use
---	--

Site Number				Subject ID Number											
5. Was IP/drug under study administered/taken prior to this event? <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, please complete all of Section 5															
IP/Drug/Amgen Device:		Date of Initial Dose			Date of Dose			Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #			
		Day	Month	Year	Day	Month	Year								
IP: talimogene laherparepvec	<input type="checkbox"/> blinded <input type="checkbox"/> open label											Lot # _____ <input type="checkbox"/> Unknown Serial # _____ <input type="checkbox"/> Unavailable / Unknown			
IP:	<input type="checkbox"/> blinded <input type="checkbox"/> open label											Lot # _____ <input type="checkbox"/> Unknown Serial # _____ <input type="checkbox"/> Unavailable / Unknown			
6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, please complete:															
Medication Name(s)	Start Date			Stop Date			Co-suspect		Continuing		Dose	Route	Freq.	Treatment Med	
	Day	Month	Year	Day	Month	Year	No✓	Yes✓	No✓	Yes✓				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? <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, please complete:															
Date	Test														
	Unit														
	Day	Month	Year												

Appendix C. Pregnancy and Lactation Notification Worksheets

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: _____

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™ Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

enter fax number

1. Case Administrative Information

Protocol/Study Number: _____

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: _____

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

A modified version of the World Health Organization (WHO) response criteria ([WHO handbook for reporting results of cancer treatment, 1979](#)) will be employed in this study.

Method of Measurement of Melanoma Tumor Lesions

Clinical Examination Using Caliper: All measurements will be determined using a ruler or calipers and reported in metric notation (mm) and will be recorded bi-dimensionally. Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in at least 2 dimensions as assessed using calipers (eg, superficial cutaneous melanoma lesion). (Note: When a lesion can be evaluated by both, clinical examination and imaging, radiographic imaging evaluations should be **preferred** since it is more objective).

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. A switch from contrast enhanced CT to noncontrast CT or to MRI (or vice versa) should not preclude response assessment if, in the judgment of the site radiologist, there is no significant difference in the assessment by changing modalities. This may occur if a subject has developed a medical contraindication to intravenous contrast for CT scans while on trial. This change would require the preapproval of the sponsor medical monitor.

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

diagnostic quality to a diagnostic CT (with intravenous and oral contrast) then the CT portion of the PET/CT can be used for tumor measurements.

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

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 tumor's longest diameter and the diameter perpendicular to that.

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

Definitions of Measurable and Nonmeasurable:

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

- measurable or
- nonmeasurable but evaluable

Measurable Lesions:

Measurable lesions are defined at baseline as lesions that can be accurately and serially measured in at least 2 dimensions and for which the longest diameter is:

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

Nonmeasurable Lesions:

All other lesions, including small lesions (longest diameter < 10 mm by CT/MRI/ultrasound for nodal/soft tissue disease [including lymph nodes] or < 10 mm caliper measurement by clinical exam for superficial cutaneous melanoma lesion) and

other truly nonmeasurable lesions are considered nonmeasurable and characterized as nonindex lesions. This will include any measurable lesions beyond the maximum number of 10 lesions that were not chosen as index lesions.

Lesions with Prior Local Treatment:

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

Coalescing or splitting lesions:

- **Coalescing lesions:** When two or more index or new measurable lesions merge without distinct borders between tumors, the smaller lesion should have 0 x 0 mm recorded for the current and all future assessments with a comment indicating that the lesion coalesced with the specified lesion, and the larger lesion should have the size of the merged lesion recorded for the current assessment with a comment indicating that the lesion coalesced with the specified lesion and be followed for future assessments. When two or more nonindex or new non-measurable lesions merge, the smaller lesion should be recorded as absent for the current and all future assessments, and the larger lesion should be recorded as present for the current assessment (with a comment indicating that the lesion coalesced with the specified lesion) and followed for future assessments. If an index or new measurable lesion and a non-index or new non-measurable lesion merge, the non-index or new non-measurable lesion should be absent for the current and all future assessments while the index lesion or new measurable lesion should include both merged lesions for recording measurements with a comment indicating that the lesion coalesced with the specified lesion.
- **Splitting lesions:** When an index or new measurable lesion splits into two or more lesions the largest measurable part of the split lesion should be considered to be the previously recorded index or new measurable lesion with measurements provided for the current assessment with the comment indicating that the lesion split from the specified lesion, and followed for future assessments. The remaining lesions would be reported as a new measurable lesions or new non-measurable lesions depending on measurability with a comment indicating that the lesion split from the specified lesion. In this case, appearance of a new lesion from a previous lesion will not be considered a disease progression solely due to appearance of a new lesion (may be considered a disease progression due to > 25% increase in the sum of the products of the perpendicular diameters of all index tumors since baseline, or the unequivocal appearance of a new tumor, other than the product of the split tumor, since the last response assessment time point).

Measureable Tumor Assessment/Burden:

Baseline Documentation of “Index Lesions”:

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

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

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

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

Baseline Documentation of "Nonindex Lesions":

All other lesions (or sites of disease), including any measurable lesions that were not chosen as index lesions will be identified as nonindex lesions. Nonindex lesions should be recorded and assessed qualitatively over the course of therapy.

Follow-up "Index Lesions":

At each subsequent tumor assessment, the SPD of the index lesions are added together to provide the total tumor burden.

Follow-up "Nonindex Lesions":

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

Response Criteria

Evaluation of Objective Response:

The subject response will be assessed based on the response of the index lesions and nonindex lesion, and presence or absence of new lesions. Confirmation of complete or partial response is not required. The overall response is derived from time point response assessments as described in [Table 5](#), [Table 6](#), and [Table 7](#).

Table 5. Definition of Index Lesion Tumor Response Including New Lesions

Complete Response (CR):	Complete disappearance of all index lesions, including any new tumors which might have appeared. Any residual cutaneous or subcutaneous index lesions must be documented by representative biopsy to not contain viable tumor.
Partial Response (PR):	Achieving a 50% or greater reduction in the SPD of the perpendicular diameters of all index lesions at the time of assessment as compared to the sum of the products of the perpendicular diameters of all index lesions at baseline. If any new lesions have appeared, the sum of products of the perpendicular diameters of new measurable lesions must have reduced by 50% or more from when first documented.
Disease Progression (PD):	<p>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.</p> <p>There are 2 types of PD defined in this protocol:</p> <p>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 overall response as PDn will be allowed to continue study treatment.</p> <p>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.</p>
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 6. 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 tumor(s).
Disease Progression (PD):	<p>Unequivocal progression of one or more nonindex lesions</p> <p>There are 2 types of PD defined in this protocol:</p> <p>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 as overall response will be allowed to continue study treatment.</p> <p>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.</p>
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 7. 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 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 1

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

Talimogene Laherparepvec
Amgen Protocol Number (Talimogene Laherparepvec) 20120325

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

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

Rationale:

- Removed [Inclusion Criterion 105](#) to allow subjects to join the study after having received first-line therapy.
- Removed exclusion of subjects receiving any non-oncology vaccine therapies used for the prevention of infectious disease within 28 days prior to enrollment and during treatment period ([Exclusion criterion 210](#)).
- Clarified that if no viable cells were found following surgery, the response definition will be complete response (CR).
- Added testing for herpes simplex virus type 2 (HSV-2) within 3 days prior to dose at day 1 of week 1 [Cycle 1], week 6 [Cycle 3], and week 12 [Cycle 6].
- Increased the window to 5 days for tumor biopsy for biomarker analysis for the Week 1 biopsy, 7 days for the Week 6 biopsy, and to 7 days after documentation of disease progression at PD.
- Added assessment of Eastern Cooperative Oncology Group (ECOG) performance status every 3 months during treatment period.
- Revised photography assessments in the schedule of assessments to remove requirement at screening, update cycles, and removed the word “measurable.”
- In Schedule of Assessments, clarified that the week 1 biopsy should not be collected prior to the subject being enrolled.
- Removed word “uninjected” from the correlation between changes in intratumoral CD8+ cell density during treatment and objective response rate in the study endpoints.
- Revised the number of planned sites to be 50.
- Added exclusion criterion to avoid potential viral transmission during sexual contact.
- Specified how lesions that separate or merging are to be assessed.

- Added an interim analysis.
- Added reporting of treatment related adverse events during the long-term follow-up.
- Added addition of anti-cancer therapy for melanoma during long term period follow-up.
- In [Table 5](#): Definition of Index Lesion Tumor Response Including New Lesions, removed the following text from the definition of partial response, “Any residual cutaneous or subcutaneous index or new lesions that must be tumor free for the subject to meet the criteria for partial response (PR) must be documented as such by representative biopsy”.
- Updated text throughout document to specify cycle number corresponding to study week.
- Implemented minor administrative and formatting changes.
- Added references in [Section 2.2](#) and in the reference list.
- Added ECOG and physical examination during treatment period and follow-up period.
- Defined the final analysis after 24 months from LSE rather than keeping it open ended.
- Clarified that unless patient dies or withdraws full consent after they have completed the LTFU portion of the study they will then be transferred to the registry protocol where they will continue to be followed up, until death or full consent withdraw.

Description of Changes:

[Section: Global](#)

Replace:

5 December 2014

With:

21 September 2015

[Section: Synopsis, Secondary Objective\(s\)](#)

Bullet 2

Replace:

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

With:

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

[Section: Synopsis, Secondary Endpoints](#)

Bullet 1

Replace:

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

With:

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

[Section: Synopsis, Study Design](#)

Paragraph 3

Replace:

Subjects will be followed for safety 30 (+ 7) days after the last dose of talimogene laherparepvec and for survival every 12 weeks (\pm 28 days) for up to approximately

24 months after the last subject is enrolled. Thereafter, subjects will be followed under an ongoing separate registry protocol (Study 20120139) for the long-term survival follow-up of subjects treated with talimogene laherparepvec. The registry protocol will also monitor for late and long-term adverse events thought to be potentially related to talimogene laherparepvec.

With:

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

[Section: Synopsis, Study Design](#)

Paragraph 4

Replace:

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

With:

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

with the objective response rate in subjects with unresected stage IIIB-IVM1c melanoma treated with talimogene laherparepvec.

[Section: Synopsis, Key Inclusion Criteria](#)

Replace:

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

With:

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

[Section: Synopsis, Key Exclusion Criteria](#)

Replace:

Subject must not have clinically active cerebral metastases, greater than 3 visceral metastases (this does not include lung or nodal metastases associated with visceral organs), or any bone metastases, primary ocular or mucosal melanoma, or history or evidence of symptomatic autoimmune pneumonitis, glomerulonephritis, vasculitis, or other symptomatic autoimmune disease. Subject must not have evidence of clinically significant immunosuppression or active herpetic skin lesions or prior complications of

HSV-1 infection (eg, herpetic keratitis or encephalitis) and must not require intermittent or chronic systemic treatment with an antiherpetic drug (eg, acyclovir), other than intermittent topical use. Subjects known to have acute or chronic active hepatitis B, hepatitis C, or human immunodeficiency virus infection will also be excluded. Subjects must not have any nononcology vaccine therapies used for the prevention of infectious disease within 28 days prior to enrollment and must not have been treated previously with talimogene laherparepvec.

With:

Subject must not have clinically active cerebral metastases, greater than 3 visceral metastases (this does not include lung or nodal metastases associated with visceral organs), or any bone metastases, primary ocular or mucosal melanoma, history or evidence of symptomatic autoimmune **disease (such as** pneumonitis, glomerulonephritis, vasculitis, or other) **or history of autoimmune disease that required systemic treatment (ie, use of corticosteroids, immunosuppressive drugs or biological agents used for treatment of autoimmune diseases) in past 2 months prior to enrollment. Replacement therapy (eg, thyroxine for hypothyroidism, insulin for diabetes mellitus) is not considered a form of systemic treatment for autoimmune disease.** Subject must not have evidence of clinically significant immunosuppression or active herpetic skin lesions or prior complications of HSV-1 infection (eg, herpetic keratitis or encephalitis) and must not require intermittent or chronic systemic treatment with an antiherpetic drug (eg, acyclovir), other than intermittent topical use. Subjects known to have acute or chronic active hepatitis B, hepatitis C, or human immunodeficiency virus infection will also be excluded. Subjects must not have been treated previously with talimogene laherparepvec.

[Section: Synopsis, Screening](#)

Bullet 8

Delete:

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

[Section: Synopsis, Treatment](#)

Bullet 2

Add:

physical examination

[Section: Synopsis, Treatment](#)

Bullet 3

Add:

ECOG Performance Status assessment

[Section: Synopsis, Treatment](#)

Bullet 6, subbullet 2

Replace:

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

With:

blood samples for herpes simplex virus (HSV) serostatus

[Section: Synopsis, Treatment](#)

Bullet 8

Replace:

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

With:

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

[Section: Synopsis, Treatment](#)

Bullet 10

Replace:

administration of talimogene laherparepvec at day 1 of each cycle

With:

administration of talimogene laherparepvec at day 1 of each **treatment** cycle

[Section: Synopsis, Long-term Follow-up/End of Study](#)

Paragraph 1

Replace:

All subjects who permanently discontinue talimogene laherparepvec for any reason other than withdrawal of full consent or death will be contacted by telephone or clinic visit to assess survival every 12 weeks (\pm 28 days) following the safety follow-up visit until death, subject withdraws full consent, or up to 24 months after the last subject is enrolled.

With:

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

[Section: Synopsis, Long-term Follow-up/End of Study](#)

Paragraph 2

Replace:

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

With:

If subject has discontinued talimogene laherparepvec for reason other than disease progression or death, radiographic tumor imaging, clinical tumor assessments, **ECOG Performance Status assessment, assessment of swabs of lesions of suspected**

herpetic origin by qPCR for talimogene laherparepvec DNA, and tumor response assessments will be performed until documented disease progression beyond 6 months of treatment, per modified WHO response criteria (Appendix D), or until the start of a new anticancer therapy **or end of study, whichever the earliest**.

[Section: Synopsis, Long-term Follow-up/End of Study](#)

Paragraph 3

Replace:

After the long term follow-up period of this study has ended, subjects who end the study for any reason other than death or withdrawal of full consent will be followed for survival under an ongoing separate registry protocol (Study 20120139) that is in place for the long-term follow-up of all subjects treated with talimogene laherparepvec in clinical trials. The registry protocol will also monitor for late and long-term adverse events thought to be potentially related to talimogene laherparepvec.

With:

After the long term follow-up period of this study has ended, subjects who end the study for any reason other than death or withdrawal of full consent will be followed for survival under an ongoing separate registry protocol (Study 20120139) that is in place for the long-term follow-up of all subjects treated with talimogene laherparepvec in clinical trials. The registry protocol will also monitor for late and long-term adverse events thought to be potentially related to talimogene laherparepvec **and use of anti-cancer therapies for melanoma**.

[Section: Synopsis, Statistical Consideration](#)

Paragraph 2

Replace:

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

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

With:

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

[Section: Synopsis, Statistical Consideration](#)

Paragraph 3

Add:

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

[Section: Synopsis, Statistical Consideration](#)

Paragraph 4

Replace:

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

With:

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

[Section: Study Glossary](#)

Delete:

AE(s)	adverse event(s)
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[Section: Study Glossary](#)

Add:

HLA	human leukocyte antigen
------------	--------------------------------

[Section: 1.2 Secondary](#)

Bullet 2

Replace:

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

With:

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

[Section: 2.1 Melanoma](#)

Paragraph 1, sentence 1

Replace:

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

With:

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

Section: 2.1 Melanoma

Paragraph 3, sentence 3

Delete:

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

Section: 2.1 Melanoma

Paragraph 4, sentence 1

Replace:

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

With:

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

Section: 2.1 Melanoma

Paragraph 4, sentence 3

Replace:

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

With:

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

[Section: 2.1 Melanoma](#)

Paragraph 6

Replace:

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

With:

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

[Section: 2.1 Melanoma](#)

Paragraph 7

Add:

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

(Weber et al, 2015), and improved PFS and ORR (either alone or in combination with ipilimumab) compared to ipilimumab alone in treatment naïve subjects (Larkin et al, 2015).

[Section: 2.1 Melanoma](#)

Paragraph 8

Add:

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

[Section: 2.1 Melanoma](#)

Paragraph 9, sentence 3

Add:

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

[Section: 2.1 Melanoma](#)

Paragraph 9, sentence 3

Replace:

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

With:

The safety profiles of vemurafenib and dabrafenib include increased incidence of cutaneous squamous cell carcinoma or high grade keratoacanthoma in almost 20% of

patients treated with vemurafenib and > 5% of patients treated with dabrafenib (Zelboraf[®], 2015; Tafinlar[™], 2013).

Section: 2.1 Melanoma

Paragraph 9, sentence 7

Replace:

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

With:

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

Section: 2.1 Melanoma

Paragraph 10, sentence 7

Replace:

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

With:

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

Section: 2.1 Melanoma

Paragraph 10, sentence 3

Replace:

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

With:

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

Section: 2.1 Melanoma

Paragraph 11

Add:

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

Section: 2.2 Talimogene Laherparepvec Investigational Product Background

Paragraph 1, sentence 1

Replace:

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

With:

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

[Section: 2.2 Talimogene Laherparepvec Investigational Product Background](#)

Paragraph 3, sentences 1 and 2

Replace:

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

With:

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

[Section: 2.2 Talimogene Laherparepvec Investigational Product Background](#)

Paragraph 1, sentence 3

Replace:

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

With:

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

Section: 2.2 Talimogene Laherparepvec Investigational Product Background

Paragraph 5

Replace:

Primary analysis of the OPTIM Study showed a statistically significant difference between the rate of durable response among subjects treated with talimogene laherparepvec (16%; 95% CI: 12%, 21%) versus those treated with GM-CSF (2%; 95% CI: 0%, 5%) (p-value < 0.0001). A trend toward improved OS was also seen in a preplanned interim analysis (HR 0.79; 95% CI: 0.61, 1.02; p-value = 0.07) (Andtbacka et al, 2013). Survival at 12, 24, and 36 months in the talimogene laherparepvec arm was estimated to be 74%, 50%, and 41%, respectively, and 69%, 41%, and 28% in the GM-CSF arm, respectively. The most common side effects were fatigue, chills, and pyrexia. Serious adverse events occurred in 26% of the talimogene laherparepvec subjects and 13% of the GM-CSF subjects. No grade 3/4 adverse events occurred in $\geq 3\%$ of subjects in either arm.

With:

Primary analysis of the OPTIM Study showed a statistically significant difference between the rate of durable response among subjects treated with talimogene laherparepvec (16%; 95% CI: 12%, 21%) versus those treated with GM-CSF (2%; 95% CI: 0%, 5%) (p-value < 0.0001). **Overall response rate was also improved from 6% with GM-CSF to 26% with talimogene laherparepvec ($P < 0.0001$, descriptive). Similarly, 11% of patients had a CR in the talimogene laherparepvec arm versus < 1% in the GM-CSF arm. In the event-driven primary OS analysis (secondary end point), median OS with talimogene laherparepvec treatment was 23.3 months compared with 18.9 months with GM-CSF treatment (HR, 0.79 [95% CI, 0.62–1.00]; $P=0.051$) (Andtbacka et al, 2015). At the final planned analysis of OS which happened when last enrolled subject completed 3 years of follow-up, median OS was 23.3 months in the talimogene laherparepvec arm and 18.9 months in the GM-CSF arm (HR, 0.79; 95% CI, 0.62–1.00; $P=0.049$, (descriptive) (Andtbacka et al, 2015).**

The most common side effects were fatigue, chills, and pyrexia. Serious adverse events occurred in **36%** of the talimogene laherparepvec subjects and **21%** of the GM-CSF subjects. **The only grade 3/4 adverse event occurring in $\geq 2\%$ of patients was cellulitis (talimogene laherparepvec, n=6 [2.1%]; GM CSF, n=1 [$< 1\%$]). Of 10 fatal**

events in the talimogene laherparepvec arm, none were considered treatment-related per investigator and most (80%) were associated with disease progression with the exception of sepsis in the setting of salmonella infection and myocardial infarction (Andtbacka et al, 2015).

Section: 2.2 Talimogene Laherparepvec Investigational Product Background

Paragraph 7

Replace:

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

With:

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

Section: 2.3 Rationale

Paragraph 1, sentence 8

Replace:

CCI

11

5

□ □ □ □ □

Section: 3.1 Study Design

Paragraph 2, sentence 3

Replace:

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

With:

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

Section: 3.1 Study Design

Paragraph 3

Replace:

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

With:

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

Section: 3.1 Study Design

Paragraph 4

Replace:

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

With:

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

Section: 3.2 Number of Sites

Replace:

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

With:

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

Section: 3.5.1 Study Duration for Subjects

Paragraph 2

Replace:

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

With:

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

Section: 3.5.1 Study Duration for Subjects

Paragraph 3

Add:

After the end of the long term follow up subjects who end the study for any reason other than death or withdrawal of full consent will continue to be followed for survival under an ongoing separate registry protocol (Study 20120139). The

registry protocol will also monitor for adverse events thought by the investigator to be potentially related to talimogene laherparepvec and use of anti-cancer therapies for melanoma.

[Section: 3.5.2 End of Study](#)

Paragraph 2

Replace:

End of Trial: the time when the last subject is assessed or receives an intervention for evaluation in the study. The end of study will occur when the last subject discontinues talimogene laherparepvec and has had the opportunity to complete the safety follow-up visit or the last long term follow-up visit, whichever occurs later.

With:

End of Trial: the time when the last subject is assessed or receives an intervention for evaluation in the study. The end of study will occur **24 months after the last subject has been enrolled or** when the last subject discontinues talimogene laherparepvec and has had the opportunity to complete the safety follow-up visit, whichever occurs later.

[Section: 4.1.1 Inclusion Criteria](#)

Criterion 105

Replace:

Subject who is treatment naïve: must not have received any prior systemic anticancer treatment consisting of chemotherapy, immunotherapy, or targeted therapy for unresected stage IIIB to IV M1c melanoma

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

With:

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

Section: 4.1.2 Exclusion Criteria

Criterion 201

Replace:

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

With:

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

Section: 4.1.2 Exclusion Criteria

Criterion 205

Replace:

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

With:

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

Section: 4.1.2 Exclusion Criteria

Criterion 206, bullet 3

Replace:

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

With:

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

Section: 4.1.2 Exclusion Criteria

Criterion 210

Delete:

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

Section: 4.1.2 Exclusion Criteria

Criterion 216, bullet 2

Replace:

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

With:

adequately treated non-melanoma skin cancer without evidence of disease

Section: 4.1.2 Exclusion Criteria

Criterion 223

Add:

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

Section: 6.1 Classification of Product

Paragraph 2

Replace:

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

With:

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

Section: 6.2.1 Amgen Investigational Product Talimogene Laherparepvec

Paragraph 1, sentence 3

Replace:

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

With:

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

Section: 6.2.1 Amgen Investigational Product Talimogene Laherparepvec

Paragraph 1, sentence 5

Add:

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

Section: 6.2.1.1 Dosage, Administration, and Schedule

Paragraph 1

Replace:

Talimogene laherparepvec must be prepared and administered by a qualified healthcare professional. Subjects should be assessed clinically for adverse events/toxicity prior to

each dose using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (Appendix A). Complete blood count with differential and chemistry panels including liver function laboratory tests (such as ALT, AST, and total bilirubin) should be obtained according to the Schedule of Assessments (see Table 2) and the results should be checked before each scheduled dose. Dosing will occur only if these test values are acceptable, per Section 6.2.1.2.

With:

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

[Section: 6.2.1.1 Dosage, Administration, and Schedule](#)

Paragraph 6, sentence 1

Replace:

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

With:

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

[Section: 6.2.1.1 Dosage, Administration, and Schedule](#)

Paragraph 6, sentence 2

Add:

(No biopsy will be taken at week 6 for subjects with 1 lesion present at baseline).

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

Paragraph 3

Replace:

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

With:

Subjects who are receiving talimogene laherparepvec may not receive systemic antiherpetic drugs (eg, acyclovir, valacyclovir, famciclovir), but **may receive a topically administered antiherpetic drug more than 20 cm from a talimogene laherparepvec injection site. If a subject requires treatment with systemic antiherpetic drugs (eg, acyclovir, valacyclovir, famciclovir) talimogene laherparepvec should be withheld and the investigator or designee should notify the Amgen medical monitor as soon as possible. Subject may be allowed to continue treatment after discussion between the Amgen medical monitor and the investigator to determine the appropriateness of treatment resumption.**

Dosing should be permanently discontinued if, in the opinion of the investigator, the subject develops clinical evidence of any systemic herpes infection (such as encephalitis or disseminated infection).

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

Paragraph 5

Replace:

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

With:

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

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

Paragraph 10, bullet 6

Replace:

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

With:

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

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

Paragraph 11

Replace:

For additional information related special warnings and precautions for the use of talimogene laherparepvec please refer to the latest version of the Talimogene Laherparepvec Investigator's Brochure, 2014.

With:

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

Section: 6.4 Concomitant Therapy

Paragraph 2

Replace:

All prescription and nonprescription concomitant medication administered up to 28 days prior to enrollment, on an ongoing basis at enrollment, as well as changes in such concomitant medication, and any new concomitant medication taken while the subject is on study, should be recorded on the appropriate case report form (CRF) until 30 days (+ 7 days) after the last dose of talimogene laherparepvec. The therapy name, indication, dose, unit, frequency, start date, and stop date will be collected.

With:

All prescription and nonprescription concomitant medication administered up to 28 days prior to enrollment, on an ongoing basis **after** enrollment, as well as changes in such concomitant medication, and any new concomitant medication taken while the subject is on study, should be recorded on the appropriate case report form (CRF) until 30 days (+ 7 days) after the last dose of talimogene laherparepvec. The therapy name, indication, dose, unit, frequency, start date, and stop date will be collected.

Section: 6.5 Other Treatment Procedures

Paragraph 1, sentence 3

Replace:

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

With:

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

Section: 6.5 Other Treatment Procedures

Paragraph 1, sentence 4

Replace:

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

With:

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

[Section: 6.5 Other Treatment Procedures](#)

Paragraph 1, sentence 7

Replace:

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

With:

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

[Section: 6.5 Other Treatment Procedures](#)

Paragraph 1, sentence 8

Add:

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

[Section: 6.5 Other Treatment Procedures](#)

Paragraph 3, sentences 2 and 3

Replace:

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

With:

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

[Section: 6.8 Excluded Treatments and/or Procedures During Study Period](#)

Bullet 4

Replace:

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

With:

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

[Section: 6.8 Excluded Treatments and/or Procedures During Study Period](#)

Bullet 5

Delete:

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

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

Bullet 6

Delete:

~~any surgery for melanoma (other than the exceptions noted in Section 6.5~~

Section: 7.1 Schedule of Assessments

Replace:

	Screening ^a	Treatment Period ^b									Follow-up Period	
Cycle ^t	≤ 28 days	1	2	3	4	5	6	7	8	Cycle 8 and Beyond	Safety ^e	Survival ^d
Day		1	1	1	1	1	1	1	1	1	30 (+7) Days	12 (±28 days) Weeks
GENERAL & SAFETY ASSESSMENTS												

Concomitant Medications ^e	X											X
--------------------------------------	---	--	--	--	--	--	--	--	--	--	--	---

Physical Exam ^g	X										X	
----------------------------	---	--	--	--	--	--	--	--	--	--	---	--

ECOG Performance Status	X										X	
-------------------------	---	--	--	--	--	--	--	--	--	--	---	--

Swab of Herpetic Lesion for qPCR ^m		Within 3 days of occurrence of suspected lesion of herpetic origin									X	
Blood for HSV-1 Antibody Serostatus ⁿ		Within 3 days prior to dose at day 1 of week 1, week 6, and week 12										

Tumor Biopsy for Biomarker Analysis ^o		Within 3 days prior to dose at day 1 of week 1 and week 6 and at disease progression (beyond 6 months of treatment)										
--	--	---	--	--	--	--	--	--	--	--	--	--

Photographs of Visible Tumor Lesions ^s (Select Sites Only)	X	Monthly until End of Treatment										
--	---	--------------------------------	--	--	--	--	--	--	--	--	--	--

With:

	Screening ^a	Treatment Period ^b									Follow-up Period	
Cycle ^t	≤ 28 days	1	2	3	4	5	6	7	8	Cycle 8 and Beyond ^t	Safety ^c	Survival ^d
Day		1	1	1	1	1	1	1	1	1	30 (+7) Days	Every 12 (±28 days) Weeks
GENERAL & SAFETY ASSESSMENTS												

Concomitant Medications ^e	X											
--------------------------------------	---	--	--	--	--	--	--	--	--	--	--	--

Adverse Events Thought to Be Related to Talimogene Laherparepvec ^f		X										X
Physical Exam ^g	X	X					X			Q6C	X	

ECOG Performance Status ^w	X	X					X			Q6C	X	
--------------------------------------	---	---	--	--	--	--	---	--	--	-----	---	--

Anti-cancer therapy for melanoma ^x											X	X
---	--	--	--	--	--	--	--	--	--	--	---	---

Swab of Herpetic Lesion for qPCR ^m		Within 3 days of occurrence of suspected lesion of herpetic origin									X	X
Blood for HSV Serostatus ⁿ		Within 3 days prior to dose at day 1 of week 1, week 6, and week 12										

Tumor Biopsy for Biomarker Analysis ^p		Within 5 days prior to dose at day 1 of week 1, within 7 days prior to dose at week 6 and within 7 days after the documentation of disease progression followed by treatment discontinuation										
--	--	--	--	--	--	--	--	--	--	--	--	--

Photographs of all Visible Tumor Lesions ^s (Select Sites Only)		X	X		X		X		X	Q2C		
---	--	---	---	--	---	--	---	--	---	-----	--	--

Section: 7.1 Schedule of Assessments

Footnote b

Replace:

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

With:

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

Section: 7.1 Schedule of Assessments

Footnote d

Replace:

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

With:

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

[Section: 7.1 Schedule of Assessments](#)

Footnote e

Replace:

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

With:

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

[Section: 7.1 Schedule of Assessments](#)

Footnote f

Replace:

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

With:

All nonserious adverse events **(related or not related to talimogene laherparepvec)** that occur after **the first dose** through 30 (+7) days after the last administration of talimogene laherparepvec will be recorded in the case report form. **In addition, all adverse events deemed by the investigator to be potentially related to talimogene laherparepvec will be recorded in the case report form through the survival**

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

[Section: 7.1 Schedule of Assessments](#)

Footnote m

Replace:

Swabs of any lesion suspected to be herpetic in origin will be collected as follows:
Subject should return to clinic within 3 days of the occurrence of reportable lesion suspected to be herpetic in origin, such as cold sores or vesicles. The lesion should be evaluated by the investigator and swabbed if HSV infection is suspected. A qPCR analysis will be performed at a central lab on the swab to evaluate whether the talimogene laherparepvec DNA is detectable in the sample.

With:

Swabs of any lesion suspected to be herpetic in origin will be collected as follows:
Subject should return to clinic within 3 days of the occurrence of reportable lesion suspected to be herpetic in origin, such as cold sores or vesicles. The lesion should be evaluated by the investigator and swabbed if **herpetic** infection is suspected. A qPCR analysis will be performed at a central lab on the swab to evaluate whether the talimogene laherparepvec DNA is detectable in the sample.

[Section: 7.1 Schedule of Assessments](#)

Footnote n

Replace:

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

With:

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

Section: 7.1 Schedule of Assessments

Footnote o

Replace:

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

With:

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

Section: 7.1 Schedule of Assessments

Footnote p

Replace:

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

With:

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

Section: 7.1 Schedule of Assessments

Footnote q, sentence 1

Replace:

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

With:

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

Section: 7.1 Schedule of Assessments

Footnote r, sentence 1

Replace:

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

With:

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

[Section: 7.1 Schedule of Assessments](#)

Footnote s

Replace:

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

With:

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

[Section: 7.1 Schedule of Assessments](#)

Footnote v

Replace:

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

With:

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

[Section: 7.1 Schedule of Assessments](#)

Footnote w

Add:

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

[Section: 7.1 Schedule of Assessments](#)

Footnote x

Add:

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

[Section: 7.2 General Study Procedures](#)

Paragraph 2

Replace:

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

With:

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

[Section: 7.2 General Study Procedures, Table 3, Biomarkers](#)

Replace:

HSV-1 Antibody

With:

HSV **Serostatus**

[Section: 7.2 General Study Procedures](#)

Paragraph 4

Replace:

The chemistry, hematology, PT(or INR), PTT and pregnancy tests are to be performed at a local laboratory and test results are to be fully and routinely recorded on the

electronic CRFs (eCRFs). Missed tests that are not done must be reported as such on the eCRFs. The real-time polymerase chain reaction (qPCR) and biomarker tests will be performed at a central laboratory and tests results will not be reported on the eCRFs.

With:

The chemistry, hematology, PT(or INR), PTT and pregnancy tests are to be performed at a local laboratory and test results are to be fully and routinely recorded on the electronic CRFs (eCRFs). Missed tests that are not done must be reported as such on the eCRFs **and should not be completed as unscheduled tests between cycles.**

The real-time **quantitative** polymerase chain reaction (qPCR) and biomarker/**antibody** tests will be performed at a central laboratory and tests results will not be reported on the eCRFs.

[Section: 7.2.1 Screening and Enrollment](#)

Bullet 11

Delete:

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

[Section: 7.2.2 Treatment](#)

Paragraph 2, bullet 2

Add:

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

[Section: 7.2.2 Treatment](#)

Paragraph 2, bullet 3

Add:

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

Section: 7.2.2 Treatment

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

Replace:

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

- subject should return to clinic within 3 days of the occurrence of a reportable lesion suspected to be herpetic in origin, such as cold sores or vesicles. The lesion should be evaluated by the investigator and swabbed if HSV infection is suspected. A qPCR analysis will be performed on the swab sample to evaluate whether the talimogene laherparepvec DNA is detectable in the sample.

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

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

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

With:

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

- subject should return to clinic within 3 days of the occurrence of a reportable lesion suspected to be herpetic in origin, such as cold sores or vesicles. The lesion should be evaluated by the investigator and swabbed if **herpetic** infection is suspected. A qPCR analysis will be performed on the swab sample to evaluate whether the talimogene laherparepvec DNA is detectable in the sample.

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

blood sample for biomarker analysis (within 3 days prior to talimogene laherparepvec administration) at day 1 of week 1, week 6, week 12 and week 24. Note: Lymphocyte

subsets will be measured by flow cytometric determination of the following markers including but not limited to: T cells: CD3, CD4, CD8; B cells; CD19; activation markers: HLA-DR; T-regs: CD25, CD127.

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

[Section: 7.2.2 Treatment](#)

Bullet 6, subbullet 1

Replace:

radiographic imaging must include CT scan, PET/CT, MRI, or ultrasound of the chest, abdomen, and pelvis and all other sites of disease. In addition, CT scan or MRI of the brain will only be performed if symptoms or signs suggestive of CNS metastasis are present. The imaging modality selected (eg, CT or MRI) should remain constant for any individual subject.

With:

radiographic imaging must include CT scan, PET/CT, MRI, or ultrasound **(if applicable)** of the chest, abdomen, and pelvis and all other sites of disease. In addition, CT scan or MRI of the brain will only be performed if symptoms or signs suggestive of CNS metastasis are present. The imaging modality selected (eg, CT or MRI) should remain constant **throughout the study** for any individual subject.

Section: 7.2.2 Treatment

Bullet 9

Replace:

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

With:

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

Section: 7.2.3 Safety Follow-up Visit

Bullet 3

Replace:

- Determination of ECOG performance status (Appendix E)

With:

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

Section: 7.2.3 Safety Follow-up Visit

Bullet 8

Replace:

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

With:

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

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

Paragraph 1

Replace:

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

With:

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

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

Paragraph 2

Replace:

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

With:

If subject has discontinued talimogene laherparepvec for reason other than disease progression or death, radiographic tumor imaging, clinical tumor assessments, **ECOG Performance Status assessments, reporting of pregnancy or lactation, assessment of swabs of lesions of suspected herpetic origin for presence of**

talimogene laherparepvec DNA by qPCR test, and tumor response assessments will be performed as documented in Section 7.2.2 until documented disease progression beyond 6 months of treatment, per modified WHO response criteria (Appendix D), until the start of a new anticancer therapy, **or end of study, whichever the earliest**.

[Section: 7.2.4 Long-term Follow-up/End of Study](#)

Paragraph 3

Replace:

After the long term follow-up period of this study has ended, subjects who end the study for any reason other than death or withdrawal of full consent will be followed for survival under an ongoing separate registry protocol (Study 20120139) that is in place for the long-term follow-up of all subjects treated with talimogene laherparepvec in clinical trials. The registry protocol will also monitor for late and long-term adverse events thought to be potentially related to talimogene laherparepvec.

With:

After the long term follow-up period of this study has ended, subjects who end the study for any reason other than death or withdrawal of full consent will be followed for survival under an ongoing separate registry protocol (Study 20120139) that is in place for the long-term follow-up of all subjects treated with talimogene laherparepvec in clinical trials. The registry protocol will also monitor for late and long-term adverse events thought to be potentially related to talimogene laherparepvec **and use of anti-cancer therapies for melanoma**.

[Section: 7.2.6 Optional Photography Substudy \(Select Sites Only\)](#)

Paragraph 1, sentence 1

Replace:

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

With:

For sites selected to participate in the photography substudy, photographs of **all** visible (ie, visible protrusion from skin surface) cutaneous and subcutaneous tumor lesions will

be performed as detailed in Section 7.2.2 until end of treatment (**always within 3 days prior to investigational product administration**).

Section: 7.3.1 Blood Samples

Paragraph 2, sentence 2

CCI

[REDACTED]

Section: 7.3.2 Tumor Tissue Samples

Paragraph 1

Replace:

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

With:

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

Section: 7.3.2 Tumor Tissue Samples

Paragraph 4

Replace:

On study biopsies will be collected, as described in the Schedule of Assessments (Table 2) and in Section 7.2.2, to characterize the mechanism of systemic action of

talimogene laherparepvec. Collecting a biopsy from an uninjected lesion during the treatment period (eg, at week 6) is critical for identifying the changes in intratumoral CD8+ cell density that occur following talimogene laherparepvec treatment and that may be associated with clinical benefit. Refer to the Laboratory Manual for specific instructions on tumor biopsy procedures.

With:

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

[Section: 9.2.1 Reporting Procedures for Adverse Events That do not Meet Serious Criteria](#)

Paragraph 1

Replace:

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

With:

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

[Section: 9.3 Pregnancy and Lactation Reporting](#)

Paragraph 2

Replace:

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

With:

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

[Section: 9.3 Pregnancy and Lactation Reporting](#)

Paragraph 5

Replace:

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

With:

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

[Section: 9.4 Reporting of Exposure to Talimogene Laherparepvec](#)

Paragraph 1, sentence 3

Add:

Please refer to your study specific documents for reporting details.

[Section: 9.4 Reporting of Exposure to Talimogene Laherparepvec](#)

Paragraph 2, sentence 3

Replace:

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

With:

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

[Section: 10.1.1.2 Secondary Endpoints](#)

Bullet 2

Replace:

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

With:

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

[Section: 10.1.2 Analysis Sets](#)

Paragraph 3, sentence 4

Replace:

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

With:

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

[Section: 10.1.3 Covariates and Subgroups](#)

Bullet 1

Replace:

Region, if applicable (USA or non-USA)

With:

Region, if applicable

[Section: 10.1.3 Covariates and Subgroups](#)

Bullet 6

Replace:

ECOG (0 vs 1)

With:

ECOG **Performance Status** (0 vs 1)

[Section: 10.3.1 Interim Analyses](#)

Replace:

No interim analysis is planned.

With:

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

Section: 10.3.3 Final Analysis

Replace:

The final analysis will occur when the last subject discontinues the study treatment and has had the opportunity to complete the long term follow -up. The CSR will be amended with the updated results from the final analysis at the completion of the study.

With:

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

Section: 13 References

Delete:

~~Andtbacka RHIA, Collichio FA, Amatruda T, et al. OPTiM: a randomized phase III trial of talimogene laherparepvec (T-VEC) versus subcutaneous (SC) granulocyte-macrophage colony-stimulating factor (GM-CSF) for the treatment (tx) of unresected stage IIIB/C and IV melanoma. *J Clin Oncol*. 2013;31(suppl). Abstract LBA9008.~~

Section: 13 References

Add:

Andtbacka RHIA, Kaufman H, Collichio FA, et al. Talimogene laherparepvec improves durable response rate in patients with advanced melanoma. *J Clin Oncol* 2015[Epub ahead of print].

Section: 13 References

Add:

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

http://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf.

Accessed on 27 August 2015.

Section: 13 References

Add:

Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated Melanoma. *N Engl J Med*. 2015;373:23-34

Long GV, Stroyakovskiy D, Gogas H, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. *Lancet* 2015, 386:444-451

Section: 13 References

Replace:

Mekinist™ (trametinib) Prescribing Information. Research Triangle Park, NC, GlaxoSmithKline, USA, 2013.

With:

Mekinist™ (trametinib) Prescribing Information. Research Triangle Park, NC, GlaxoSmithKline, USA, 2014. https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Mekinist/pdf/MEKINIST-PI-PIL.PDF. Accessed on 27 August 2015.

Section: 13 References

Add:

Opdivo® (Nivolumab) Prescribing Information. Princeton, NJ: Bristol-Myers Squibb, USA; 2015. http://packageinserts.bms.com/pi/pi_opdivo.pdf. Accessed on 27 August 2015.

Section: 13 References

Add:

Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science*. 2015;348:124-128.

Robert C, Karaszewska B, Schachter J, et al. Improved Overall Survival in Melanoma with Combined Dabrafenib and Trametinib. *New Engl J Med* 2015, 372, 30-39

Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med*. 2015;372:320-330.

Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. *N Engl J Med*. 2015;372:2521-2532.

Section: 13 References

Add:

Siegel RL, Miller KD, and Jemal A. Cancer statistics, 2015. *Cancer Clin J* 2015; 65:5-29.

Section: 13 References

Add:

Snyder A, Makarov V, Merghoub T, et al. Genetic basis for clinical response to CTLA-4 blockade in melanoma. *N Engl J Med*. 2014;371:2189-2199.

Section: 13 References

Replace:

Talimogene Laherparepvec Investigator's Brochure, Edition 10.0. Woburn, MA. BioVEX (a wholly owned subsidiary of Amgen); 17 January 2014.

With:

Talimogene Laherparepvec Investigator's Brochure, Edition **13.0**. Amgen; **2015**.

Section: 13 References

Add:

Weber JS, D'Angelo SP, Minor D, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2015;16:375-384.

Section: 13 References

Replace:

Yervoy® (ipilimumab) Prescribing Information. Princeton, NJ: Bristol-Myers Squibb, USA; 2013.

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

With:

Yervoy® (ipilimumab) Prescribing Information. Princeton, NJ: Bristol-Myers Squibb, USA; 2015. http://packageinserts.bms.com/pi/pi_yervoy.pdf . Accessed on 27 August 2015.

Zelboraf® (vemurafenib) Prescribing Information. South San Francisco, CA; Genentech USA, Inc: 2015. http://www.gene.com/download/pdf/zelboraf_prescribing.pdf. Accessed on 27 August 2015.

Section: 14 Appendices, Appendix B

Replace:

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.*

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 20120325 Talimogene Laherparepvec	Electronic Serious Adverse Event (eSAE) Contingency Reporting Form For Restricted Use
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Complete either Section A or Section B and follow the instructions provided:

Section A	
<input type="checkbox"/> 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):	
<input type="checkbox"/> An event that applies to a specialty CRF page titled _____ (eg, clinical fracture)	<input type="checkbox"/> Screening event (as defined by the protocol)
OR	<input type="checkbox"/> 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	
<input type="checkbox"/> Access to the EDC system (eg, Rave) has either not begun or has ended for this study. I am submitting (check all that apply):	
<input type="checkbox"/> Screening event (as defined by the protocol)	<input type="checkbox"/> Event after access to the EDC system (eg, Rave) has ended (provide subject's End of Study date in Section 2)
<input type="checkbox"/> This is a new event report	<input type="checkbox"/> This is a new event report
<input type="checkbox"/> This is follow-up information for a previously reported event	<input type="checkbox"/> 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	

US: +888 814 8653

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 <input type="checkbox"/> F <input type="checkbox"/> 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	Date Ended	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	
	Day Month Year	Day Month Year			No Yes	No Yes	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 - _____ <i>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.</i>	Title _____	Date _____
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Version 3.0 Effective Date 04-FEB-2013

AMGEN Study 20120325 Talimogene Laherparepvec	Electronic Serious Adverse Event (eSAE) Contingency Reporting Form For Restricted Use
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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 to this event? <input type="checkbox"/> No <input type="checkbox"/> 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? <input type="checkbox"/> No <input type="checkbox"/> Yes, If yes, please complete all of Section 5			
IMP: _____ <input type="checkbox"/> (✓) Blinded <input type="checkbox"/> (✓) 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? <input type="checkbox"/> No <input type="checkbox"/> 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? <input type="checkbox"/> No <input type="checkbox"/> Yes, If yes, please complete:			
Test			
Unit			
Date Day Month Year			

With:

Amgen Study # 20120325 Talimogene laherparepvec	Electronic Adverse Event Contingency Report Form For Restricted Use
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Reason for reporting this event via fax The Clinical Trial Database (eg. Rave): <input type="checkbox"/> Is not available due to internet outage at my site <input type="checkbox"/> Is not yet available for this study <input type="checkbox"/> Has been closed for this study [If the protocol provides instructions to submit certain types of events ONLY to Amgen Safety and not to the Clinical Trial Database, state that reason below and remove these instructions. If no protocol-specific reasons, remove these instructions and the following bullet.] Protocol specific reason(s): <input type="checkbox"/> <<Note protocol instruction/reason here and change text from italics to standard.>> <div style="text-align: center; color: red;"><<For completion by Amgen prior to providing to sites: SELECT OR TYPE IN A FAX#>></div>																																																																			
1. SITE INFORMATION <table border="1" style="width: 100%;"> <tr> <td style="width: 15%;">Site Number</td> <td style="width: 40%;">Investigator</td> <td style="width: 45%;">Country</td> </tr> <tr> <td> </td> <td> </td> <td> </td> </tr> <tr> <td>Reporter</td> <td>Phone Number ()</td> <td>Fax Number ()</td> </tr> </table>												Site Number	Investigator	Country				Reporter	Phone Number ()	Fax Number ()																																															
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If this is a follow-up to an event reported in the EDC system (eg. Rave), provide the adverse event term: _____ and start date: Day ____ Month ____ Year ____																																																																			
3. ADVERSE EVENT Provide the date the Investigator became aware of this information: Day Month Year																																																																			
<table border="1" style="width: 100%;"> <tr> <th rowspan="3">Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report 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.</th> <th rowspan="3">Date Started Day Month Year</th> <th rowspan="3">Date Ended Day Month Year</th> <th rowspan="3">Check only if event occurred before first dose of IPdrug under study</th> <th rowspan="3">Is event serious? <input type="checkbox"/> Yes <input type="checkbox"/> No</th> <th rowspan="3">If serious, enter Serious Criteria (see codes below)</th> <th colspan="4">Relationship Is there a reasonable possibility that the Event may have been caused by IPdrug under study or an Amgen device used to administer the IPdrug under study?</th> <th rowspan="3">Outcome of Event -Resolved -Not resolved -Fatal -Unknown</th> <th rowspan="3">Check only if event is related to study procedure eg, biopsy</th> </tr> <tr> <th colspan="4"> <div style="display: flex; justify-content: space-around;"> <Pdevice> No/ Yes/ <Pdevice> No/ Yes/ <Pdevice> No/ Yes/ <Pdevice> No/ Yes/ </div> </th> </tr> <tr> <th colspan="4"> <div style="display: flex; justify-content: space-around;"> No/ Yes/ No/ Yes/ No/ Yes/ No/ Yes/ </div> </th> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> <td> </td> <td> </td> <td> </td> <td> </td> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> <td> </td> <td> </td> <td> </td> <td> </td> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> <td> </td> <td> </td> <td> </td> <td> </td> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </table>												Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report 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 IPdrug under study	Is event serious? <input type="checkbox"/> Yes <input type="checkbox"/> No	If serious, enter Serious Criteria (see codes below)	Relationship Is there a reasonable possibility that the Event may have been caused by IPdrug under study or an Amgen device used to administer the IPdrug under study?				Outcome of Event -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy	<div style="display: flex; justify-content: space-around;"> <Pdevice> No/ Yes/ <Pdevice> No/ Yes/ <Pdevice> No/ Yes/ <Pdevice> No/ Yes/ </div>				<div style="display: flex; justify-content: space-around;"> No/ Yes/ No/ Yes/ No/ Yes/ No/ Yes/ </div>																																							
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4. Was subject hospitalized or was a hospitalization prolonged due this event? <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, please complete all of Section 4																																																																			
Date Admitted Day Month Year						Date Discharged Day Month Year																																																													

Amgen Study # 20120325 Talimogene laherparepvec	Electronic Adverse Event Contingency Report Form For Restricted Use
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		Site Number			Subject ID Number							
5. Was IP/drug under study administered/taken prior to this event? <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, please complete all of Section 5												
IP/Drug/Amgen Device:		Date of Initial Dose			Date of Dose			Dose	Route	Frequency	Action Taken with Product	Lot # and Serial #
		Day	Month	Year	Day	Month	Year				01 Still being Administered 02 Permanently discontinued 03 Withheld	
IP: talimogene laherparepvec	<input type="checkbox"/> blinded <input type="checkbox"/> open label											Lot # _____ <input type="checkbox"/> Unknown Serial # _____ <input type="checkbox"/> Unavailable / Unknown
IP:	<input type="checkbox"/> blinded <input type="checkbox"/> open label											Lot # _____ <input type="checkbox"/> Unknown Serial # _____ <input type="checkbox"/> Unavailable / Unknown
6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, please complete:												
Medication Name(s)	Start Date	Stop Date	Co-suspect	Continuing	Dose	Route	Freq.	Treatment Med				
	Day Month Year	Day Month Year	No✓ Yes✓	No✓ Yes✓				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? <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, please complete:												
Date	Test											
	Unit											
	Day Month Year											

9. OTHER RELEVANT TESTS (diagnostics and procedures)								Any Other Relevant tests? <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, please complete:																				
Date Day Month Year			Additional Tests							Results								Units										
			Site Number				Subject ID Number																					
10. CASE DESCRIPTION (<i>Provide narrative details of events listed in section 3</i>) Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.																												
Signature of Investigator or Designee - _____ <i>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.</i>														Title _____							Date _____							

Section: 14 Appendices, Appendix C

Replace:

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: 20120325				
Study Design: <input type="checkbox"/> Interventional <input type="checkbox"/> Observational (If Observational: <input type="checkbox"/> Prospective <input type="checkbox"/> Retrospective)				
2. Contact Information				
Investigator Name		Site #		
Phone ()		Fax ()		Email
Institution				
Address				
3. Subject Information				
Subject ID #		Subject Gender: <input type="checkbox"/> Female <input type="checkbox"/> Male		Subject DOB: mm / dd / yyyy
4. Amgen Product Exposure				
Amgen Product	Dose at time of conception	Frequency	Route	Start Date
Talimogene Laherparepvec				mm / dd / yyyy
Was the Amgen product (or study drug) discontinued? <input type="checkbox"/> Yes <input type="checkbox"/> No				
If yes, provide product (or study drug) stop date: mm / dd / yyyy				
Did the subject withdraw from the study? <input type="checkbox"/> Yes <input type="checkbox"/> No				
5. Pregnancy Information				
Pregnant female's LMP		mm / dd / yyyy		<input type="checkbox"/> Unknown
Estimated date of delivery		mm / dd / yyyy		<input type="checkbox"/> Unknown <input type="checkbox"/> N/A
If N/A, date of termination (actual or planned) mm / dd / yyyy				
Has the pregnant female already delivered? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown <input type="checkbox"/> N/A				
If yes, provide date of delivery: mm / dd / yyyy				
Was the infant healthy? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown <input type="checkbox"/> 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				

With:

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: _____

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: _____

[Section: 14 Appendices, Appendix D](#)

paragraph 2

Replace:

Clinical Examination Using Caliper: All measurements will be determined using a ruler or calipers and reported in metric notation (mm) and will be recorded bi dimensionally. Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in at least 2 dimensions as assessed using calipers (eg, superficial cutaneous melanoma lesion). (Note: When a lesion can be evaluated by both, clinical examination and imaging, radiographic imaging evaluations should be undertaken preferred since it is more objective).

With:

Clinical Examination Using Caliper: All measurements will be determined using a ruler or calipers and reported in metric notation (mm) and will be recorded bi-dimensionally. Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in at least 2 dimensions as assessed using calipers (eg, superficial cutaneous melanoma lesion). (Note: When a lesion can be evaluated by both, clinical examination and imaging, radiographic imaging evaluations should be **preferred** since it is more objective).

[Section: 14 Appendices, Appendix D](#)

Add:

Coalescing or splitting lesions:

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

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

Section: 14 Appendices, Appendix D

Add:

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

Section: 14 Appendices , Appendix D

Replace:

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

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