Title: A phase 1, Multi-center, Open-label, Dose De-escalation Study to Evaluate the Safety and Efficacy of Talimogene Laherparepvec in Japanese Subjects With Unresectable Stage IIIB-IV Malignant Melanoma

Amgen Protocol Number (Talimogene Laherparepvec) 20140270

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Amendment 4:	05 December 2017
Amendment 5	**01 September 2020**

To comply with local regulatory requirements, all uses of the term "clinical study" in the protocol, other study-related documents, and forms that have been issued or to be issued in future, is replaced with "post-marketing clinical study" after Talimogene Laherparepvec has been approved by regulatory authority.

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Investigator's Agreement

I have read the attached protocol entitled A phase 1, Multi-center, Open-label, Dose De-escalation Study to Evaluate the Safety and Efficacy of Talimogene Laherparepvec in Japanese Subjects with Unresectable Stage IIIB-IV Malignant Melanoma, dated **01 September 2020**, and agree to abide by all provisions set forth therein.

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

The study will be conducted in compliance with the Ministerial Ordinance on Good Clinical Practice for Drugs (Ministry of Health and Welfare Ordinance No. 28, 27 March 1997).

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 1 year after the study is completed, if there are changes that affect my financial disclosure status.

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

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Name of Investigator Date (DD Month YYYY)

Protocol Synopsis

Title: A phase 1, Multi-center, Open-label, Dose De-escalation Study to Evaluate the Safety and Efficacy of Talimogene Laherparepvec in Japanese Subjects with Unresectable Stage IIIB-IV Malignant Melanoma

Study Phase: phase 1

Indication: Melanoma

Primary Objective(s):

There are 2 fold of purposes for this study. 1 is to evaluate safety and tolerability and the other is to study the anti-tumor effects of talimogene laherparepvec in Japanese patients with unresectable stage IIIB-IV malignant melanoma.

- To evaluate the safety and tolerability of talimogene laherparepvec, subjects will be assessed by incidence of dose limiting toxicities (DLTs).
- These subjects will also be evaluated for the anti-tumor activity of talimogene laherparepvec as assessed by durable response rate (DRR) using modified World Health Organization (WHO) response criteria. DRR is defined as the rate of objective response (Complete response [CR] or partial response [PR]) lasting continuously for $\geq$ 6 months and starting any time within 12 months of initiating therapy.

Secondary Objective(s):

- To evaluate the anti-tumor activity of talimogene laherparepvec, as assessed by overall response rate (ORR), time to response (TTR), duration of response (DOR), progression free survival (PFS) using modified World Health Organization (WHO) response criteria by investigators
- To evaluate overall survival (OS)

Safety Objective:

- To evaluate the safety of talimogene laherparepvec as determined by subject incidence of adverse events and clinically relevant laboratory abnormalities, where not defined as DLTs.

Hypotheses:

No formal statistical hypothesis will be tested for safety endpoints in this trial. Based on the well tolerated safety profile from a global phase 3 study, it is hypothesized that talimogene laherparepvec will be safe and well tolerated in Japanese subjects with unresectable stage IIIB-IVM1c malignant melanoma. A DRR is hypothesized to be consistent with results from the global phase 3 study.

Primary Endpoint(s):

- Subject incidence of DLTs
- DRR using modified WHO response criteria by investigators

Secondary Endpoint(s):

- ORR, TTR, DOR, and PFS using modified WHO response criteria by investigators
- OS

Study Design:

This is a phase 1, multicenter, open-label study of talimogene laherparepvec in Japanese subjects with unresectable stage IIIB-IV malignant melanoma who are candidates for intralesional therapy. Up to approximately 18 subjects will be enrolled in the study. Subjects may be included in the evaluation for both safety and efficacy. The DLT evaluation period is 35 days from the initial administration of talimogene laherparepvec. Initially, 6 DLT-evaluable subjects will be

enrolled and treated at Dose 1 (up to 4.0 mL of 10^6 PFU/mL talimogene laherparepvec will be administered on day 1, followed by a dose of up to 4.0 mL of 10^8 PFU/mL 3 weeks [+ 5 days] later and then up to 4.0 mL of 10^8 PFU/mL every 2 weeks [± 3 days] thereafter). Upon demonstration of safety based on DLT rules, an additional 12 subjects will be enrolled and treated at Dose 1 to obtain additional safety data. If dose de-escalation is needed based on the DLT evaluation of the first 6 DLT-evaluable subjects, then an additional 6 subjects will be treated at Dose -1 (up to 4.0 mL of 10^6 PFU/mL talimogene laherparepvec will be administered on day 1, followed by dose of up to 4.0 mL of 10^7 PFU/mL 3 weeks [+ 5 days] later and then up to 4.0 mL of 10^7 PFU/mL every 2 weeks [± 3 days] thereafter). The same DLT rules will be used to evaluate safety based on the initial 6 DLT-evaluable subjects after dose de-escalation. Upon demonstration of safety, additional subjects will be enrolled (up to a total of 18 subjects) at Dose-1 to obtain additional safety data. The hypothesis test for DRR will include all subjects enrolled after dose de-escalation who received at least 1 dose of talimogene laherparepvec. If no dose de-escalation is needed the DRR hypothesis test will include the first 18 subjects dosed.

Treatment with talimogene laherparepvec will continue until the subject has a DLT during the DLT evaluation period, subject has achieved a CR, no injectable lesions, clinically relevant (resulting in clinical deterioration or requiring change in therapy) disease progression beyond 24 weeks of treatment per modified WHO response criteria, safety concern, **a maximum treatment duration of 48 months, or the drug is commercially available in Japan,** whichever occurs first. Due to the mechanism of action of talimogene laherparepvec, subjects may experience growth in existing tumors or the appearance of new tumors prior to maximal clinical benefit. Therefore, treatment with talimogene laherparepvec should be continued for at least 6 months even in the presence of progression, including the appearance of new lesions to allow for delayed-immune-based antitumor effects to occur unless other therapy for melanoma is required.

All subjects will complete a safety follow-up Visit 30 (+ 7) days after the last dose of study treatment. Subjects will be followed for survival, subsequent anticancer therapies and talimogene laherparepvec related adverse events every 12 weeks (± 28 days) for 24 months after the last subject is enrolled. **Subjects that are being treated beyond 24 months after the last subject enrolled will not enter long-term follow-up and their last visit will be safety follow-up.**

Sample Size: Approximately 18 subjects will be enrolled. Subjects may be included in the evaluation for both safety and efficacy.

Summary of Subject Eligibility Criteria: Key inclusion criteria include: male or female subjects, ≥ 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 and is determined by the physician to be not suitable or eligible for the approved systemic anticancer drug therapy in Japan. Subject may also have received prior systemic anticancer treatment consisting of chemotherapy, immunotherapy, or targeted therapy. 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; to be classified as malignant, and measurable lymph nodes must be ≥ 15 mm in shortest diameter. 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. Female subjects of childbearing potential must have a negative pregnancy test.

Key exclusion criteria include: subject must not have clinically active cerebral metastases or > 3 visceral metastases (this does not include lung or nodal metastases associated with visceral organs). For subjects with ≤ 3 visceral metastases, no lesion > 3 cm in longest dimension and liver lesions must be stable for at least 1 month prior to enrollment. In addition, subject must not have any bone metastases. Subjects will be excluded if they have 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. Subjects must not have active herpetic skin lesions or prior complications of herpetic 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 4.1 and 4.2.

Investigational Product

Amgen Investigational Product Dosage and Administration: Talimogene laherparepvec will be manufactured and packaged by Amgen Inc. Talimogene laherparepvec is supplied as a sterile frozen liquid in a single-use vial. Each vial contains a minimum of 1.0 mL talimogene laherparepvec at either 10^6 plaque-forming unit (PFU)/mL or 10^8 PFU/ mL concentrations. Talimogene laherparepvec will be administered by intralesional injection only into injectable cutaneous, subcutaneous, and nodal tumors, with or without image ultrasound guidance. On day 1 (week 0) 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 or 10^7 PFU/mL, should be administered 3 weeks (+ 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). The dose of 10^8 PFU/mL will be diluted 1:10 to obtain a concentration of 10^7 PFU/mL immediately prior to injection. Subsequent injections up to 4.0 mL of 10^8 or 10^7 PFU/mL should be given every 2 weeks (± 3) days. The maximum volume of talimogene laherparepvec to be administered at each treatment visit is 4.0 mL. Refer to Section 6.2.1.

Procedures: Written informed consent must be obtained from all subjects or legally acceptable representative before any study specific screening procedures are performed. The following procedures will occur per the Schedule of Assessments: medical, surgical and medication history; physical examination, vital signs, body weight and height; ECOG performance status; 12-lead electrocardiogram (ECG); recording of concomitant medications; survival assessment; review of adverse events, disease related events and serious adverse events; and reporting of potential or known unintended exposure to talimogene laherparepvec by a household member, caregiver, or healthcare provider. Blood will be collected for local laboratory testing including: chemistry, hematology, lactate dehydrogenase, coagulation, hepatitis B surface antigen, hepatitis B core antibody, and hepatitis C virus antibody. In females of childbearing potential. urine or serum pregnancy test will be performed locally. Clinical and radiological tumor assessments will be performed. Blood for herpes simplex virus type-1 (HSV-1) antibody serostatus will be collected and swabs of any cold sores, vesicles or lesions suspected to be of herpetic origin will be collected for qPCR testing of talimogene laherparepvec DNA . Talimogene laherparepvec will be administered at day 1 (week 0), at week 3 (+ 5 days) and every 2 weeks (± 3 days) thereafter.

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:

Planned method of analyses: No formal interim efficacy analysis is planned for this study. Interim safety analyses will be performed to support the evaluation of safety by a Dose Level Review Team (DLRT). The primary efficacy analysis will occur when a durable response outcome has been assessed for all subjects included in the primary efficacy analysis.

The DLT analysis set will be used to summarize the subject incidence of DLT for the study and the safety analysis set will be used for all other analyses of safety endpoints (including but not limited to all adverse events, grade ≥ 3 adverse events, serious adverse events, fatal adverse events, adverse events requiring discontinuation of study drug, and adverse events defined as events of interest). A 1-sided 5% significance level exact binomial test will be performed to test the null hypothesis of a 2% DRR. The expectation is that this test will be based on the first

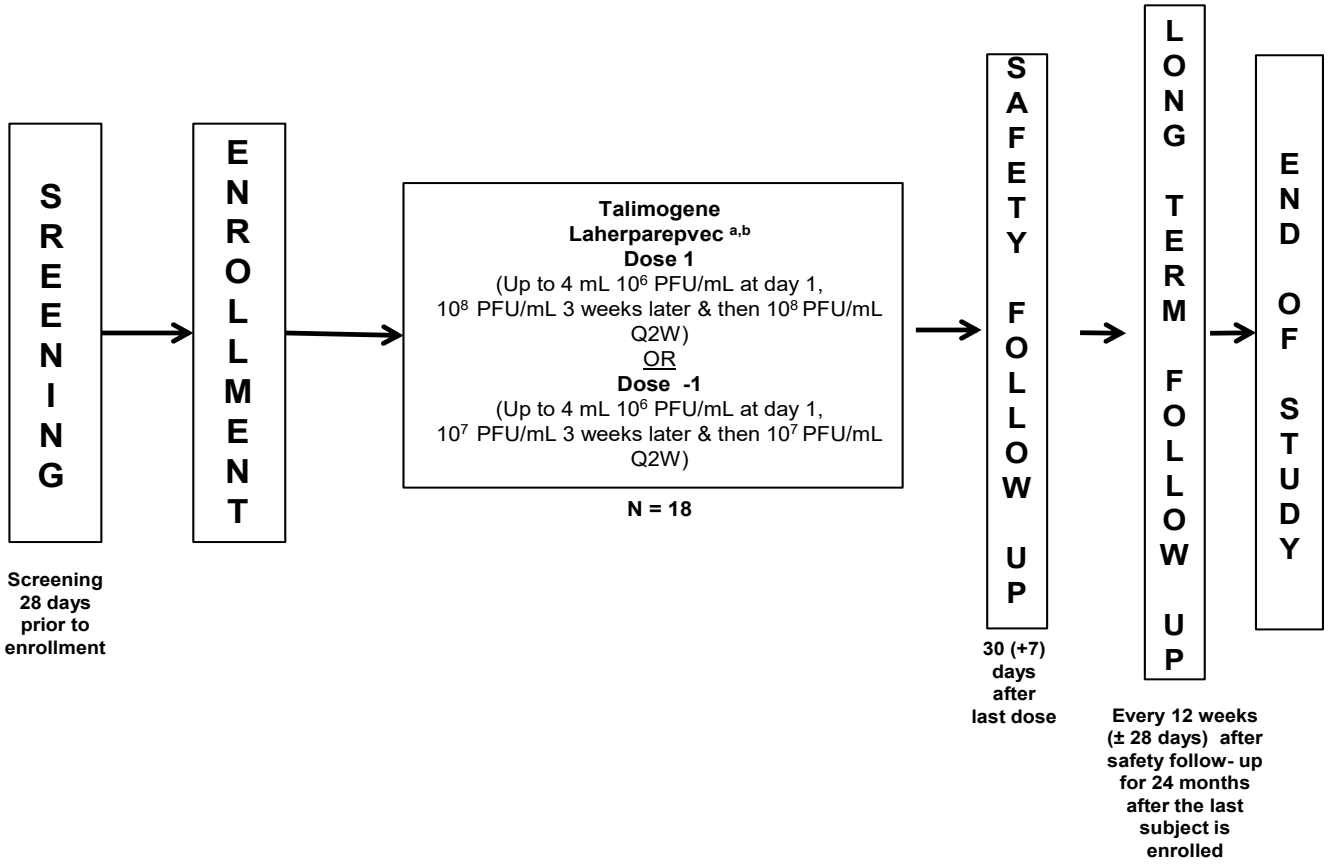
18 subjects that receive at least 1 dose of talimogene laherparepvec. The null hypothesis will be rejected if at least 2 subjects achieve a durable response (DR). Assuming a DRR of 16.3% consistent with the global phase 3 study, this analysis will have 81% power. DRR will be summarized with an associated exact 90% and 95% confidence interval. DOR among responders, TTR, PFS and OS will be estimated using the Kaplan-Meier method. Treatment-emergent adverse events are defined as adverse events with an onset from the first dose of study therapy up to 30 days after the last dose of study therapy. Subject incidences of treatment-emergent and treatment-related adverse events (including all adverse events, grade ≥ 3 adverse events, serious adverse events, fatal adverse events, adverse events of interest and events requiring the discontinuation of study therapy) will be summarized. Medical Dictionary for Regulatory Activities will be used to code adverse events to a system organ class and a preferred term within the system organ class. Common Terminology Criteria for Adverse Events version 4.0 will be used to grade severity of adverse events.

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

Sponsor: Amgen Inc. and Amgen K.K.

Data Element Standards Version(s)/Date(s):	5: 20 March 2015

Study Design and Treatment Schema



CR = complete response; PD= disease progression; PFU= plaque-forming unit; Q2W = every 2 weeks

[a] Up to approximately 18 subjects will be enrolled in the study. Subjects may be included in the evaluation for both safety and efficacy. The DLT evaluation period is 35 days from the initial administration of talimogene laherparepvec. Initially, 6 DLT-evaluable subjects will be enrolled and treated at Dose 1. Upon demonstration of safety based on DLT rules, an additional 12 subjects will be enrolled and treated at Dose 1 to obtain additional safety data. However, if Dose 1 is declared unsafe based on DLT rules, then an additional 6 DLT-evaluable subjects will be enrolled at Dose -1.

[b] Treatment will continue until subject experiences a DLT (during the DLT evaluation period), subject achieved a CR, no injectable lesions, clinically relevant (resulting in clinical deterioration or requiring change of therapy) disease progression beyond 24-weeks of treatment, per modified WHO response criteria, safety concern**, a maximum treatment duration of 48 months, or the drug is commercially available in Japan,** whichever occurs first.

Study Glossary

Abbreviation or Term	Definition/Explanation
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BOR	best overall response
$BRAF^{V600E/K}$	serine/threonine protein kinase B-Raf V600E/K
CI	confidence interval
CNS	central nervous system
CR	complete response
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug-induced liver injury
DLRT	Dose Level Review Team
DLT	dose limiting toxicity
DOR	duration of response
DR	durable response
DRR	durable response rate
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
End of Study for Individual Subject	The last day that protocol-specified procedures are conducted for an individual subject (ie, the date the subject withdraws full consent from the study, completes the safety follow-up visit or long-term follow-up [whichever is later] or death).
End of Study (primary completion)	The date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purpose of conducting the primary efficacy analysis, whether the study concluded as planned in the protocol or was terminated early. This will be the date when the last subject has been assessed for a durable response outcome.
End of Study (end of trial)	The date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable.
End of Treatment	The day of the last assessment for the protocol-specified treatment phase of the study for an individual subject
EU	European Union
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice

Abbreviation or Term	Definition/Explanation
GM-CSF	granulocyte macrophage colony-stimulating factor
HCP	Health care professional
Heart rate	number of cardiac cycles per unit of time
HIV	human immunodeficiency virus
HR	hazard ratio
HRT	hormonal replacement therapy
HSV-1	herpes simplex virus type-1
ICH	International Conference on Harmonisation
ICP	infected cell protein
INR	international normalization ratio
IPIM	Investigational Product Instruction Manual
IEC/IRB	independent ethics committee/institutional review board
Interactive Voice Response (IVR)	telecommunication technology that is linked to a central computer in real time as an interface to collect and process information.
LDH	lactate dehydrogenase
MRI	magnetic resonance imaging
NA	not applicable
ND	not done
ORR	overall response rate
OS	overall survival
PD	disease progression
PD-1	programmed death receptor 1
PDn	non-clinically relevant disease progression
PDr	clinically relevant disease progression
PET	positron emission tomography
PFS	progression-free survival
PFU	plaque-forming unit
PR	partial response
PR Interval	PR interval is measured from the beginning of the P wave to the beginning of the QRS complex in the heart's electrical cycle as measured by ECG
PT	prothrombin time
aPTT	activated partial thromboplastin time
qPCR	real-time polymerase chain reaction
QRS interval	QRS interval is the interval between the Q wave and the S wave in the heart's electrical cycle as measured by ECG; represents the time it takes for the depolarization of the ventricles

Abbreviation or Term	Definition/Explanation
QT interval	QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle as measured by ECG.
QTc interval	QT interval corrected for heart rate using accepted methodology
SD	stable disease
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include subject identification, randomization identification, and stratification value.
Study day 1	The first day that protocol-specified investigational product is administered to the subject
TTR	time to response
ULN	upper limit of normal
UE	unable to evaluate
vs	versus
WHO	World Health Organization

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1. OBJECTIVES

1.1 Primary

There are 2 fold purposes for this study. 1 is to evaluate safety and tolerability and the other is to study the anti-tumor effects of talimogene laherparepvec in Japanese patients with unresectable stage IIIB-IV malignant melanoma.

- To evaluate the safety and tolerability of talimogene laherparepvec, subjects will be assessed by incidence of dose limiting toxicities (DLTs).
- These subjects will also be evaluated for the anti-tumor activity of talimogene laherparepvec as assessed by durable response rate (DRR) using modified World Health Organization (WHO) response criteria. DRR is defined as the rate of objective response (Complete response [CR] or partial response [PR]) lasting continuously for ≥6 months and starting any time within 12 months of initiating therapy.

1.2 Secondary

- To evaluate the anti-tumor activity of talimogene laherparepvec, as assessed by overall response rate (ORR), time to response (TTR), duration of response (DOR), progression free survival (PFS) using modified World Health Organization (WHO) response criteria by investigators
- To evaluate overall survival (OS)

1.3 Safety

To evaluate the safety of talimogene laherparepvec as determined by subject incidence of adverse events and clinically relevant laboratory abnormalities where not defined as DLTs.

2. BACKGROUND AND RATIONALE

2.1 Disease

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; Tannous et al, 2005; Siegel et al, 2015). 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).

Melanoma is a relatively rare disease in Japan. The estimated incidence rate of melanoma is 2/100,000 (Takata et al, 2007) and approximately 4000 patients were diagnosed with the disease in 2011 according to the Patient Survey by Ministry of Health, Labour, and Welfare (MHLW, 2011). The prognosis of unresectable advanced melanoma is generally poor. The 10-year survival rates of stage III and IV disease were reported as 54 % and 7%, respectively (Ishihara et al, 2008). Although clinical data of chemotherapy in Japanese melanoma patients are limited, the reported 8-year survival rate of chemotherapy alone in stage M1b/M1c melanoma was 7.6% (Ishihara et al, 2008).

Until recently, traditional nonsurgical therapies for unresectable or advanced melanoma in adults included chemotherapy (dacarbazine, temozolomide, or other agents either alone or in combination), or interleukin-2. Although some regimens produced objective responses, they were usually short-lived. For example, dacarbazine or temozolomide achieved a 7% to 12% objective response rate, but an objective response did not appear to be associated with a prolongation in OS (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.

In recent years, novel therapeutic agents such as nivolumab, ipilimumab, and vemurafenib have been approved for advanced melanoma in Japan. In the phase

2 study of nivolumab in Japanese patients (n = 35), the objective response rate and median OS were 22.9% and 473.0 days (90% [CI]: 276.0, not reached), respectively (Yamazaki and Maeda, 2015). Approval of Vemurafenib in December 2014 was based on the results from the global phase 3 trial (Chapman et al, 2011) along with the Japanese phase 1/2 clinical trial that demonstrated safety and efficacy of vemurafenib in melanoma patients from Japan (Yamazaki et al, 2015).

The Food and Drug Administration (FDA), European Commission, and other regulatory agencies have approved 4 novel therapies for advanced melanoma in the last 5 years: 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™, 2014) and the *MEK* inhibitor trametinib (Mekinist™, 2013). The studies upon which approvals for ipilimumab and vemurafenib were based demonstrated improved survival compared to control treatments. The pivotal study of ipilimumab showed an OS improvement in subjects with HLA-A2*0201 genotype previously treated metastatic melanoma as compared with a gp100 peptide vaccine (Hodi et al, 2010; Yervoy® 2013). The median OS was 10.0 months in the group that received ipilimumab in combination with the gp100 peptide vaccine and 6.4 months in the group that received gp100 peptide vaccine alone (hazard ratio [HR] = 0.68, $p < 0.001$) (Hodi et al, 2010). Approximately 8% more patients survived 2 years in the ipilimumab arm than in the control arm (21.6% versus [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™, 2014) 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 OS. Additionally, dabrafenib and trametinib were approved recently as a combination therapy for *BRAF*-mutant unresectable or metastatic melanoma. (Flaherty et al, 2012b). The combination of dabrafenib and trametinib has shown to improve overall survival when compared to BRAF inhibition (vemurafenib) alone in previously untreated patients with metatstatic melanoma with BRAF V600E or V600K mutations (Robert et al, 2015)

In 2014, the FDA approved 2 programmed death receptor-1 (PD-1) blocking antibodies: pembrolizumab and nivolumab for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF^{V600} mutation positive, a BRAF inhibitor (Keytruda®, 2015; Opdivo™, 2015). Approval of these agents was based on response rates and duration of response. Recently, phase 3 studies reported OS benefit with the use of pembrolizumab (Robert et al, 2015) and nivolumab (Larkin et al, 2015).

2.2 Amgen Investigational Product Background: Talimogene Laherparepvec

Talimogene laherparepvec is an intralesionally delivered oncolytic immunotherapy comprised of a genetically engineered herpes simplex virus type-1 (HSV-1) that selectively replicates in tumor tissue. The neurovirulence factor infected-cell protein (ICP) 34.5 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 and II molecules by blocking the transporter associated with antigen processing 1 and 2. This deletion also allows the increased expression of the US11 gene. This promotes virus growth in cancer cells without decreasing tumor selectivity.

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

In the United States, talimogene laherparepvec (IMLYGIC™) is indicated for the local treatment of unresectable cutaneous, subcutaneous and nodal lesions in patients with melanoma recurrent after initial surgery.

The investigational product contains attenuated infectious herpes simplex virus-1. Refer to the specific section of the Investigator's Brochure for additional information related to the physical, chemical, and pharmaceutical properties and formulation(s).

Talimogene Laherparepvec in Melanoma

Efficacy:

The efficacy of talimogene laherparepvec in subjects with regionally and distantly metastatic melanoma was evaluated in a pivotal, controlled, phase 3 study (Study 005/05) and a supportive, single-arm, phase 2 study (Study 002/03). Talimogene laherparepvec up to 4.0 mL 10^6 PFU/mL was administered at day 1, followed by dose of up to 4.0 mL of 10^8 PFU/mL 3 weeks later and then every 2 weeks. The phase 2 study was a single arm study conducted in 50 patients with unresectable late stage III or stage IV melanoma (Senzer et al, 2009). The overall response rate was 28%. More than half of the responses were complete and many were durable, with the majority lasting longer than 6 months. An important finding was that transient locoregional or distant progression, including new lesions, sometimes preceded response. 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 was durable response rate (objective response is maintained for at least 6 months). 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 occurred when the 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]). 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.

Safety:

The overall safety evaluation of talimogene laherparepvec in melanoma is based on exposure of 292 patients in the phase 3 study and 50 patients in the phase 2 study. In both the phase 2 and phase 3 studies, talimogene laherparepvec was administered at a dose of up to 4 mL of 10^8 PFU/mL every 2 weeks except for the second administration which was given 3 weeks after the 10^6 PFU/mL initial dose. The safety profile was similar in the phase 2 and phase 3 studies with talimogene laherparepvec.

In the phase 3 study (Study 005/05) the safety population consisted of 419 subjects (292 talimogene laherparepvec; 127 GM-CSF). The median duration of treatment was 23 weeks in the talimogene laherparepvec arm. At least 1 adverse event was reported for 99.3% of talimogene laherparepvec treated subjects. Most adverse events were mild or moderate in severity (63.4% talimogene laherparepvec) and generally resolved within 72 hours. The most common adverse drug reactions (≥ 25%) in talimogene laherparepvec-treated patients were fatigue, chills, pyrexia, nausea, influenza-like illness, and injection site pain. The most common grade 3 or higher adverse reaction was cellulitis in the talimogene laherparepvec arm. Disease progression was the most frequently reported serious adverse event in 3.1% of talimogene laherparepvec treated subjects, followed by cellulitis (2.4%), pyrexia (1.7%), and tumor pain (1.4%).

In summary, talimogene laherparepvec has a favorable safety profile in subjects with stage IIIB-IVM1c melanoma at the dose evaluated (up to 4 mL of 10^8 PFU/mL). Most adverse events were mild to moderate with the most common being flu-like symptoms. Adverse events infrequently led to treatment discontinuation and deaths were usually in the setting of disease progression.

2.3 Rationale

While the approval of the newer agents represents a clear milestone in the treatment of advanced melanoma, limitations still exist. The 2-year OS following ipilimumab remains only approximately 20% and the drug is associated with severe and potentially fatal immunological adverse effects (Hodi et al, 2010). Vemurafenib, dabrafenib, and trametinib are indicated only in patients with $BRAF^{V600}$ mutations, and are associated with early development of resistance in most cases, leading to short durations of response. The safety profiles of vemurafenib and dabrafenib include increased incidence of cutaneous squamous cell carcinoma or high grade keratoacanthoma in almost 20% of patients treated with vemurafenib and > 5% of patients treated with dabrafenib (Zelboraf®, 2013; Tafinlar™, 2014). Additionally, grade 2 or higher dermatologic reactions including rash, pruritus, and hyperkeratosis are common with both agents. Trametinib is associated with cuneiform dermatitis, peripheral edema, hypertension, decreased cardiac ejection fraction, and ocular events (Mekinist™, 2013). Response rates are more modest with the PD-1 blocking antibodies, but can be durable. Their overall benefit-risk profiles have been determined primarily in patients with the most advanced stages of melanoma.

An unmet medical need exists for additional treatment options that can provide patients with regionally or distantly metastatic melanoma an opportunity to achieve durable responses with a favorable safety profile. A clear unmet need continues to exist for patients with advanced melanoma in Japan as well in spite of recent approvals of targeted and immunotherapy agents, for reasons described above. The proposed phase 1 study will evaluate the safety and tolerability and efficacy of talimogene laherparepvec for the treatment of metastatic melanoma in Japanese patients, which will potentially help define a role for talimogene laherparepvec in the treatment landscape of melanoma in Japan.

2.4 Clinical Hypotheses

No formal statistical hypothesis will be tested for safety endpoints in this trial. Based on the well tolerated safety profile from a global phase 3 study, it is hypothesized that talimogene laherparepvec will be safe and well tolerated in Japanese subjects with unresectable Stage IIIB-IVM1c melanoma. A DRR is hypothesized to be consistent with results from the global phase 3 study.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a phase 1, multicenter, open-label study of talimogene laherparepvec in Japanese subjects with unresectable stage IIIB-IVM1c malignant melanoma that are candidates for intralesional therapy.

Approximately 18 subjects will be enrolled in the study. Subjects may be included in the evaluation for both safety and efficacy. The DLT evaluation period is 35 days from the initial administration of talimogene laherparepvec. Initially, 6 DLT-evaluable subjects will be enrolled and treated at 100% of the dose regimen of talimogene laherparepvec (Dose 1) as described below. The first dose administered will be up to 4.0 mL of 10^6 PFU/mL (day 1, week 0) followed by dose of up to 4.0 mL of 10^8 PFU/mL 3 weeks (+ 5 days) later. Subsequent doses of up to 4.0 mL of 10^8 PFU/mL will be administered every 2 weeks (± 3 days) thereafter (see Section 6.2.1.1). A Dose Level Review Team (DLRT) meeting will be convened after 6 DLT-evaluable subjects are enrolled. Further enrollment will be temporarily paused until the DLRT meeting is convened and a decision is made on the dose level. Upon demonstration of safety based on DLT incidence < 33% in the first 6 subjects, an additional 12 subjects will be enrolled and treated at Dose 1 to obtain additional safety data.

However, if at any time there are 2 or more subjects with a DLT prior to enrollment of the first 6 DLT-evaluable subjects, an ad hoc DLRT meeting will be convened to determine if dose de-escalation is required.

The safety data during the enrollment of the additional 12 subjects will be monitored on an going basis and an ad hoc DLRT meeting may be called, if needed, to determine the further course of the study.

The hypothesis test for DRR will include all subjects enrolled after dose de-escalation who received at least 1 dose of talimogene laherparepvec. If no dose de-escalation is needed, the DRR hypothesis test will include the first 18 subjects dosed.

Dose De-escalation

If dose de-escalation is needed then the remaining subjects will be treated at the lower dose regimen of talimogene laherparepvec (Dose -1). The initial dose administered will be up to 4.0 mL of 10^6 PFU/mL (day 1, week 0) followed by dose of up to 4.0 mL of 10^7 PFU/mL 3 weeks (+ 5 days) later. Subsequent doses of up to 4.0 mL of 10^7 PFU/mL will be administered every 2 weeks (± 3 days) thereafter (see Section 6.2.1.2). The

DLRT will review the safety data after the first 6 DLT-evaluable subjects at Dose -1 have been enrolled. Enrollment will be temporarily paused during the DLT review period to evaluate the 6 DLT-evaluable subjects at Dose -1. Upon demonstration of safety, additional subjects will be enrolled (up to a total of 18 subjects) at Dose -1 to obtain additional safety data.

The safety data of the subjects enrolled at the Dose-1 level will be monitored on an going basis and an ad hoc DLRT meeting may be called, if needed, to determine the further course of the study.

All subjects will complete a safety follow-up Visit 30 (+7) days after the last dose of study treatment. Adverse events and disease related events will be collected as described in Section 9.2. After the safety follow-up visit, subjects will enter the long-term follow-up**, unless they did not receive at least 1 dose of study treatment or received study treatment for more than 24 months after the last subject enrolled. In long-term follow-up, s**ubjects will be followed for survival and subsequent anticancer therapies every 12 weeks (± 28 days) **until** approximately 24 months after the last subject is enrolled. In addition, talimogene laherparepvec related adverse events that occur through the end of the long-term follow-up will be reported.

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

The study endpoints are defined in Section 10.1.1.

3.2 Number of Sites

The study will be conducted at approximately 7 sites in Japan. Sites that do not enroll subjects within approximately 4 months of site initiation may be closed.

3.3 Number of Subjects

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

Approximately 18 subjects will be enrolled. Refer to Section 10.2 for sample size considerations.

3.4 Replacement of Subjects

Subjects enrolled may be replaced if they are not evaluable for DLT (eg, a subject did not receive study treatment, or ended the study treatment before completion of DLT evaluation period for a reason other than experiencing a DLT).

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

The duration of screening for each subject will be approximately 28 days. The duration of treatment will vary for each subject. Subjects will be treated until the subject has a DLT during the DLT evaluation period, subject has achieved a CR, no injectable lesions, clinically relevant (resulting in clinical deterioration or requiring change in therapy) disease progression beyond 24-weeks of treatment per modified WHO response criteria (Appendix D), safety concern, **a maximum treatment duration of 48 months, or until the drug is commercially available in Japan,** whichever occurs first. Maximum treatment duration will be **48** months. All subjects will complete a safety follow-up Visit 30 (+7) days after the last dose of study treatment. After the safety follow-up visit subjects will enter long-term follow-up **(not applicable for subjects treated longer than 24 months after the last subject is enrolled)**. During this period, subjects will be followed for approximately 24 months after the last subject is enrolled. The total study duration for an individual subject can be up to 4 years.

3.5.2 End of Study

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary efficacy analysis, whether the study concluded as planned in the protocol or was terminated early.

The primary completion date is the date when the last subject has been assessed for a durable response outcome.

If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination of the study), then the primary completion will be the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

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

4. SUBJECT ELIGIBILITY

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

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

4.1 Inclusion Criteria

1. 101 Subject has provided informed consent prior to initiation of any study-specific activities/procedures
2. 102 Subject's legally acceptable representative has provided informed consent when the subject is legally too young (ie, subject age < 20 years) to provide informed consent and the subject has provided written assent based on local regulations and/or guidelines prior to any study-specific activities/procedures being initiated
3. 103 Male or female age ≥ 18 years at the time of informed consent
4. 104 Histologically confirmed diagnosis of melanoma
5. 105 Subject with stage IIIB to IVM1c melanoma that is not surgically resectable
6. 106 Subject who is treatment naive and is determined by the physician to be not suitable or eligible for the approved systemic anticancer drug therapy in Japan. Subject may also have received prior systemic anticancer treatment consisting of chemotherapy, immunotherapy, or targeted therapy. Treatment for melanoma must have been completed at least 28 days prior to enrollment.
7. 107 Candidate for intralesional therapy (ie, disease is appropriate for direct injection or through the use of ultrasound guidance, where appropriate) defined as 1 or more 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 (see Appendix D for guidance on lesions that may be aggregated)
8. 108 Measurable disease defined as 1 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 longest 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 (excluding lymph nodes). To be classified as malignant and measurable a lymph node must be ≥ 15 mm in shortest diameter.
   - at least 1 ≥ 10 mm longest diameter superficial cutaneous or subcutaneous melanoma lesion as measured by calipers

- multiple superficial melanoma lesions which in aggregate have a longest total diameter of ≥ 10 mm (see Appendix D for guidance on lesions that may be aggregated; if the only measurable lesion is an aggregate, a photograph of the aggregate lesion must be provided and the case reviewed by the Amgen medical monitor for approval prior to enrollment)

9. 109 Serum lactate dehydrogenase (LDH) levels ≤ 1.5 X upper limit of normal (ULN) within 28 days prior to enrollment

10. 110 Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

11. 111 Adequate organ function determined within 28 days prior to enrollment, defined as follows:

- absolute neutrophil count ≥ 1500/mm^3
- platelet count ≥ 75,000/mm^3
- hemoglobin ≥ 8 g/dL without need for hematopoietic growth factor or transfusion support
- serum creatinine ≤ 1.5 x ULN
- serum bilirubin ≤ 1.5 x ULN
- aspartate aminotransferase (AST) ≤ 2.5 x ULN
- alanine aminotransferase (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 x ULN)
- activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN

Note: Prolongation of INR, PT, and aPTT when the results 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.

12. 112 Female subjects of childbearing potential must have a negative urine or serum pregnancy test within 3 days prior to enrollment. If urine pregnancy test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

4.2 Exclusion Criteria

13. 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 craniotomy, with no evidence of progression and have not required steroids for at least 2 months prior to enrollment.

14. 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 in longest dimension and liver lesions must be stable for at least 1 month prior to enrollment.

15. 203 Bone metastases

16. 204 Primary ocular or mucosal melanoma

17. 205 History or evidence of symptomatic autoimmune disease (eg, 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) is not considered a form of systemic treatment for autoimmune disease.

18. 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 within 2 months prior to enrollment.

19. 207 Active herpetic skin lesions or prior complications of herpetic infection (eg, herpetic keratitis or encephalitis).

20. 208 Requires intermittent or chronic systemic (intravenous or oral) treatment with an antiherpetic drug (eg, acyclovir), other than intermittent topical use.

21. 209 Previous treatment with talimogene laherparepvec

22. 210 Currently receiving treatment with another investigational device or drug study, or $<$ 28 days since ending treatment with another investigational device or drug study(s)

23. 211 Other investigational procedures while participating in this study are excluded.

24. 212 Known to have acute or chronic active hepatitis B infection, acute or chronic active hepatitis C infection or human immunodeficiency virus (HIV) infection

25. 213 History of other malignancy within the past 3 years with the following exceptions:
    - Adequately treated mucosal gastric cancer
    - malignancy treated with curative intent and with no known active disease present for $\geq$ 3 years before enrollment and felt to be at low risk for recurrence by the treating physician
    - adequately treated non-melanoma skin cancer or lentigo maligna 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

26. 214 Subject has known sensitivity to bovine- or porcine-derived components or to any of the products or components to be administered during dosing.

27. 215 Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures to the best of the subject and investigator's knowledge.

28. 216 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

29. 217 Subject previously has entered this study

30. 218 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, or planning to breastfeed after starting treatment.
Note: Subjects who suspend breast-feeding prior to starting treatment with talimogene laherparepvec and do not intend to resume breast-feeding can be enrolled.

31. 219 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

32. Note: Acceptable methods of effective contraception are defined in Section 6.9 and the informed consent form.

33. 220. 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. For those with latex allergies, polyurethane condoms may be used.

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

5. SUBJECT ENROLLMENT

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written independent ethics committee/institutional review board (IEC/IRB) approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see Section 11.2). All subjects or legally acceptable representatives must personally sign and date the IEC/IRB and

Amgen approved informed consent form before commencement of study-specific activities/procedures.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment case report form (CRF).

Each subject who enters into the screening period for the study (defined when the subject signs the informed consent) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned by the Interactive voice response (IVR) system. 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. Subjects who are determined not eligible after screening must be screen-failed in the IVR system and the reason for the screen-failure provided. Subjects who do not meet all eligibility criteria may be rescreened 1 time at the discretion of the investigator. Prior to rescreening, subjects may need to reconsent to the study to ensure that the IEC/IRB 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 IVR system and the reason for the screen-failure provided. Subjects may only be enrolled once into this study.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened.

5.1 Treatment Assignment

All subjects enrolled will receive open-label talimogene laherparepvec. The treatment assignment date is to be documented in the subject's medical record and on the enrollment CRF.

6. TREATMENT PROCEDURES

6.1 Classification of Product(s) and/or Medical Device(s)

The Amgen Investigational Product (except if required by local regulation) used in this study includes: talimogene laherparepvec.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, 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 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 the 10^6 PFU/mL concentration will be packaged separately from the supply for the 10^8 PFU/mL concentration. As necessary, talimogene laherparepvec 10^8 PFU/mL will be diluted 1:10 for a concentration of 10^7 PFU/mL immediately prior to injection.

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 4.0 (Appendix A). Complete blood count with differential and chemistry panels including liver function laboratory tests (ALT, AST, and total bilirubin) should be obtained according to the Schedule of Assessments (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.

Hospitalization for $<$ 24 hours may be allowed when subjects are administered the first dose of talimogene laherparepvec. Need for hospitalization more than 1 day should be discussed between the treating physician and the Amgen medical monitor.

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.

On day 1 (week 0) 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 or 10^7 PFU/mL, should be administered 3 weeks ($+$ 5) days after the initial injection (ie, no sooner than day 22 but should not be delayed more than 5 days after the 3-week time point). Subsequent injections up to 4.0 mL of 10^8 or 10^7 PFU/mL should be given every 2 weeks ($\pm$ 3) days.

The maximum volume of talimogene laherparepvec to be administered at each treatment visit is 4.0 mL. Investigators are encouraged to administer the maximum volume possible into each injected lesion based on lesion size, not to exceed 4.0 ml in any individual lesion. Dose reduction for adverse events is not allowed. However, if during the process of administering talimogene laherparepvec in the clinic, 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 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

On each treatment day, prioritization of injections is should be as follows:

- any new injectable tumor that has appeared since the last injection
- by tumor size, beginning with the largest tumor

The lesions injected and volume will be recorded on the CRF.

A subject will be treated with talimogene laherparepvec until the subject has a DLT during the DLT evaluation period, subject has achieved a CR, no injectable lesions, clinically relevant (resulting in clinical deterioration or requiring change of therapy) disease progression beyond 24-week of treatment, per modified WHO response criteria (see Appendix D), or safety concern, **a maximum treatment duration of 48 months, or the drug is commercially available in Japan**, 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, treatment with talimogene laherparepvec should be continued for at least 24-weeks even in the presence of progression, including the appearance of new lesions to allow for delayed-immune-based anti tumor effects to occur unless other therapy for melanoma is required. After 24 weeks, subjects will remain on treatment until clinically relevant disease progression occurs as defined in Appendix D.

The dose, lesion site, start date, and lot number of talimogene laherparepvec are to be recorded on each subject's CRF.

6.2.1.2 Dose-cohort Study De-escalation and Stopping Rules

6.2.1.2.1 Rules for DLT Evaluation

The DLT evaluation period is 35 days from the first dose of talimogene laherparepvec. To be evaluable for a DLT, subjects must have received at least 1 dose of talimogene laherparepvec and had the opportunity to be followed for the entire DLT evaluation period or have experienced a DLT within the DLT evaluation period. To obtain the first 6 DLT-evaluable subjects, subjects will be replaced if they are not evaluable for DLT (eg, a subject did not receive study treatment, or ended the study treatment before completion of DLT evaluation period for a reason other than experiencing a DLT).

A DLRT composed of the investigator(s), Amgen Medical Monitor, Amgen Global Safety Officer or designated safety scientist, Amgen Clinical Research Study Manager and Amgen Biostatistics representative will review data, monitor safety, and make dose and dose de-escalation decisions. Additional members may be added to the DLRT as needed (eg, Global Development Leader) (see Section 10.3.2). The DLRT will review the safety data after 6 DLT-evaluable subjects have been enrolled at Dose 1 (see below). Enrollment will be temporarily paused during the DLT review period to evaluate the 6 DLT-evaluable subjects. The decision to continue to enroll 12 additional subjects at the Dose 1 will be based on observing $< 33\%$ subject incidence of a DLT in the initial 6 subjects during the DLT evaluation period.

If at any time there are 2 or more subjects with a DLTs prior to enrollment of the first 6 DLT-evaluable subjects, an ad hoc DLRT meeting will be convened to determine if dose de-escalation (Dose -1) is required. The safety data during the enrollment of the additional subjects will be monitored on an going basis and an ad hoc DLRT meeting may be called, if needed, to determine the further course of the study.

Dose De-escalation

If dose de-escalation is needed, then the remaining subjects will be treated at the lower dose regimen of talimogene laherparepvec (Dose -1).

Dose	Initial dose	Subsequent doses
1	10^6 PFU/mL (day 1, week 0)	10^8 PFU/mL (3 weeks later and then every 2 weeks thereafter)
-1	10^6 PFU/mL (day 1, week 0)	10^7 PFU/mL (3 weeks later and then every 2 weeks thereafter)

Dose -1 will be administered as an initial dose up to 4.0 mL of 10^6 PFU/mL (day 1, week 0) followed by dose of up to 4.0 mL of 10^7 PFU/mL 3 weeks later (+ 5 days). Subsequent doses of up to 4.0 mL of 10^7 PFU/mL will be administered every 2 weeks (± 3 days) thereafter.

The DLRT will review the safety data after the first 6 DLT-evaluable subjects at Dose -1 have been enrolled. Enrollment will be temporarily paused during the DLT review period to evaluate the 6 DLT-evaluable subjects at Dose -1. Upon demonstration of safety, additional subjects will be enrolled (up to a total of 18 subjects) at Dose -1 to obtain additional safety data.

The safety data of the subjects enrolled at the Dose-1 level will be monitored on an going basis and an ad hoc DLRT meeting may be called, if needed, to determine the further course of the study.

6.2.1.2.2 Definition of DLT

All toxicities will be graded using the CTCAE version 4.0 (see Appendix A). The occurrence of any of the following toxicities during the DLT evaluation period will be considered a DLT, if judged by the investigator to be related to the administration of talimogene laherparepvec:

- grade 4 non-hematologic toxicity
- grade 3 non-hematologic toxicity lasting > 3 days despite optimal supportive care
  - grade 3 fatigue will not be classified as DLT, irrespective of duration
- Any grade 3 or higher non-hematologic laboratory value reported as an adverse event if:
  - medical intervention is required, or
  - the abnormality leads to hospitalization, or
  - the abnormality persists for > 1 week (Laboratory values that persist for > 1 week but are deemed not clinically important per both investigator and sponsor will not be considered DLTs)
- Febrile neutropenia grade 3 or grade 4

- Thrombocytopenia $< 25 \times 10^9$/L associated with bleeding event requiring intervention
- Serious herpetic event (eg, herpetic encephalitis, encephalomyelitis, or disseminated herpetic infection)
- grade 5 toxicity (ie, death)
- Any other intolerable toxicity leading to permanent discontinuation of talimogene laherparepvec

If a subject experiences a DLT during the DLT evaluation period, study treatment will be discontinued for that subject.

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

Dose reduction for adverse events is not allowed. However, if during the process of administering talimogene laherparepvec in the clinic, 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.

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 will be permanently discontinued if a subject has a DLT during the DLT evaluation period, subject achieved a CR, no injectable lesions, clinically relevant (resulting in clinical deterioration or requiring change of therapy) disease progression beyond 24-weeks of treatment, per modified WHO response criteria (Appendix D), or safety concern (refer to Section 8.1)**, reaches a maximum treatment duration of 48 months, or the drug becomes commercially available in Japan,** whichever occurs first.

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 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 non-prescription concomitant therapies are to be collected in the CRF from informed consent through 30 (+7) days after the last dose of talimogene laherparepvec.

For concomitant therapies collect therapy name, indication, dose, unit, frequency, route, start date, and stop date.

6.5 Other Treatment Procedures

Treatment with talimogene laherparepvec may result in the reduction of tumor burden such that surgical resection of a previously unresected lesion becomes possible. Investigators may choose to resect lesions which become suitable for resection to render the subject free of macroscopic disease. 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 procedure should be recorded in the source document and CRF. In these instances, if the response of other lesions is at least PR (if other lesions remain), the response should be designated PR with the date of surgery as the date of response. If no residual disease remains following surgery, this should also be noted in the CRF, the response definition again being PR 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 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 CRF. Best overall response (BOR) determination of such subjects who received palliative radiation should be done based on tumor assessments prior to radiation treatment.

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 treatment 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, sterile needles, alcohol prep pads) that are commercially available are not usually provided or reimbursed by the Sponsor (except, for example, 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 a drug(s) or device(s) after it is released for distribution to market or

clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material.

This includes any drug(s) or device(s) provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) includes investigational product.

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

6.8 Excluded Treatments, Medical Devices, 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 drugs 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.

6.9 Contraceptive Requirements

A female is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Female in the following categories are not considered of child bearing potential:

1. Premenopausal female with 1 of the following:
    a. Documented hysterectomy

b. Documented bilateral salpingectomy

c. Documented bilateral oophorectomy

Note: Site personnel documentation from the following sources is acceptable: 1) review of subject medical records, 2) subject medical examination, or 3) subject medical history interview.

2. Premenarchal female

3. Postmenopausal female

a. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

b. Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

The naturally occurring herpes simplex virus (HSV-1) can be transmitted through sexual contact. It is not known if talimogene laherparepvec will behave the same way, thus you or your partner should use a latex condom during treatment and for up to 30 days after your last dose when engaging in sexual activity to prevent possible transmission of talimogene laherparepvec. For those with latex allergies, polyurethane condoms may be used.

6.9.1 Female Subject

Female subjects of childbearing potential must agree to use 1 acceptable method of effective contraception (as described in the table below) during treatment and for an additional 3 months after the last dose of talimogene laherparepvec.

Acceptable Methods of Effective Contraception for Female Subjects
• Combined (estrogen and progestogen) or Progestogen-only hormonal methods given orally • Intrauterine device (IUD) • Intrauterine hormonal-releasing system (IUS) • Bilateral tubal ligation • Vasectomized partner (Provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success) • Sexual abstinence (Defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject.) • Double barrier method: the male uses a condom and the female may choose either a cap, diaphragm, or sponge with spermicide. (A female condom is not an option due to the risk of tearing when both partners use a condom.)

If a female subject is suspected of being pregnant, the talimogene laherparepvec must be stopped immediately and may not be resumed until absence of pregnancy has been medically confirmed.

6.9.2 Male Subjects

If the male's sole sexual partner is of non-childbearing potential or has had a bilateral tubal ligation, he is not required to use additional forms of contraception during the study. The definition of non-childbearing potential is provided above.

Male subjects with a partner of childbearing potential must agree to not father a child during treatment and for an additional 30 days after the last dose of talimogene laherparepvec.

Contraceptive options for male subjects include:

- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with talimogene laherparepvec). The reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject. or
- Use a latex condom during treatment and for an additional 30 days after the last dose of talimogene laherparepvec. For those with latex allergies, polyurethane condoms may be used.

The female partner is to use an acceptable method of effective contraception such as: hormonal, IUD, IUS, female barrier method (diaphragm, cervical cap, contraceptive sponge [a female condom is not an option because there is a risk of tearing when both partners use a condom]). Male subjects must not donate sperm during treatment and for an additional 30 days after the last dose of talimogene laherparepvec.

Male subjects with a pregnant partner must practice sexual abstinence or wear a latex condom to prevent exposure of the unborn child to talimogene laherparepvec. For those with latex allergies, polyurethane condoms may be used.

6.9.3 Unacceptable Methods of Birth Control for Male and Female Subjects

Birth control methods that are considered unacceptable in clinical trials include: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method.

Male and female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to fetus if they become pregnant or father a child during treatment and for 3 months after the last dose of talimogene laherparepvec.

Additional medications given during the study may alter the contraceptive requirements. These additional medications may require female subjects to use highly effective methods of contraception and for an increased length of time. In addition, male subjects may also be required to use contraception. The investigator must discuss these contraceptive changes with the subject.

7. STUDY PROCEDURES

7.1 Schedule of Assessments

For Schedule of Assessments refer to Table 2 .

Table 2. Schedule of Assessments

	Screening	Treatment Period[a]									Follow-up Period	
Week		**0 (day 1)**	**3**	**5**	**7**	**9**	**11**	**13**	**15**	**15 and beyond**	**Safety follow-up**	**Long-term follow-up[e]**
GENERAL & SAFETY ASSESSMENTS												
Informed Consent	X											
Demographics	X											
Review of Medical History and Prior Cancer Therapy	X											
Review of Eligibility Criteria	X											
Recording of Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	
Review of Adverse events, Serious Adverse Events and Disease Related Events	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X	X					X[h]			Every 12 weeks[h]	X	
Vital Signs	X	X	X		X		X		X	Every 4 weeks	X	
Weight		X					X			Every 12 weeks	X	
Height		X										
12-lead ECG	X											
BRAF status, if known[b]	X											
ECOG Performance Status	X	X					X[h]			Every 12 weeks[h]	X	X[g]
Survival Assessment												X
Reporting exposure of caregiver, close contact or health care provider		X	X	X	X	X	X	X	X	X	X	
Reporting of pregnancy or lactation		X	X	X	X	X	X	X	X	X	X	X

Footnotes defined on last page of the table

Table 2. Schedule of Assessments

	Screening	Treatment Period[a]									Follow-up Period	
Week		**0 (day 1)**	**3**	**5**	**7**	**9**	**11**	**13**	**15**	**15 and beyond**	**Safety follow-up**	**Long-term follow-up[e]**
LOCAL LABORATORY ASSESSMENTS												
Urine or Serum Pregnancy Test[c]	X										X	
Hematology[d]	X	X	X	X				X		Every 8 weeks	X	
Chemistry[d]	X	X	X	X				X		Every 8 weeks	X	
Serum LDH	X											
PT (or INR) and aPTT	X											
Blood for viral hepatitis testing[f]	X											
DOSING												
Talimogene Laherparepvec		X	X	X	X	X	X	X	X	Every 2 weeks		
TUMOR ASSESSMENTS												
Clinical tumor assessment	X						X[h]			Every 12 weeks[h]	X[g]	X[g]
Radiological tumor assessment	X						X[h]			Every 12 weeks[h]	X[g]	X[g]
CENTRAL LABORATORY ASSESSMENTS												
Swab of Herpetic Lesion for qPCR		Within 3 days of occurrence of suspected lesion of herpetic origin									X	X[g]
Blood for HSV-1 Antibody Serostatus		Within 3 days prior to dose at day 1 (week 0) and then at week 5										

Footnotes defined on last page of the table

ECOG = Eastern Cooperative Oncology Group; ECG = electrocardiogram; PT = prothrombin time; INR = international normalization ratio; aPTT = activated partial thromboplastin time; qPCR = real-time polymerase chain reaction; BRAF = serine/threonine protein kinase B-Raf V600; LDH = lactate dehydrogenase; PDr = clinically relevant disease progression; WHO = World Health Organization

[a] During the treatment period assessments and procedures can be performed ± 3 days of the planned visit.

[b] BRAF $^{V600E/K}$ tumor status result, obtained from a local laboratory prior to screening for this study will be acceptable

[c] 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.

[d] Blood samples for hematology and chemistry will be collected at screening, within 3 days prior to talimogene laherparepvec administration on day 1 (week 0), week 3, week 5, week 13 and then every 8 weeks until end of treatment, and at the safety follow-up visit.

[e] For subjects that discontinue talimogene laherparepvec for reason other than disease progression or death, the following additional procedures will be conducted during the long-term follow-up: 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 until documented disease progression beyond 24-weeks of treatment, per modified WHO response criteria (Appendix D), until the start of a new anticancer therapy, or end of study, whichever the earliest. **Subjects treated for more than 24 months after the last subject is enrolled will not enter long-term follow-up (ie, their last visit will be the safety follow-up).**

[f] Baseline blood for viral hepatitis testing will be collected at screening for reactive testing as required during the course of the study. Testing is not required for enrollment into the study.

[g] If subject discontinues talimogene laherparepvec for a reason other than disease progression or death, tumor measurements are to be performed at the 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 PDr beyond 6 months of treatment (per modified WHO response criteria as described in Appendix D) or until the start of a new anticancer therapy. **Long-term follow-up is not applicable for subjects treated beyond 24 months after the last subject is enrolled.**

[h] The tumor assessment, physical exams, and ECOG performance status will be completed after 12 (± 1) weeks on treatment (ie, day 1 of week 11), and then every 12 (± 1) weeks (eg, weeks 23, 35, 47 etc.), or more frequently if clinically indicated, until PDr beyond 6 months of treatment (per modified WHO response criteria [see Appendix D]) or until the start of a new anticancer therapy.

7.2 General Study Procedures

The procedures performed and timing of each study visit are outlined in the Schedule of Assessments (Table 2). Details regarding each type of procedure are provided in subsequent sub-sections. Procedures that are part of routine care are not considered study-specific procedures and may be used at screening to determine eligibility.

Refer to the applicable supplemental central laboratory, IVR, IPIM, and study manuals for detailed collection and handling procedures.

7.2.1 Screening and Enrollment

Informed consent must be obtained before completing any screening procedure or discontinuation of standard therapy or any disallowed therapy. After signing the written informed consent form, the site will register the subject in IVR and screen the subject in order to assess eligibility for participation. Screening procedures are to be completed during the screening period within 28 days prior to enrollment. If a subject has not met all eligibility criteria at the end of the 28-day window, the subject will be registered as a screen fail. Screen fail subjects may be eligible for re-screening once as described in Section 7.2.2 Prior to enrollment, subject eligibility must be confirmed with screening procedures. Subjects satisfying eligibility requirements will be enrolled.

7.2.2 Re-screening

Subjects who are unable to complete or meet eligibility on initial screening will be permitted to re-screen once. Re-screen subjects must first be registered as screen failed in IVR and subsequently registered as re-screened. Subjects will retain the same subject identification number assigned at the original screening. Once the subject is registered as re-screened, a new 28-day screening window will begin. If the re-screening period begins more than 28-days after the original signing of the informed consent form, all screening procedures, including informed consent must be repeated. If the re-screening occurs less than 28 days after the original signing of the informed consent, then only those criteria that were originally failed are required to be repeated.

7.2.3 Treatment

Visits will occur per the Schedule of Assessments (Table 2) during the treatment period from day 1 (week 0). On-study visits may be completed within $\pm$ 3 days of the planned visit date. The date of the first dose of talimogene laherparepvec is defined as day 1 (week 0). All subsequent doses and study visits will be scheduled based on the day 1 (week 0) date. Study treatment should begin as soon as possible after enrollment via the IVR system but no later than 5 days after enrollment. Administration of talimogene

laherparepvec is to be performed after all other procedures are completed during each visit that it is required, unless otherwise stated. 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). A + 5 day dosing window is allowed at week 3. Subsequently a ± 3-day dosing and study procedure window is allowed.

7.2.4 Follow-up

7.2.4.1 Safety Follow-up

Upon permanent discontinuation from the study treatment for any reason, a safety follow-up visit will be performed 30 (+7) days after the last dose of talimogene laherparepvec. The safety follow-up visit is not required for those subjects who are enrolled, but did not receive any dose of investigational product.

7.2.4.2 Long-term Follow-up

All subjects who permanently discontinue talimogene laherparepvec for any reason other than withdrawal of full consent or death will be contacted by telephone, or clinic visit, to assess survival status and, if applicable, commencement of any subsequent anticancer melanoma therapy. Adverse events deemed by the investigator to be potentially related to talimogene laherparepvec and use of anti-cancer therapies for melanoma will also be recorded. Follow-up will occur every 12 weeks (± 28 days) following the safety follow-up visit until death, subject withdraws full consent, or up to 24 months after the last subject is enrolled in the study**. If a subject discontinues therapy more than 24 months after the last subject was enrolled in the study, when the long-term follow-up period ends, they will not enter long-term follow-up.** If **a** 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 until documented disease progression beyond 24-weeks of treatment, per modified WHO response criteria (Appendix D), until the start of a new anticancer therapy, or end of study, whichever the earliest.

7.3 Description of Study Procedures

The sections below provide a description of the individual study procedures for required timepoints.

7.3.1 Informed Consent

All subjects or legally acceptable representative must sign and personally date the IEC/IRB approved informed consent and if required the subject has provided assent before any study specific procedures are performed.

7.3.2 Demographic Data

Demographic data including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness.

7.3.3 Medical History

Complete medical and surgical history will be collected. Medical history will include information on the subject's concurrent medical conditions. The severity will be collected for each condition that has not resolved. Melanoma history must date back to the original diagnosis. Record all findings on the medical history CRF.

7.3.4 Prior Cancer Therapy

Prior therapies (eg, surgery, radiation, systemic agents such as chemotherapy, targeted agents, immunotherapies) that were being taken for current or prior malignancies. Collect therapy name, indication, dose, unit, frequency, and start and stop date.

7.3.5 Concomitant Therapy

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 (refer to Section 6.4). 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 period.

7.3.6 Adverse Events, Disease Related Events and Serious Adverse Events

Safety event reporting procedures are described in Section 9.2.

7.3.7 Physical Examination

Physical examination as per standard of care. Physical examination findings should be recorded on the appropriate CRF (eg, medical history, event).

7.3.8 Vital Signs

Vital signs (systolic/diastolic blood pressure, heart rate, respiratory rate, temperature): Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The

position selected and temperature location for a subject should be the same that is used throughout the study and documented on the vital sign CRF. Record all measurements on the vital signs CRF.

7.3.9 Physical Measurements

Body weight in kilograms should be measured without shoes. Height in centimeters should be measured without shoes.

7.3.10 ECG

A 12-lead electrocardiogram (ECG) per standard of care: The ECG must include the following measurements: heart rate, PR interval, QRS, QT and QTc intervals. Subject must be in supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The investigator or designated site physician will review all ECGs. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to the Sponsor.

7.3.11 BRAF $^{V600E/K}$ Status

BRAF $^{V600E/K}$ tumor status if available should be reported. BRAF $^{V600E/K}$ obtained from a local laboratory prior to screening for this study will be acceptable

7.3.12 ECOG

ECOG performance status will be collected as outlined in Appendix E.

7.3.13 Reporting of Exposure to Talimogene Laherparepvec

If a household member, caregiver, or healthcare provider who has had close contact with a subject treated with talimogene laherparepvec on this study 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, the exposure must be reported to Amgen. Refer to Section 9.4.

7.3.14 Tumor Assessments

7.3.14.1 Clinical Tumor Assessment

Investigators will perform clinical measurement of cutaneous, subcutaneous, or nodal tumors by caliper at screening, 12 weeks (± 1 week) on treatment (ie, day 1 of week 11), and then every 12 weeks (± 1 week), or more frequently if clinically indicated, until PDr beyond 6 months of treatment (per modified WHO response criteria as described

in 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 a reason other than disease progression or death, clinical tumor measurements are to be performed at the 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 PDr beyond 6 months of treatment (per modified WHO response criteria as described in Appendix D) or until the start of a new anticancer therapy.

7.3.14.2 Radiological Tumor Assessment

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, 12 weeks (± 1 week) on treatment (ie, day 1 of week 11), and then every 12 weeks (± 1 week), or more frequently if clinically indicated, until PDr beyond 6 months of treatment (per modified WHO response criteria [see 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 (± 1week) during the long-term follow-up period until PDr beyond 6 months of treatment (per modified WHO response criteria [see Appendix D]) or until the start of a new anticancer therapy.

7.4 Laboratory Assessments

Screening laboratory values may be used for day 1 (week 0) assessment if completed within 10 days of study treatment initiation. On-treatment tests should be performed within 3 days of the planned visit. Results (with the exception of herpetic lesion polymerase chain reaction [qPCR] and HSV-1 antibody for serostatus) should be reviewed prior to the administration of talimogene laherparepvec. All tests (except for herpetic lesion qPCR, and HSV-1 antibody) are to be performed at the local laboratory. Screening tests for hepatitis are acceptable within 6 weeks of study treatment initiation. Specific analytes for serum chemistry, coagulation, hematology, and other testing to be conducted on blood and swabs are below (Table 3).

Table 3. Laboratory Analytes

Serum Chemistry	Coagulation	Hematology	Other Labs
Sodium	PT or INR	Red blood cell	Urine or serum pregnancy test
Potassium	aPTT	Hemoglobin	Hepatitis B surface antigen[c] and Hepatitis B core antibody[c]
Chloride[d]		Hematocrit	Hepatitis C virus antibody[c]
Bicarbonate or CO2[d]		Platelets	qPCR for talimogene laherparepvec DNA[b]
Calcium		White blood cell	HSV-1 antibody[b]
Magnesium		Differential [a]	Lactate dehydrogenase
Phosphorus		• Neutrophils	
Uric acid		• Eosinophils	
Total protein		• Basophils	
Albumin		• Lymphocytes	
Blood urea nitrogen		• Monocytes	
Creatinine			
Total bilirubin			
Alkaline-phosphatase			
AST			
ALT			
Glucose			

AST = aspartate aminotransferase; ALT = alanine aminotransferase ; CO2 = carbon dioxide; PT = prothrombin time; INR = international normalization ratio; aPTT = activated partial thromboplastin time; qPCR = real-time polymerase chain reaction; HSV-1 = herpes simplex virus type-1

[a] 3-part differential (neutrophils, eosinophils, basophils) acceptable if 5-part unable to be performed

[b] Performed by Central Laboratory

[c] Baseline blood for viral hepatitis testing will be collected at screening for reactive testing as required during the course of the study. Testing is not required for enrollment into the study.

[d] If available as part of chemistry panel from venous blood draw

7.4.1 qPCR for Talimogene Laherparepvec

Swab of cold sore, vesicles and other lesions suspected to be herpetic in origin (if any) for qPCR testing of talimogene laherparepvec DNA must be collected. Subject should return to the clinic within 3 days of the occurrence of a reportable lesion suspected to be herpetic in origin. 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 by the central laboratory to evaluate whether the talimogene laherparepvec DNA is detectable in the sample.

7.5 Sample Storage and Destruction

Any blood or tumor sample 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. All samples obtained to perform central testing, such as HSV-1 serostatus and/or qPCR assays from swabs for the presence of talimogene laherparepvec will be sealed and shipped overseas to the central laboratory. All other samples collected as per Table 2 will be used to run tests in the respective clinical trial site.

If informed consent is provided by the subject or legally acceptable representative, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the cancer, the dose response and/or prediction of response to talimogene laherparepvec and 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.

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 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 protocol-required investigational product(s) or procedural assessments include any of the following:

- subject request
- safety concern (eg, due to an adverse event, ineligibility determined, protocol deviation, non-compliance, requirement for alternative therapy, pregnancy)
- other protocol specified criteria see Section 6.2.2 (ie, DLT during the DLT evaluation period [ie, 35 days), subject achieved a CR, no injectable lesions).
- death
- lost to follow-up
- decision by Sponsor (other than subject request, safety concern, lost to follow-up)
- disease progression

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 Definition of Safety Events

9.1.1 Disease Related Events

Disease Related Events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease. These could include events such as pain or discomfort caused by growing tumors due to overall worsening of disease. Such events do not meet the definition of an Adverse Event unless assessed to be more severe than expected for the subject's condition and/or if the investigator believes that the event is related to the investigational product(s)/study treatment/protocol required therapies.

Further, any disease related event which meets any of the seriousness criteria in Section 9.1.3 should be reported as a Serious Disease Related Event.

Note: For situations where disease related events are due to melanoma, the primary tumor type (eg, metastatic melanoma) should be used, rather than the term "disease progression."

9.1.2 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 or underlying disease (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration more than would be expected, and/or has an association with a significantly worse outcome than expected. A pre-existing condition that has not worsened more than anticipated (ie, more than usual fluctuation of disease) 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.

Note: For situations where adverse events are due to the subject's primary melanoma, the primary tumor type (eg, metastatic melanoma) should be used, rather than the term "disease progression."

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.

9.1.3 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

A disease related event (eg, PD or pain or discomfort caused by growing tumors) is to be reported as a serious adverse event if:

- the subject's pre-existing condition becomes worse than what the investigator would consider typical for a patient with the same underlying condition, or
- if the investigator believes a causal relationship exists between the investigational medicinal product(s)/protocol-required therapies and the event,
- meets at least 1 of the serious criteria above.

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."

9.2 Safety Event Reporting Procedures

9.2.1 Reporting Procedures for Disease Related Events

The investigator is responsible for ensuring that all Disease Related Events (serious or nonserious) observed by the investigator or reported by the subject that occur after the first dose of talimogene laherparepvec through the safety follow-up visit (ie, 30 [+7] days after the last dose of talimogene laherparepvec), are reported using the Event CRF. **Additionally, the investigator is required to report a fatal disease related event on the event CRF as a Disease Related Event.**

All serious disease related events will be recorded and reported to the sponsor or designee within 24 hours. The investigator will submit any updated serious disease related event data to the sponsor within 24 hours of it being available.

The investigator must assign the following attributes to each disease related event:

- disease related 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

CTCAE version 4.0 will be used to grade a disease related event. The grading scale used in this study is described in Appendix A.

Note: If the event is more severe than expected for the subject's condition or if the investigator believes there is a causal relationship between the investigational product(s)/study treatment/protocol required therapies and disease worsening, the event should be reported as an adverse event, not a disease related event.

The investigator is expected to follow reported disease related events (serious or non-serious) until stabilization or reversibility.

9.2.2 Adverse Events

9.2.2.1 Reporting Procedures for Adverse Events That Do Not Meet Serious Criteria

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after first dose of talimogene laherparepvec through the safety follow-up visit (ie, 30 [+7] days after the last dose of talimogene laherparepvec) are reported using the Event CRF. **Additionally, talimogene laherparepvec related adverse events that occur after the safety follow-up visit through the end of the long-term follow-up will be reported.**

The investigator must assign the following attributes to each adverse event:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- Dates of onset and resolution (if resolved),
- Severity (and/or toxicity per protocol),
- Assessment of relatedness to talimogene laherparepvec and,
- Action taken.

The adverse event grading scale used will be the CTCAE version 4.0. The grading scale used in this study is described in Appendix A. The investigator must assess whether the adverse event is possibly related to the talimogene laherparepvec. This relationship is indicated by a “yes” or “no” response to the question: Is there a reasonable possibility that the event may have been caused by the investigational product(s)?

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

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

9.2.2.2 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 90 (+ 7) days after the cessation of all study treatment, or 30 (+7) days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, are recorded in the subject's medical record and are submitted to Amgen/AABP. Additionally, talimogene laherparepvec related serious adverse events that occur after the safety follow-up visit through the end of the long-term follow-up will be reported. Any serious adverse event, or follow-up to a serious adverse event, including death due to any cause other than progression of the cancer under study (refer to Section 9.1.3 for additional details) that occurs to any subject must be reported within 24 hours to Amgen/AABP including serious adverse events that cause the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment, or a procedure.

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/AABP via an electronic Adverse Event Contingency Report Form within 24 hours of the investigator's knowledge of the event. See Appendix B for a sample of the electronic Adverse Event Contingency Report Form. The data must be entered into the EDC system when the system is again available.

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

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

All new information relating to a previously reported serious adverse event must be submitted to Amgen/AABP 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 Event CRF.

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

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

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

9.2.2.3 Reporting Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after end of study. However, these serious adverse events can be reported to Amgen/AABP. In some countries (eg, European Union [EU] member states), investigators are required to report serious adverse events that they become aware of after end of study. If serious adverse events are reported, the investigator is to report them to Amgen/AABP 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.

9.3 Pregnancy and Lactation Reporting

If a female subject becomes pregnant, or a male subject fathers a child, while the subject is taking talimogene laherparepvec report the pregnancy to Amgen/AABP Global Patient Safety as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should report pregnancies that occur after the last dose of talimogene laherparepvec through 3 months after the last dose of talimogene laherparepvec.

The pregnancy should be reported to Amgen's Global Patient Safety within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

If a female subject becomes pregnant during the study, the investigator should attempt to obtain information regarding the birth outcome and health of the infant. If a male subject's female partner becomes pregnant, the investigator should discuss obtaining information regarding the birth outcome and health of the infant from the pregnant partner.

If the outcome of the pregnancy meets a criterion for immediate classification as a Serious Adverse Event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a Serious Adverse Event.

If a female breastfeeds while taking talimogene laherparepvec report the lactation case to Amgen/AABP as specified below.

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

Any lactation case should be reported to Amgen's Global Patient Safety within 24 hours of the investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix C). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

9.4 Reporting of Exposure to Talimogene Laherparepvec

If a household member, caregiver, or healthcare provider who has had close contact with a subject treated with talimogene laherparepvec on this study 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/AABP as specified below. In addition to reporting an unintended exposure case during the study treatment, investigators should monitor for potential exposure cases that occur after the last dose of talimogene laherparepvec through 30 (+7) days after the last dose of talimogene laherparepvec.

Any potential or known unintended exposure should be reported to Amgen/AABP within 24 hours of the investigator's knowledge of the event of exposure. Amgen/AABP will seek to follow-up with the exposed individual, if necessary, to collect more information about the exposed individual contact with clinical trial subject, signs and/or symptoms related to the exposure, medical history, and/or outcome of the exposure. If the exposed

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

Report the herpes-related events on Clinical Trial Report of Suspected Talimogene Laherparepvec Associated Adverse Event for Health Care Professional (HCP) or Close Contact (Appendix F). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

10.1.1.1 Primary Endpoints

- Subject incidence of DLTs
- DRR using modified WHO response criteria by investigators

10.1.1.2 Secondary Endpoints

- ORR, TTR, DOR, and PFS using modified WHO response criteria by investigators
- OS

10.1.2 Safety Endpoint

- Subject incidence of all the following, where not defined as DLT:
- adverse events
- grade ≥ 3 adverse events
- serious adverse events
- clinically significant laboratory changes
- changes in vital signs

10.1.3 Analysis Sets

10.1.3.1 DLT Analysis Set

The DLT analysis set will include DLT-evaluable subjects as defined in Section 6.2.1.2.2.

10.1.3.2 Safety Analysis Set

The safety analysis set will include all subjects who received at least 1 dose of talimogene laherparepvec.

10.1.4 Covariates and Subgroups

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

- Age at baseline: < 50, ≥ 50; < 65, ≥ 65; < 75, ≥ 75 years
- Sex (female vs male)
- Disease stage at baseline: IIIB and IIIC vs IVM1a vs IVM1b vs IVM1c
- Line of therapy for current disease
- Type of prior therapy
- Baseline HSV-1 serostatus
- Baseline LDH ≤ ULN vs > ULN
- ECOG (0 vs 1)

10.2 Sample Size Considerations

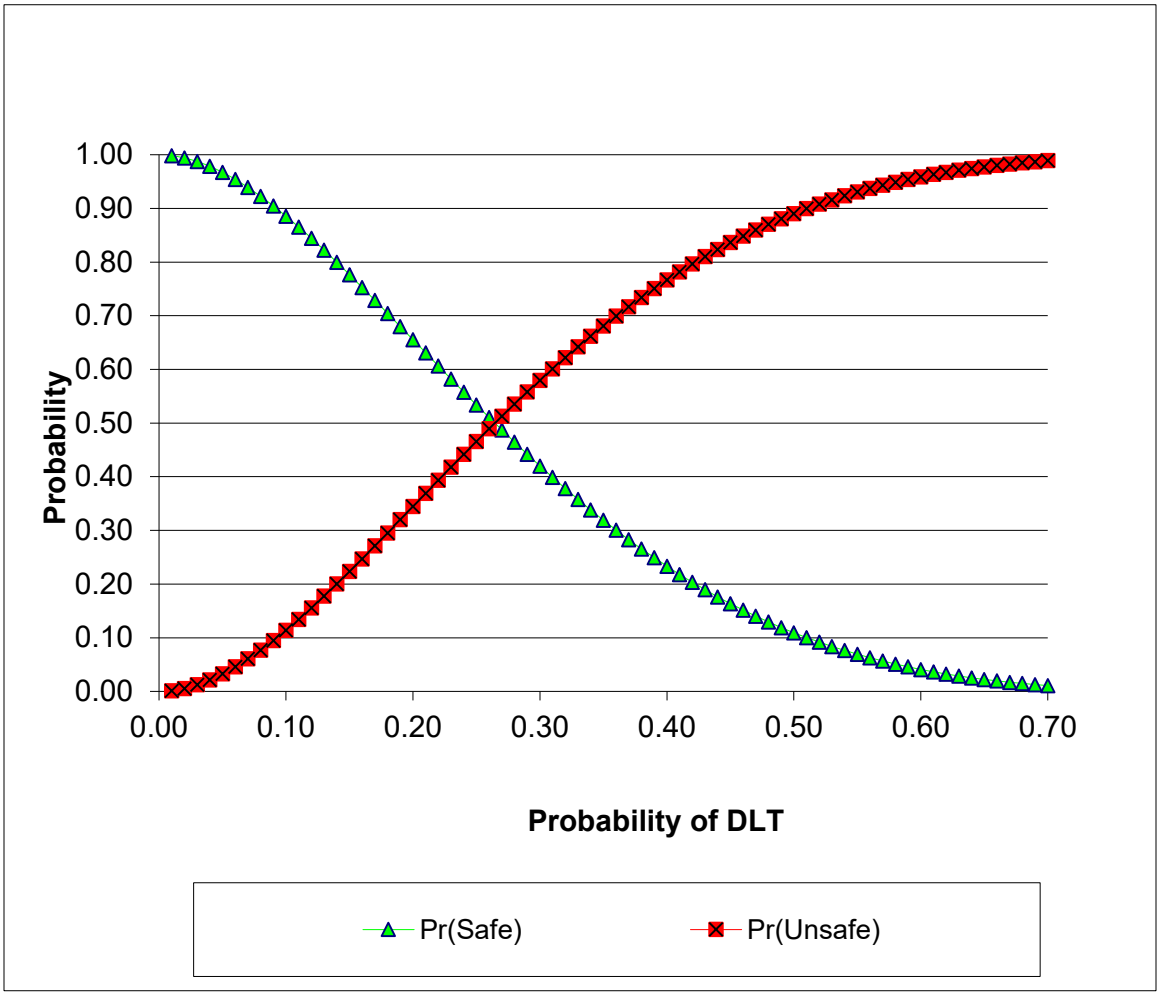
10.2.1 Sample Size Considerations

The total number of subjects that will participate in the study is approximately 18.

10.2.1.1 Sample Size Considerations for Safety Evaluation

In the current study, a dose level will be considered safe if there are 0 to 1 DLTs observed in the initial 6 DLT evaluable subjects. Table 4 and Figure 1 presents the probability of declaring a dose level safe (unsafe) for a range of true DLT rates for the protocol therapy for the 6 DLT-evaluable subjects (see triangle symbols). As shown below in Table 4, the probability of declaring a dose level safe (unsafe) in the current study (based on only 6 DLT evaluable subjects) is 89% (11%), 42% (58%), and 11% (89%) if the true DLT rate is 10%, 30%, or 50%, respectively. Hypothetically, if the study were to enroll an additional 6 DLT-evaluable subjects after the initial 6 subjects (total of 12 DLT evaluable subjects), the probability of observing a DLT rate >= 33% in the 12 subjects following the observation of 0-1 DLTs in the first 6 DLT evaluable subjects would be 0.6%, 8.6%, and 6.7% if the true DLT rate is 10%, 30%, or 50%, respectively.

Figure 1. Probability of Declaring a Cohort Safe (Unsafe)



DLT= dose-limiting toxicity; Pr = probability

Table 4. Probability of Declaring a Cohort Safe or Unsafe

True Cohort DLT Probability	Probability Declare Cohort Safe	Probability Declare Cohort Unsafe
10%	89%	11%
20%	66%	34%
30%	42%	58%
40%	23%	77%
50%	11%	89%

DLT= dose-limiting toxicity

10.2.1.2 Sample Size Considerations for Efficacy

A 1-sided 5% significance level exact binomial test will be performed to test the null hypothesis of a 2% DRR. The expectation is that this test will be based on the first 18 subjects that receive at least 1 dose of talimogene laherparepvec. The null hypothesis will be rejected if at least 2 subjects achieve a durable response

(DR). Assuming a DRR of 16.3% consistent with the global phase 3 study, this analysis will have 81% power.

10.3 Planned Analyses

10.3.1 Interim Analyses

No formal interim efficacy analysis is planned for this study. Interim safety analyses will be performed to support the evaluation of safety by the DLRT.

10.3.2 Dose Level Review Team

DLRT meetings will be held to review data, monitor safety, and make dose and dose de-escalation decisions. The review team will be composed of the investigator(s), Amgen Medical Monitor, Amgen Global Safety Officer or designated safety scientist, Amgen Clinical Research Study Manager and Amgen Biostatistics representative. Additional members may be added as needed (eg, Global Development Leader). A quorum, defined as $>$ 50% of the participating investigators or their qualified designee [ie, sub-PI or research nurse or study coordinator possessing hard copy documentation (eg, email) of the PI's vote regarding the dose level review], must be in attendance for DLRT. The DLRT will be rescheduled if a quorum is not reached. The DLRT members are responsible for dosing decisions, which may include dose de-escalation, continuation, delay, or termination of dosing. All available study data, including demographics, investigational product administration, medical history, concomitant medications, adverse events, ECGs, vital signs, laboratory results will be reviewed. In addition to DLTs, all $\geq$ grade 3 toxicities not meeting DLT criteria will be reviewed by the team and can be considered in the DLRT's decisions. Data to be reviewed will be queried.

The DLRT will review the safety data after the first 6 DLT-evaluable subjects have been enrolled. The DLRT will recommend either to declare the current dose intolerable (if 2 or more DLTs observed among the first 6 subjects), or to declare the dose safe and enroll 12 additional subjects (if 0 to1 DLTs observed among first 6 subjects).

The decision to enroll additional subjects at the same dose will be based on observing $<$ 33% subject incidence of a DLT.

If at any time there are 2 or more subjects with a DLT prior to enrollment of the first 6 DLT-evaluable subjects, an ad hoc DLRT meeting will be conveyed to determine if dose de-escalation is required.

If dose de-escalation is required, the DLRT will review the safety data after the first 6 DLT-evaluable subjects at Dose -1 have been enrolled.

The safety data of the subjects enrolled beyond the DLT evaluable period at the Dose-1 level will be monitored on an ongoing basis and an ad hoc DLRT meeting may be called, if needed, to determine further course of the study.

10.3.3 Primary Analysis

The primary analysis for safety will occur 3 months after the last subject is enrolled. The primary analysis for efficacy will occur when a durable response outcome has been assessed for all subjects included in the primary efficacy analysis. Safety will be re-analyzed at the primary efficacy analysis.

10.3.4 Final Analysis

The final analysis will occur **24 months after the last subject is enrolled. Safety and efficacy data collected after the final analysis will be summarized after the last subject completes safety follow-up.**

10.4 Planned Methods of Analysis

10.4.1 General Considerations

Descriptive statistics will be provided for demographic, safety and efficacy endpoints.

10.4.2 Primary Endpoint

The DLT analysis set will be used to summarize the subject incidence of DLTs for the study and the safety analysis set will be used for all other analyses of safety endpoints.

A 1-sided 5% significance level exact binomial test will be performed to test the null hypothesis of a 2% DRR. The expectation is that this test will be based on the first 18 subjects that receive at least 1 dose of talimogene laherparepvec. The null hypothesis will be rejected if at least 2 subjects achieve a DR. Assuming a DRR of 16.3% consistent with the global phase 3 study, this analysis will have 81% power. Exact 90% and 95% CIs will be summarized for the DRR in the analysis set.

10.4.3 Secondary Endpoint

ORR, DOR, TTR, PFS, and OS will be summarized in the overall population and by Dose level if applicable (Dose level 1 and Dose level -1). ORR will be summarized with an associated exact 95% CI. DOR among responders, TTR, PFS and OS will be estimated using the Kaplan-Meier method.

10.4.4 Safety Endpoints

Subject incidence of treatment emergent adverse events will be tabulated by system organ class and preferred term. Treatment-emergent adverse events are defined as adverse events with an onset from the first dose of study therapy up to 30 days after the last dose of study therapy. Tables of fatal adverse events, serious adverse events, all adverse events, and adverse events leading to withdrawal from investigational product, will be provided.

Subject incidence of disease- related events and fatal disease- related events will be tabulated by system organ class and preferred term.

Medical Dictionary for Regulatory Activities will be used to code adverse events to a system organ class and a preferred term within the system organ class. CTCAE version 4.0 will be used to grade severity of adverse events.

Summary statistics over time will be provided for selected key safety laboratory endpoints. Shifts in grades of these safety laboratory endpoints between the baseline and the worst on-study value will be tabulated by dose level group.

The ECG measurements from this clinical study will be performed as per standard of care for routine safety monitoring, rather than for purposes of assessment of potential QTc effect. Since these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data. Summaries and statistical analyses of ECG measurements are not planned, and these data would not be expected to be useful for meta-analysis with data from other trials.

Subject incidence of suspected herpetic lesions along with data from qPCR analysis performed to detect talimogene laherparepvec DNA will be reported.

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.

Summary statistics will also be provided for concomitant medications, dose delay, study drug discontinuation, overall exposure, and ECOG performance status.

Summary statistics will be provided for vital signs and other physical measurements. Details of the analysis will be provided in statistical analysis plan.

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 or legally acceptable representative 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. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study.

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 or a legally acceptable representative 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 or a legally acceptable representative.

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 Independent Ethics Committee/Institutional Review Board

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

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

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

11.3 Subject Confidentiality

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

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

In compliance with Federal regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the

regulatory agency(s), and the IEC/IRB direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

11.4 Investigator Signatory Obligations

Each 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 IEC/IRB must be informed of all amendments and give approval. The investigator must send a copy of the approval letter from the IEC/IRB to Amgen.

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

Subjects may be eligible for continued treatment with Amgen investigational product(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 CRFs will be included on the Amgen Delegation of Authority Form.

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

In this study, the IVR system captures the following data point and this is considered source data: subject identification number.

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

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

Elements to include:

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

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

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

12.3 Study Monitoring and Data Collection

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

The Amgen Clinical Monitor is responsible for verifying the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical

research. The Clinical Monitor is to have access to subject medical records and other study-related records needed to verify the entries on the CRFs.

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

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

Data capture for this study is planned to be electronic:

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

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

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible 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. CRFs must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language.

12.6 Publication Policy

To coordinate dissemination of data from this study, Amgen may facilitate 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 Recommendations for the Conduct of Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states Authorship credit is to be based on: (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, 3 and 4.

When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should

fully meet the criteria for authorship defined above. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship. All persons designated as authors should qualify for authorship, and all those who qualify should be listed. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

12.7 Compensation

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

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14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

The Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 is available at the following location:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Appendix B. Sample Electronic Adverse Event Contingency Report Form

AMGEN Study # 20140270 Talimogene Laherparepvec	**Electronic Adverse Event Contingency Report Form** For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

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

Protocol specific reason(s):

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

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

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

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

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

3. ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day ____ Month ____ Year ____

Adverse Event diagnosis or syndrome 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 IP/drug under study	Is event serious?	If serious, enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the Event may have been caused by IP/drug under study or an Amgen device used to administer the IP/drug under study? <Choice> No ✓ / Yes ✓	Outcome of Event 1-Resolved 2-Not resolved 3-Fatal 4-Unknown	Check only if event is related to study procedure eg, biopsy
				☐Yes ☐No				
				☐Yes ☐No				
				☐Yes ☐No				

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

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

Date Admitted Day Month Year	Date Discharged Day Month Year

AMGEN Study # 20140270 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? ☐No ☐Yes If yes, please complete all of Section 5

IP/Drug/Amgen Device:		Date of Initial Dose 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	Lot # and Serial #
Talimogene Laherparepvec	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<<IP/Drug/Device>>	☐blinded ☐open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

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

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

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

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

Date Day Month Year	Test											
	Unit											

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

Date Day Month Year	Additional Tests	Results	Units

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AMGEN Study # 20140270 Talimogene Laherparepvec	**Electronic Adverse Event Contingency Report Form** For Restricted Use

	Site Number	Subject ID Number	

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

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

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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: 20140270

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
Talimogene Laherparepvec				mm_____/dd_____/yyyy_____

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

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

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

5. Pregnancy Information

Pregnant female's LMP mm / dd / yyyy_____ ☐ Unknown

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

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

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

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

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

****

Effective Date: March 27, 2011 Page 1 of 1

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: 20140270

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
Talimogene Laherparepvec				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:** _____

****

Effective Date: 03 April 2012, version 2.

Page 1 of 1

Appendix D. Modified World Health Organization 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 the longest diameter as assessed using calipers (eg, superficial cutaneous melanoma lesion). (Note: When a lesion can be evaluated by both, clinical examination and imaging, radiographic imaging evaluations should be undertaken since it is more objective).

Computed Tomography or Magnetic Resonance Imaging

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

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

Positron Emission Tomography /CT Scans

If a combined positron emission tomorgraphy (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 serially measured in 2 dimensions and for which the longest diameter is:

- ≥ 10 mm as measured by CT scan, MRI, or ultrasound for nodal/soft tissue disease (excluding lymph nodes)
  - To be classified as malignant and measurable, a lymph node must be ≥ 15 mm in shortest diameter
- ≥ 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 longest total diameter of ≥ 10 mm
  - To be aggregated these lesions must be touching or abutting 1 another
  - An aggregated lesion should be recorded and followed according to its total (aggregated) measurement (ie, by the longest diameter and the longest perpendicular diameter of the aggregate)

Nonmeasurable Lesions

All other lesions, including small lesions (longest diameter < 10 mm by CT/MRI/ultrasound for nodal/soft tissue disease 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. If a subject has more than 20 non-measurable lesions at baseline, only 20 are required to be recorded. (The investigator may choose to record more, but will subsequently need to follow all lesions recorded at baseline).

Lymph Node Assesment Criteria

If the short axis size is ≥ 15 mm, the lymph node can be designated as a malignant lymph node and thus be classified as a measurable lesion.

If it is between ≥ 10 mm and < 15 mm in short axis, the lymph node can be classified as pathological but not measureable. As such it shall be designated as a non-measurable lesion.

When a lymph node shrinks below 10 mm in short axis, the measurement is to be entered as 0 X 0 mm into the eCRF. This will allow the lesion to be documented as no longer malignant.

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 lesions (merging or fused)

When 2 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.

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.

When 2 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.

Splitting lesions

When an index or new measurable lesion splits into 2 or more lesions the largest measurable part of the split lesion should be considered to be the previously recorded index 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).

Biopsy of Residual Lesions

- Biopsy and histological examination will be used to confirm or define responses (eg, after treatment to differentiate between residual benign lesions/pigmented areas and residual malignant lesions). A needle biopsy is acceptable.
- Biopsies are mandatory (as far as is clinically feasible) under the following circumstances:
  - If CR is suspected but residual pigmented areas or other residual masses suspected to no longer contain tumor remain – representative biopsies MUST be taken from these

  - If PR is suspected but residual pigmented areas or other residual masses suspected to no longer contain tumor remain which must be tumor free for the patient to meet the criteria for PR – representative biopsies MUST be taken from these
  - If no injectable sites remain other than residual pigmented areas or other residual masses suspected to no longer contain tumor – representative biopsies MUST be taken from these
- Where biopsy has confirmed no tumor to be present, a measure of 0 x 0 mm should be entered for that tumor and all tumors of which the biopsied tumor is representative and these will be used for assessing the patient's overall response status at each assessment

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

The procedure itself and all post-procedure lesion assessments should always be recorded in the CRF. A completely resected lesion should be assigned a default code of 0 mm (for target lesions) or "absent" (for non-target lesions). If the resected lesion contained cancer or pathology results were unknown, the recorded tumor assessments post-procedure may be used for tumor burden calculations, but determination of response will be considered unevaluable (UE) for response except in the case of PD.

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 longest diameter and the perpendicular diameter (SPD) of all index lesions will be calculated as the baseline total tumor burden.

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. 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.
Disease Progression (PD):	A > 25% increase in the sum of the products of the perpendicular diameters of all index tumors since baseline, or the unequivocal appearance of a new tumor since the last response assessment time point. There are 2 types of PD defined in this protocol: Non-clinically relevant disease progression (PDn): PD in subjects who do not suffer a decline in performance status and/or in the opinion of the investigator do not require alternative therapy. Subjects showing overall response as PDn will be allowed to continue study treatment. Clinically relevant disease progression (PDr): PD that is associated with a decline in performance status and/or in the opinion of the investigator the subject requires alternative therapy. Subjects with PDr will be allowed to remain on study until 24 weeks of therapy unless, in the opinion of the investigator, other treatment is warranted.
Stable Disease (SD):	Neither sufficient tumor shrinkage of index lesion to qualify for response (PR or CR) nor sufficient tumor increase of index lesion to qualify for PD.
Unable to Evaluate (UE):	Any index lesion present at baseline which was not assessed, was unable to be evaluated leading to an inability to determine the status of that particular tumor for that time point, or was resected but on pathological review still contained melanoma.
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 1 or more nonindex tumor(s).
Disease Progression (PD):	Unequivocal progression of 1 or more nonindex lesions There are 2 types of PD defined in this protocol: Non-clinically relevant disease progression (PDn): PD in subjects who do not suffer a decline in performance status and/or in the opinion of the investigator do not require alternative therapy. Subjects showing PDn as overall response will be allowed to continue study treatment. Clinically relevant disease progression (PDr): PD that is associated with a decline in performance status and/or in the opinion of the investigator the subject requires alternative therapy. Subjects with PDr will be allowed to remain on study until 24 weeks of therapy unless, in the opinion of the investigator, other treatment is warranted.
Unable to Evaluate (UE):	Any nonindex lesion present at baseline which was not assessed, was unable to be evaluated leading to an inability to determine the status of that particular tumor for that time point, or was resected but on pathological review still contained melanoma.
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 (ECOG) Performance Status

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to a bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Appendix F. Clinical Trial Report of Suspected Talimogene Laherparepvec Associated Adverse Event for HCP or Close Contact

AMGEN Study # 20140270	Clinical Trial Report of Suspected Talimogene Laherparepvec Associated Adverse Event for HCP or Close Contact *Notify Amgen Within 24 hours of awareness*	☐New ☐Follow-up

SELECT OR TYPE IN A FAX#

SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

INFORMATION FOR THE PERSON EXPERIENCING EVENT

Event ID	Associated Subject ID	Age at Time of Event	Gender	If female, is she currently pregnant?
___ - ___	___ ___ ___	____ years	☐ Male ☐ Female	☐ Declined to provide ☐ No ☐ Yes (date of LMP) __ __ / __ __ / __ __ __ __ (dd/mm/yyyy)

Indicate the relationship of the person experiencing the event with the associated (treated) subject:

☐ Health care professional	☐ Close contact who is: ☐ Residing with treated subject ☐ Providing medical assistance/care to subject ☐ Regularly in close contact with treated subject

1. Talimogene laherparepvec administration to the treated subject (if known)

a. Date of first dose administration
☐ __ __ / __ __ / __ __ __ __ (dd/mm/yyyy)

b. Date of last dose administration
☐ __ __ / __ __ / __ __ __ __ (dd/mm/yyyy)
☐ Not applicable (e.g. exposure occurred during administration preparation)
Product Lot Number: _____ or Unknown (✔):_____

2. History of person experiencing event

a. Previous history of herpetic infections:
☐ No
☐ Yes: Date of last episode __ __ / __ __ / __ __ __ __ (dd/mm/yyyy)

b. If the answer to a. above is YES, please complete:

Signs / Symptoms of herpetic infections prior to known or suspected exposure to talimogene laherparepvec	Present	How many times per year?
☐ Oral herpes (cold sores/fever blisters) ☐ Genital herpes (blister lesions in genital area)		
Other suspected symptoms (describe): _____		

c. Has the person ever been treated with antivirals, eg, acyclovir, for herpetic infection?
☐ No ☐ Not sure ☐ Yes (Date): __ __ / __ __ / __ __ __ __ (dd/mm/yyyy)
Method of treatment administration: ☐ Topical ☐ Oral ☐ Intravenous

d. Was the person taking any medications (other than antivirals addressed in 2c above) at the time of the event?
☐ No ☐ Not sure ☐ Yes (Provide details below)

Medication	Indication	Start Date (dd/mm/yyyy)	Dose/Frequency	Continuing? If no, stop date (dd/mm/yyyy)
		___/___/_____		☐ Yes ☐ No ___/___/_____
		___/___/_____		☐ Yes ☐ No ___/___/_____

AMGEN Study # 20140270	**Clinical Trial Report of Suspected Talimogene Laherparepvec Associated Adverse Event for HCP or Close Contact** *Notify Amgen Within 24 hours of awareness*	☐New ☐Follow-up

3. Details of each known or suspected exposure prior to this event:

Exposure Information	Check all boxes that apply to known exposure(s)	
	Physical Direct Contact with Treated Patient	**Caregiver**
Date and Exposure ID ____/____/________ dd mm yyyy Exposure ID: ☐ Date and Exposure ID not known	☐ Sleep together ☐ Intimate physical contact (kissing, sexual intercourse) ☐ Touched lesion facing side of dressing ☐ Touched injected lesion directly ☐ Other (describe below):	☐ Touched lesion facing side of dressing ☐ Touched injected lesion directly ☐ Needle stick ☐ Splash back /Direct contact with talimogene laherparepvec to unprotected skin/mucosa ☐ Other (describe below):
Date and Exposure ID ____/____/________ dd mm yyyy Exposure ID: - ☐ Date and Exposure ID not known	☐ Sleep together ☐ Intimate physical contact (kissing, sexual intercourse) ☐ Touched lesion facing side of dressing ☐ Touched injected lesion directly ☐ Other (describe below):	☐ Touched lesion facing side of dressing ☐ Touched injected lesion directly ☐ Needle stick ☐ Splash back /Direct contact with talimogene laherparepvec to unprotected skin/mucosa ☐ Other (describe below):
Date and Exposure ID ____/____/________ dd mm yyyy Exposure ID: - ☐ Date and Exposure ID not known	☐ Sleep together ☐ Intimate physical contact (kissing, sexual intercourse) ☐ Touched lesion facing side of dressing ☐ Touched injected lesion directly ☐ Other (describe below):	☐ Touched lesion facing side of dressing ☐ Touched injected lesion directly ☐ Needle stick ☐ Splash back /Direct contact with talimogene laherparepvec to unprotected skin/mucosa ☐ Other (describe below):

4. Evaluations, Diagnosis & Laboratory Measures

Diagnostic	Results/Units	Reference Range/Units	Date (dd/mm/yyyy)	
Live virus assay			___/___/_______	
Quantitative Polymerase Chain Reaction (PCR)			___/___/_______	
Serologic test (antibody test)			___/___/_______	
Other (specify):			___/___/_______	
Other (specify):			___/___/_______	

Talimogene laherparepvec PCR swab done? ☐ **Yes:** **If yes**, provide date(s) lesion(s) was/were swabbed:_____________

____

☐ **No:** **If no**, indicate reason swab was not done ☐ Declined to consent ☐ Other (please specify):__________________

____

AMGEN Study # 20140270	Clinical Trial Report of Suspected Talimogene Laherparepvec Associated Adverse Event for HCP or Close Contact *Notify Amgen Within 24 hours of awareness*	☐New ☐Follow-up

5. Adverse Event Information:

a. Complete each row below for person experiencing herpetic signs and symptoms since the associated subject began treatment with talimogene laherparepvec. *Populate each row of the following table:*

Signs or Symptoms	Present?	Location on body	If Serious, enter Serious Criteria code *(see codes below)*	Relationship to talimogene laherparepvec	Date started (dd/mm/yyyy)	Date ended (dd/mm/yyyy)
Oral herpes (cold sores/fever blister, eg, on face, mouth, lip or nose single or multiple red papular or ulcerated lesions at muco-cutaneous junction, around mouth or on face, with pain, tingling or itching)	☐Yes ☐No			☐Yes ☐No ☐Unknown	___/___/_____	___/___/_____
Herpetic whitlow (painful, itchy blister lesion on fingertips of hand)	☐Yes ☐No			☐Yes ☐No ☐Unknown	___/___/_____	___/___/_____
Genital herpes (blister lesions in genital area)	☐Yes ☐No			☐Yes ☐No ☐Unknown	___/___/_____	___/___/_____
Herpes keratitis - eye signs and/or symptoms (redness, pain, photophobia (intolerance to light), blurred vision, tearing)	☐Yes ☐No			☐Yes ☐No ☐Unknown	___/___/_____	___/___/_____
Herpes simplex encephalitis - neurological signs and/or symptoms (eg, fever associated with headache, vomiting, lethargy, psychiatric symptoms, seizures, weakness, confusion, or memory loss)	☐Yes ☐No			☐Yes ☐No ☐Unknown	___/___/_____	___/___/_____
Skin lesion/rash	☐Yes ☐No			☐Yes ☐No ☐Unknown	___/___/_____	___/___/_____
Other signs/symptoms: (DESCRIBE)	☐Yes ☐No			☐Yes ☐No ☐Unknown	___/___/_____	___/___/_____

Serious Criteria:	01 Fatal 02 Immediately life-threatening 03 Required hospitalization 04 Prolonged hospitalization 05 Persistent or significant disability /incapacity 06 Congenital anomaly / birth defect 07 Other significant medical hazard

b. Provide if available, final diagnosis or syndrome:

_____

_____

AMGEN Study # 20140270	Clinical Trial Report of Suspected Talimogene Laherparepvec Associated Adverse Event for HCP or Close Contact *Notify Amgen Within 24 hours of awareness*	☐New ☐Follow-up

6. Action Taken:

a. Did either of the following occur since the associated subject began treatment with talimogene laherparepvec?

☐ Hospitalization ☐ No ☐ Yes: Date of hospitalization __ __ / __ __ / __ __ __ __ (dd/mm/yyyy)

☐ Consultation with other healthcare provider(s) ☐ No ☐ Yes: Date of consult(s)

Provide available hospitalization and consult reports with this document. Conceal personal identifiers and write the assigned Event ID number on reports.

__ __ / __ __ / __ __ __ __ (dd/mm/yyyy)

__ __ / __ __ / __ __ __ __ (dd/mm/yyyy)

b. Did the exposed/potentially exposed person receive treatment with antivirals, eg, acyclovir, for herpetic infection?

☐ No ☐ Not sure ☐ Yes (Date): __ __ / __ __ / __ __ __ __ (dd/mm/yyyy)

Method of treatment administration: ☐ Topical ☐ Oral ☐ Intravenous

c. Did the person receive any other treatment?

☐ No ☐ Not sure ☐ Yes (Provide details below)

Medication	Indication	Start Date (dd/mm/yyyy)	Dose/Frequency	Continuing? If no, stop date (dd/mm/yyyy)
		___/___/_____		☐ Yes ☐ No ___/___/_____
		___/___/_____		☐ Yes ☐ No ___/___/_____

d. Chronological summary of symptoms (narrative of events):

_____

_____

_____

_____

_____

Signature of Investigator or Designee	Title	Date of report

Amendment #5

Protocol Title: A phase 1, Multi-center, Open-label, Dose De-escalation Study to Evaluate the Safety and Efficacy of Talimogene Laherparepvec in Japanese Subjects With Unresectable Stage IIIB-IV Malignant Melanoma

Amgen Protocol Number Talimogene Laherparepvec 20140270

Amendment Date: 01 September 2020

Rationale:

This protocol is amended with the following:

- Administrative and editorial updates
- Subjects that are being treated beyond 24 months after the last subject enrolled will not enter long term follow up and their last visit will be safety follow up.
- A maximum treatment duration of 48 months, or the drug is commercially available in Japan.
- Removal of “Subjects that have discontinued investigational product and/or protocol-required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on the study to undergo safety surveillance and/or collection of outcome data.”
- Addition of the following safety reporting requirements
    - The investigator is required to report a fatal disease related event on the event case report form as a Disease-Related Event. All serious disease-related events will be recorded and reported to the sponsor or designee within 24 hours.
    - The investigator will submit any updated serious disease related event data to the sponsor within 24 hours of it being available.
    - Talimogene laherparepvec related adverse events that occur after the safety follow-up visit through the end of the long-term follow-up will be reported.

Amendment 4

Protocol Title: A Phase 1, Multi-center, Open-label, Dose De-escalation Study to Evaluate the Safety and Efficacy of Talimogene Laherparepvec in Japanese Subjects With Unresectable Stage IIIB-IV Malignant Melanoma

Amgen Protocol Number (Talimogene Laherparepvec 20140270)

NCT number: NCT03064763

Amendment 4 Date: 05 December 2017

Rationale:

This protocol was amended to:

- Update Appendix D – Modified World Health Organization Response Criteria for further clarification
- Update Inclusion criteria #107 and #108 for further clarification
- Update the Schedule of Assessments to:
  - Add physical exams at Day 1 and every 12 weeks after the Week 15 visit
  - Add Eastern Cooperative Oncology Group (ECOG) Performance Status at Day 1 and every12 weeks after the Week 15 visit
- Update laboratory assessments section to :
  - Clarify which results needed prior to the administration of talimogene laherparepvec
  - Which laboratory will be used for certain assessments (local or central)
  - Clarify that Bicarbonate or Carbon Dioxide can be done if available as part of chemistry panel from venous blood draw
- Update the following sections to align with current protocol template language;
  - Section 3.5.2 - End of Study
  - Section 12.6 - Publication Policy
- Updated the following to align with other protocols within the talimogene laherparepvec program
  - Section 9 – Safety Data Collection, Recording, and Reporting: Updated language for disease-related events
  - Section 6.2.2 – Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation: Added clarification for talimogene laherparepvec if dosing is delayed by more than 4 weeks to align with other protocols within the talimogene laherparepvec program
- Clarify Safety Follow-up information for subjects who do not receive treatment
- Update Key Sponsor Contact

Amendment 3

Protocol Title: A Phase 1, Multi-center, Open-label, Dose De-escalation Study to Evaluate the Safety and Efficacy of Talimogene Laherparepvec in Japanese Subjects with Unresectable Stage IIIB-IV Malignant Melanoma

Amgen Protocol Number 20140270

Amendment 3 Date: 08 September 2016

Rationale:

This protocol is being amended to:

- To meet the requests of the PMDA:
  - Additional information was provided to note that the investigational product contains attenuated infectious herpes simplex virus-1.
  - Inclusion criteria #106 was updated to add subjects who are determined by the physician to be not suitable or eligible for the approved systemic anticancer drug therapy in Japan.
  - Exclusion criteria #214 was updated to specifically note sensitivity to bovine- or porcine-derived components.
  - Exclusion criteria #218 was updated to clarify that subjects who suspend breast-feeding after starting treatment with talimogene laherparepvec should not intend to resume.
  - A new section (Section 6.9) was added to describe in detail the contraceptive requirements for male and female subjects. As a result, exclusion criteria #219 was updated accordingly.
  - Details regarding samples shipped overseas to the central laboratory were added.
- Correct the Schedule of Assessments to add assessments during the Long-term follow-up, and add additional rows to detail the investigational product (IP) dosing.

Amendment 2

Protocol Title: A Phase 1, Multi-center, Open-label, Dose De-escalation Study to Evaluate the Safety and Efficacy of Talimogene Laherparepvec in Japanese Subjects With Unresectable Stage IIIB-IV Malignant Melanoma

Amgen Protocol Number 20140270

EudraCT number *N/A*

Amendment 2 Date: 08 August 2016

Rationale:

This protocol is being amended to:

- Add information on reporting herpes-related events
  - This includes adding Appendix F- Clinical Trial Report of Suspected Talimogene Laherparepvec Associated Adverse Event for HCP or Close Contact
- Correct the reference date of Tafinlar™

Amendment 1

Protocol Title: A Phase 1, Multi-center, Open-label, Dose De-escalation Study to Evaluate the Safety and Efficacy of Talimogene Laherparepvec in Japanese Subjects with Unresectable Stage IIIB-IV Malignant Melanoma

Amgen Protocol Number 20140270

EudraCT number *N/A*

Amendment Date: 19 July 2016

Rationale:

This protocol is being amended to:

- Remove the assessment of DRR from the secondary objective as it is now a primary objective
- Update the hypotheses to clarify that no formal hypothesis will be tested for safety endpoints, and added that a DRR is hypothesized to be consistent with results from the global phase 3 study
    - The hypothesis testing for DRR will be conducted on the first 18 treated subjects at dose level 1 if no dose de-escalation is required
- Update the Statistical Considerations, which included:
    - The primary efficacy analysis will occur when a durable response outcome has been assessed for all subjects
    - The analysis set was defined for dose de-escalation and no dose de-escalation
- Clarify that subjects may be included in the evaluation for both safety and efficacy
- Update the primary completion definition
- Update Table 2. Schedule of Assessments, Tumor Assessments, to match the text
- Update the women not of childbearing definition to match other TVEC protocols
- Definition of DLT (dose limiting toxicity) was updated to match 20140318 study
- Section 9.3-Pregnancy and Lactation Reporting was updated to reflect new protocol template language
- Update Key Sponsor Contact