Title: A Phase 2, Multicenter, Randomized, Open-label Trial Assessing the Efficacy and Safety of Talimogene Laherparepvec Neoadjuvant Treatment Plus Surgery Versus Surgery Alone for Resectable, Stage IIIB to IVM1a Melanoma

Amgen Protocol Number (Talimogene Laherparepvec) 20110266

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Amendment 2 Date: 31 March 2016

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Amendment 3 Date: 23 March 2018

Confidentiality Notice

Investigator's Agreement

I have read the attached protocol entitled A Phase 2, Multicenter, Randomized, Open-label Trial Assessing the Efficacy and Safety of Talimogene Laherparepvec Neoadjuvant Treatment Plus Surgery Versus Surgery Alone for Resectable, Stage IIIB to IVM1a Melanoma, dated **23 March 2018**, and agree to abide by all provisions set forth therein.

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

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

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

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

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

Signature	
Name of Investigator	Date (DD Month YYYY)

Protocol Synopsis

Title: A Phase 2, Multicenter, Randomized, Open-label Trial Assessing the Efficacy and Safety of Talimogene Laherparepvec Neoadjuvant Treatment Plus Surgery Versus Surgery Alone for Resectable, Stage IIIB to IVM1a Melanoma

Study Phase: 2

Indication: Neoadjuvant treatment of talimogene laherparepvec for resectable, stage IIIB to IVM1a melanoma.

Primary Objective: To estimate the treatment effect of neoadjuvant talimogene laherparepvec plus surgery compared to surgery alone on recurrence-free survival (RFS).

Secondary Objectives: The secondary objectives are:

- To estimate the effect of neoadjuvant talimogene laherparepvec plus surgery compared to surgery alone on **1-year,** 2-year, 3-year, and 5-year RFS
- To estimate the effect of neoadjuvant talimogene laherparepvec plus surgery compared to surgery alone on rate of histopathological tumor-free margin (R0) surgical resection
- To estimate the effect of neoadjuvant talimogene laherparepvec on rate of pathological complete response (pCR)
- To estimate the effect of neoadjuvant talimogene laherparepvec plus surgery compared to surgery alone on local recurrence-free survival (LRFS), regional recurrence-free survival (RRFS), and distant metastases-free survival (DMFS)
- To estimate the effect of neoadjuvant talimogene laherparepvec plus surgery compared to surgery alone on **1-year,** 2-year, 3-year, 5-year, and overall survival (OS)
- To estimate response to neoadjuvant talimogene laherparepvec overall and separately in injected and uninjected lesions during treatment (Arm 1 only)
- To evaluate the safety of neoadjuvant talimogene laherparepvec plus surgery compared to surgery alone

Hypotheses: Formal hypotheses will not be tested in this trial. The study will provide an estimate of the treatment effect, as measured by the difference in RFS of talimogene laherparepvec neoadjuvant therapy followed by surgery compared to surgery alone in subjects with resectable, stage IIIB to IVM1a melanoma.

Primary Endpoint: RFS.

Secondary Endpoints: The secondary endpoints are:

- **1-year,** 2-year, 3-year, and 5-year RFS
- Rate of histopathology tumor-free margin (R0) surgical resection
- Rate of pCR
- LRFS
- RRFS
- DMFS
- **1-year,** 2-year, 3-year**,** and 5-year, and overall survival
- Overall tumor response and tumor response in injected and uninjected lesions (Arm 1 only)
- Subject incidence of treatment-emergent and treatment-related adverse events

Study Design: This is a phase 2, multicenter, randomized, open-label study to estimate the efficacy of talimogene laherparepvec as a neoadjuvant treatment followed by surgery compared to surgery alone in subjects with completely resectable stage IIIB, IIIC, or IVM1a melanoma. Approximately 150 subjects will be randomized 1:1 to receive the following:

- **Arm 1:** Talimogene laherparepvec for 6 doses followed by surgical resection of melanoma tumor lesion(s).
  - **Talimogene Laherparepvec:**

    Talimogene laherparepvec will be administered by intralesional injection into the injectable cutaneous, subcutaneous, and nodal tumors initially at a dose of 10^6 plaque forming units (PFU)/mL at day 1 of week 1 followed by a dose of 10^8 PFU/mL at day 1 (±3 days) of week 4, 6, 8, 10 and 12 or until all injectable tumors have disappeared, or intolerance of study treatment, whichever occurs first. Due to the mechanism of action of talimogene laherparepvec, subjects may experience transient growth in existing tumors or the appearance of new tumors prior to maximal clinical benefit of talimogene laherparepvec. Subjects who experience growth in existing tumors or the appearance of new tumors will be allowed to remain on talimogene laherparepvec treatment until week 12 of therapy unless, in the opinion of the investigator, immediate surgical resection or any other treatment for melanoma is warranted. If talimogene laherparepvec treatment will end prior to week 12, the investigator or designee should notify the sponsor's medical monitor as soon as possible.
  - **Surgical Resection of Melanoma Tumor Lesions(s):**

    For subjects who complete 12 weeks of talimogene laherparepvec treatment, surgical resection of melanoma lesion(s) will be performed at any time during weeks 13 to 18. Refer to Appendix F for surgery guidelines. Subjects who stop talimogene laherparepvec prior to week 12 due to disappearance of all injectable tumor lesions, intolerance to talimogene laherparepvec, or any other reason will undergo surgical resection of melanoma lesion(s) or tissues where melanoma was present before achieving complete response (CR) within 1 to 6 weeks after the last dose of talimogene laherparepvec. If surgery will be performed prior to week 12, the investigator or designee should notify the sponsor's medical monitor as soon as possible.

- **Arm 2:** Immediate surgical resection of melanoma tumor lesion(s)
  - Surgical resection of melanoma tumor lesion(s) will be performed after randomization any time during weeks 1 to 6. Refer to Appendix F for surgery guidelines.

Randomization will be stratified by disease stage (IIIB nodal versus IIIB in-transit versus IIIC nodal versus IIIC in-transit with nodal versus IVM1a), planned adjuvant therapy (adjuvant systemic therapy [eg, interferon alpha (INFα), ipilimumab] with or without radiotherapy versus radiotherapy without adjuvant systemic therapy versus none).

Following surgery, adjuvant systemic therapy and/or radiotherapy may be administered at the investigator's discretion and per the institutional standard of care.

Subjects will be followed for safety approximately 30 (+15) days after surgery and for disease recurrence (local, regional, or distant), subsequent anticancer therapy for melanoma, adverse events thought to be potentially related to talimogene laherparepvec (Arm 1 only), and survival every 3 months (±30 days) for first 3 years after the end of the safety follow-up period and then every 6 months (±30 days) until death, subject withdraws full consent, or up to 5 years after the last subject is randomized. Thereafter, subjects randomized to Arm 1 who received at least a single dose of talimogene laherparepvec will be followed under an ongoing separate registry protocol (Study 20120139) for the long-term survival follow-up of subjects treated with talimogene laherparepvec. The registry protocol will also monitor for late and long-term adverse events thought to be potentially related to talimogene laherparepvec and use of subsequent anticancer therapy for melanoma. Subjects who after the long-term follow-up period of this study

(Study 20110266) will elect to participate in the registry study must sign new informed consent form before any registry protocol-specific activities.

Sample Size: 150 subjects.

Summary of Subject Eligibility Criteria:

Key Inclusion Criteria:

Male or female ≥ 18 years of age with histologically confirmed diagnosis of stage IIIB, IIIC or IVM1a melanoma eligible for complete surgical resection. Prior systemic, regional and radiation anticancer therapies for melanoma must have been completed at least 3 months prior to randomization. Subject must have measurable disease and must be a candidate for intralesional therapy with at least one injectable cutaneous, subcutaneous, or nodal melanoma lesion (≥ 10 mm in longest diameter) or with multiple injectable lesions that in aggregate have a longest diameter of ≥ 10 mm. Also, subject must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and must have a serum lactate dehydrogenase (LDH) ≤ 1.5 x upper limit of normal (ULN) for stages IIIB/C melanoma and LDH ≤1.0 x ULN for stage IVM1a melanoma and adequate hematologic, hepatic, renal, and coagulation organ functions.

Key Exclusion Criteria:

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

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

Investigational Product

Talimogene Laherparepvec Dosage and Administration (Arm 1 only):

Talimogene laherparepvec will be administered to subjects randomized to Arm 1 by intralesional injection into injectable cutaneous, subcutaneous, and nodal lesions with or without image ultrasound guidance. Talimogene laherparepvec must not be administered into visceral organ metastases. The initial dose of talimogene laherparepvec is up to 4.0 mL of 10^6 PFU/mL. Subsequent doses of talimogene laherparepvec are up to 4.0 mL of 10^8 PFU/mL. The second dose up to 4.0 mL of 10^8 PFU/mL should be administered 21 (+5) days after the initial dose (ie, no sooner than day 22, but should not be delayed more than 5 days after the day-21 time point). Subsequent doses up to 4.0 mL of 10^8 PFU/mL should be given every 14 (± 3) days until week 12, all injectable tumors have disappeared, or intolerance of study treatment, whichever occurs first.

Refer to Section 6.2.1.1 for additional information regarding the dosage and administration of talimogene laherparepvec.

Other Protocol-required Therapy

Surgical Resection of Melanoma Lesion(s):

Surgical radical resection of melanoma lesion(s) aimed to achieve negative margins will be performed at any time during weeks 13 to 18 (Arm 1) or week 1 to 6 (Arm 2). Subjects randomized to Arm 1 who ends talimogene laherparepvec prior to week 12 due to disappearance of all injectable tumor lesions, intolerance to talimogene laherparepvec, or any other reason will

undergo surgical resection of melanoma lesion(s) or tissue where melanoma was present before CR within 1 to 6 weeks after the last dose of talimogene laherparepvec. Refer to Appendix F for surgery guidelines.

Refer to Section 6.3 for additional information regarding other protocol-required therapies.

Procedures:

Screening:

The following procedures will be performed during the screening period:

- confirmation that the informed consent form has been signed
- review of medical and surgical history, physical examination
- demographics, vital signs, and ECOG performance status assessment
- local laboratory tests including, hematology panel, chemistry panel, serum LDH, prothrombin time (PT) (or international normalization ratio [INR]) and partial thromboplastin time (PTT) (or activated PTT), and serum or urine pregnancy test for female subjects of childbearing potential
- clinical tumor assessment and radiographic tumor imaging
- recording of concomitant medications, recording/reporting of any serious adverse events that occur after subject signs informed consent
- review of inclusion criteria and randomization in Interactive Voice Response (IVR) system

For a full list of screening procedures, including the timing of each procedure, please refer to Section 7.2.1 and the Schedule of Assessments (Table 2 and Table 3).

Treatment:

The following procedures will be performed during the treatment period (Note: Some of the following procedures are not applicable to subjects randomized to Arm 2 [surgery alone]):

- vital signs
- ECOG performance status
- physical examination
- local laboratory tests including hematology panel and chemistry panel
- central laboratory tests including blood samples for herpes simplex virus (HSV-1) antibody serostatus and biomarker analyses, tumor biopsy for biomarker analyses, swabs of cold sore, vesicles and other lesions suspected to be herpetic origin (if any) for real-time polymerase chain reaction (qPCR) analysis of talimogene laherparepvec DNA
- archived tumor tissue for serine/threonine protein kinase B-Raf V600 ($BRAF^{V600}$) mutation testing and biomarker analyses
- radiographic tumor imaging, clinical tumor assessment, and tumor response assessment
- histological tumor assessment of the surgical specimen, including assessment for tumor-free margins (R0 resection for negative margins, R1 or R2 resections for tumor positive margins) and pathological complete response (Arm 1 only), recording of concomitant medications, adverse events, at each visit, and reporting serious adverse events Amgen within 24 hours following the investigator's knowledge of the event
- reporting pregnancy or lactation in a female subject or a female partner of a male subject
- administration of talimogene laherparepvec at day 1 of each cycle and/or surgical resection of melanoma lesion based on the randomization arm

For a full list of applicable treatment procedures by treatment arm, including the timing of each procedure, please refer to Section 7.2.2 and the Schedule of Assessments (Table 2 and Table 3).

Safety Follow-Up Visit:

The following will be performed during the safety follow-up visit (Note: Some of the following procedures are not applicable to subjects randomized to Arm 2 [surgery alone]):

- physical examination, vital signs and ECOG performance status assessment
- surgical safety evaluation
- documentation of subsequent anticancer therapy for melanoma (including local, regional, or systemic therapy)
- local laboratory tests including hematology panel, chemistry panel and serum or urine pregnancy test for female subjects of childbearing potential
- central laboratory tests of swabs of cold sores, vesicles, and other lesions suspected to be herpetic in origin (if any) for qPCR testing of talimogene laherparepvec DNA within 24 hours following the investigator's knowledge of the event
- recording of concomitant medications, adverse events, and reporting serious adverse events
- reporting pregnancy or lactation in a female subject or a female partner of a male subject

For a full list of applicable safety procedures by treatment arm, including the timing of each procedure, please refer to Section 7.2.3 and the Schedule of Assessments (Table 2 and Table 3).

Long-term Follow-up:

All randomized subjects will be contacted by telephone, or clinic visit, to assess survival status, collect adverse events deemed by the investigator to be potentially related to talimogene laherparepvec (Arm 1 only), and, if applicable, commencement of any subsequent anticancer melanoma therapy (including local, regional, or systemic therapy). Follow-up will occur every 3 months (±30 days) for 3 years following the safety follow-up visit and then every 6 months (±30 days) until death, subject withdraws full consent, or up to 5 years after the last subject is randomized.

Radiographic tumor imaging, clinical tumor assessments, and tumor response assessments, will be performed as documented in Section 7.2.2 every 3 months (±30 days) for 3 years following the safety follow-up visit and then every 6 months (±30 days) until distant disease recurrence, death, subject withdraws full consent, or up to 5 years after the last subject is randomized, whichever is first.

After the long-term follow-up period of this study has ended, subjects randomized to Arm 1 who received at least a single dose of talimogene laherparepvec and who end the study for any reason other than death or withdrawal of full consent will be followed for survival under an ongoing separate registry protocol (Study 20120139) that is in place for the long-term follow-up of all subjects treated with talimogene laherparepvec in clinical trials. The registry protocol will also monitor for late and long-term adverse events thought to be potentially related to talimogene laherparepvec and use of subsequent anticancer therapy for melanoma. Subjects who after the long-term follow-up period of this study (Study 20110266) will elect to participate in the registry study must sign new informed consent form before any registry protocol-specific activities.

Reporting Exposure to Talimogene Laherparepvec (Arm 1 only):

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

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

Statistical Considerations:

The primary analysis for the primary endpoint will occur at the later time of either the occurrence of approximately 64 events (local, regional, or distant recurrence of melanoma or death) or approximately 2 years after the end of randomization. An 80% confidence interval (CI) will be

estimated for the RFS hazard ratio (HR) and the between-arm difference (Arm 2 – Arm 1) in 2-year RFS, ie, Δ 2-year RFS. It is assumed that: (i) RFS is exponential over the first 2 years, (ii) the 2-year RFS for Arm 1 is about 0.60 (Eggermont et al, 2008), and that there will be a 10% exponential probability of drop-out by the primary analysis. The average width of the Δ 2-year RFS 80% CI was 0.20 based on the simulation with an approximately 150 subjects randomized 1:1 to the two arms.

Two interim analyses with no formal stopping rules are planned to evaluate safety and some efficacy endpoints (eg, R0 resection rate, pCR rate, response to neoadjuvant treatment) when approximately 40 and 75 subjects randomized to talimogene laherparepvec have had the opportunity to complete the safety follow-up visit. The primary analysis for certain secondary endpoints (eg, response to neoadjuvant treatment, R0 resection rate, pCR rate, and safety) will be performed using the data from the second interim analysis.

An additional third interim analysis with no formal stopping rule is planned to evaluate RFS approximately 1 year after the end of randomization. This analysis will be conducted by the Amgen study team.

The primary analyses for RFS will occur at the later time of either the occurrence of approximately 64 events (local, regional, or distant recurrence of melanoma or death) or approximately 2 years after end of randomization.

The final analyses will occur approximately 5 years after the end of randomization. An additional analysis will also occur approximately 3 years after the end of randomization.

Ad hoc analyses for safety or some efficacy endpoints (eg, response to neoadjuvant treatment, R0 resection rate, pCR rate) may be conducted before the planned primary and/or final analyses if interim data are required for submission to regulatory authorities.

All efficacy analyses will be descriptive with no formal hypothesis testing. Kaplan-Meier (KM) estimates and CI will be calculated for RFS, LRFS, RRFS, DMFS, OS landmarks (**1-,** 2-, 3- and 5-year rates) and quartiles. Estimates and CIs for between-group differences will also be calculated. An overall between-group difference in RFS, LRFS, RRFS, DMFS, and OS will be evaluated with a log-rank test and corresponding proportional hazards model with or without two randomization stratification factors. Estimates and exact CIs for binary endpoints (eg, overall tumor response, response in injected and uninjected lesions, R0 rate, pCR) and their associated between-group differences will be calculated.

Subject incidence rates of treatment-emergent adverse events (including all adverse events, grade ≥ 3 adverse events, fatal adverse events, serious adverse events, adverse events of interest and events requiring the discontinuation of study drug, local effects on the tumor [ie, pain, inflammation and ulceration]) will be summarized.

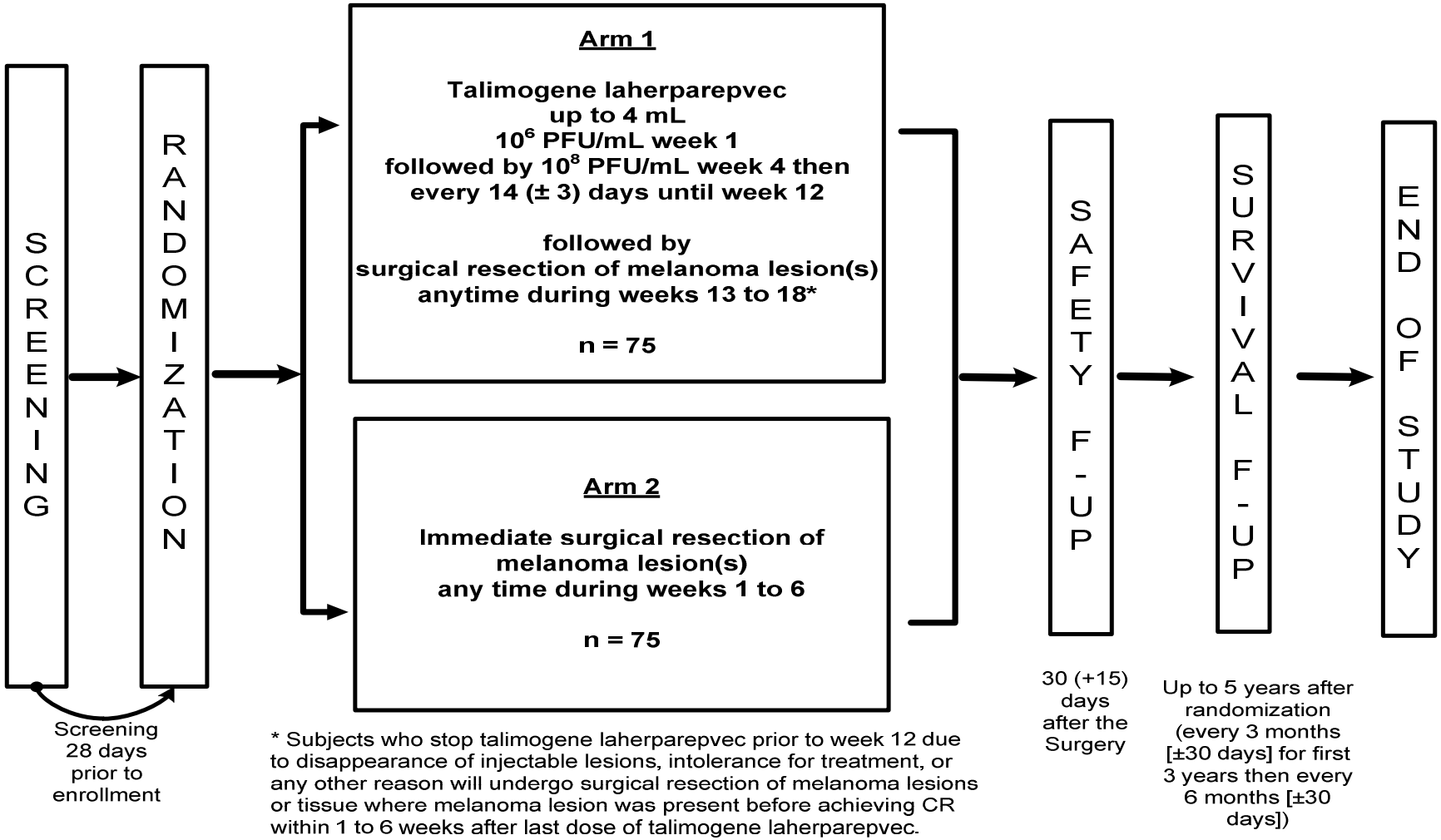
The analyses of tumor tissue or serum biomarkers may be performed after collection of all samples during the conduct of the study and therefore may be reported after the primary analysis of efficacy endpoint.

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

Sponsor: Amgen Inc

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

Study Design and Treatment Schema



* Subjects who stop talimogene laherparepvec prior to week 12 due to disappearance of injectable lesions, intolerance for treatment, or any other reason will undergo surgical resection of melanoma lesions or tissue where melanoma lesion was present before achieving CR within 1 to 6 weeks after last dose of talimogene laherparepvec.

Study Glossary

Abbreviation or Term	Definition/Explanation
AJCC	American Joint Committee on Cancer
ANC	absolute neutrophil count
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BRAF, $BRAF^{V600}$	serine/threonine protein kinase B-Raf, serine/threonine protein kinase B-Raf V600
BUN	blood urea nitrogen
CI	confidence interval
CNS	central nervous system
CR	complete response
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic lymphocyte associated antigen 4 (CTLA-4)
DMFS	distant metastases-free survival
DRR	durable response rate
DRT	Data Review Team
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
End of Follow-up	defined as when the last subject completes the last protocol-specified long-term follow-up assessment in the study
End of Study for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject
End of Study (primary completion)	defined as when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary endpoint (s). The primary completion is anticipated to occur at the later time of either occurrence of approximately 64 events (local, regional, or distant recurrence of melanoma or death) or approximately 2 years after the end of randomization.
End of Study (end of trial)	defined as when the last subject is assessed or receives an intervention for evaluation in the study. The end of trial will occur when the last subject has had the opportunity to complete the long-term follow-up. The end of trial is anticipated to occur approximately 5 years after the end of randomization.
End of Treatment	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
eSAE	electronic serious adverse event
ESMO	European Society for Medical Oncology
GCP	Good Clinical Practice

Abbreviation or Term	Definition/Explanation
GM-CSF	granulocyte macrophage colony-stimulating factor
HD	high-dose
HR	hazard ratio
HSV, HSV-1	herpes simplex virus, herpes simplex virus type 1
ICH	International Conference on Harmonisation
KM	Kaplan-Meier
IL	interleukin
INR	international normalization ratio
Interactive Voice Response (IVR)	telecommunication technology that is linked to a central computer in real time as an interface to collect and process information.
IFNα	interferon alpha
IPIM	Investigational Product Instruction Manual
IRB/IEC	institutional review board/independent ethics committee
LDH	lactate dehydrogenase
LRFS	local recurrence-free survival
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
OS	overall survival
pCR	pathological complete response
PD-1	program cell death-1
PD-L1	programmed cell death-1 ligand 1
PET	positron emission tomography
PFU	plaque forming unit
PKR	double-stranded RNA activated protein kinase
PR	partial response
PT	prothrombin time
PTT/aPTT	partial thromboplastin time/activated partial thromboplastin time
qPCR	real-time polymerase chain reaction
RBC	red blood cell
RFS	recurrence-free survival
RRFS	regional recurrence-free survival
SD	stable disease
SOC	system organ class

Abbreviation or Term	Definition/Explanation
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
Study Day 1	defined as the first day that protocol-specified investigational product/protocol required therapies is/are administered to the subject
ULN	upper limit of normal
USA	United States of America
WBC	white blood cell
WHO	World Health Organization

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1. OBJECTIVES

1.1 Primary

To estimate the treatment effect of neoadjuvant talimogene laherparepvec plus surgery compared to surgery alone on recurrence-free survival (RFS).

1.2 Secondary

The secondary objectives are:

- To estimate the effect of neoadjuvant talimogene laherparepvec plus surgery compared to surgery alone on **1-year,** 2-year, 3-year, and 5-year RFS
- To estimate the effect of neoadjuvant talimogene laherparepvec plus surgery compared to surgery alone on rate of histopathological tumor-free margin (R0) surgical resection
- To estimate the effect of neoadjuvant talimogene laherparepvec on rate of pathological complete response (pCR)
- To estimate the effect of neoadjuvant talimogene laherparepvec plus surgery compared to surgery alone on local recurrence-free survival (LRFS), regional recurrence-free survival (RRFS), and distant metastases-free survival (DMFS)
- To estimate the effect of neoadjuvant talimogene laherparepvec plus surgery compared to surgery alone on **1-year,** 2-year, 3-year, 5-year, and overall survival (OS)
- To estimate response to neoadjuvant talimogene laherparepvec overall and separately in injected and uninjected lesions during treatment (Arm 1 only)
- To evaluate the safety of neoadjuvant talimogene laherparepvec plus surgery compared to surgery alone

1.3 Exploratory

The exploratory objectives are:

- To explore the correlation between baseline intratumoral CD8+ cell density and clinical outcomes
- To explore the correlation between changes in an intratumoral CD8+ cell density during talimogene laherparepvec treatment and clinical outcomes
- To investigate the correlation between the changes in the population of tumor-specific cytotoxic T-cells during treatment and clinical outcomes
- To assess blood and tumor for potential biomarkers which correlate with or predict clinical outcomes to talimogene laherparepvec

2. BACKGROUND AND RATIONALE

2.1 Melanoma and Adjuvant and Neoadjuvant Therapy for Melanoma

Cutaneous melanoma is the fifth most common cancer in men and the seventh most common cancer in women in the United States of America (USA), with an estimated 76, 100 new cases and 9,710 deaths expected in 2014 (Siegel et al, 2014). 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 (Ferlay et al, 2013). In Europe as a whole, 100, 442 new cases of skin melanoma and 22, 212 deaths from melanoma were estimated in 2012 (Ferlay et al, 2013). The incidence of melanoma in Australia is the highest in the world, with the age-standardized incidence rate of approximately 50 per 100,000 people in 2009 (Australian Institute of Health and Welfare, 2012). 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 thyroid cancer in women (Edwards et al, 2005; Siegel et al, 2014). Median age for diagnosis of melanoma (59 years) is significantly lower than the median age of diagnosis for the more common solid tumors. As such, melanoma is second only to adult leukemia in terms of loss of years of potential life per adult cancer-related death (Coit et al, 2013).

When discovered in earlier stages and fully excised, melanoma is highly curable with 10-year overall survival (OS) approaching 95% for stage I and 45-77% for stage II (American Joint Committee on Cancer [AJCC], 7th edition) melanoma (Balch et al, 2009). It is estimated that about 10% of subjects with melanoma present with regionally-advanced disease (stage III) and approximately 30% will have nodal and/or in-transit metastasis as their first site of recurrence (Kirkwood et al, 2000; SEER, 2014). While radical resection is a cornerstone of treatment for subjects with stage III melanoma (Slingluff et al, 2011; Coit et al, 2013), the majority of subjects with clinically detectable nodal metastases and/or in-transit disease will experience recurrence, with 5-year OS of 59% for subjects with stage IIIB disease and 40% for IIIC disease (Balch et al, 2009). In one of the latest adjuvant trials utilizing pegylated interferon alpha (IFNα)-2b, 4-year RFS and OS of all subjects with palpable nodal disease (N2-N3, AJCC, 7th edition) in the observation group were 33.9 ± 2.6% and 46.8 ± 2.6% respectively, dropping sharply with the amount of lymph nodes involved (Eggermont et al, 2008).

Approximately 20% of subjects with earlier stages of melanoma will develop distant cutaneous/subcutaneous or distant nodal metastasis in the absence of visceral disease or elevated lactate dehydrogenase (LDH) (stage IVM1a) (Kirkwood et al, 2000). Stage IVM1a melanoma has better prognosis compared with metastases located in any other distant anatomic site, with 1-year OS of 62%, and 5-year OS approaching 30%

(Balch et al, 2009). Resection, if feasible, is often recommended for this group of subjects (Slingluff et al, 2011; Coit et al, 2013).

High-dose (HD) IFNα (Intron® A, 2013) or pegylated IFNα (Sylatron™, 2013) are the FDA-approved systemic therapies that can be considered in subjects after resection of stage III melanoma. Other treatment options recommended by the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) Guidelines include participation in clinical trials, or observation (Dummer et al, 2012; Coit et al, 2013). Even with a higher rate of relapse than stage III disease, there is little evidence to support adjuvant treatment with IFNα for resected IVM1a melanoma.

HD IFNα has shown a modest, but significant RFS benefit when given as adjuvant therapy to subjects with melanomas at high risk for recurrence (Kirkwood et al, 2000; Kirkwood et al, 1996). A pooled analysis of three major adjuvant trials with HD IFNα found an improvement in RFS in subjects with melanomas that are 4 mm or thicker with no evidence of lymph node involvement, or stage III melanomas with either lymph node involvement and/or in-transit metastases (hazard ratio [HR] 0.77, two-sided $p < 0.006$, median follow-up of 7.2 years), but failed to demonstrate a significant improvement in OS (HR 0.93, two-sided $p = 0.42$) (Kirkwood et al, 2004). Major toxicities of HD IFNα include flu-like symptoms, auto-immune disorders, hepatotoxicity, significant laboratory abnormalities, depression, and suicide (Slingluff et al, 2011). As such, adjuvant HD IFNα after resection of stage III melanoma is decreasingly being utilized (Coit et al, 2013) and is not recommended as a standard of care for adjuvant therapy according to the guidelines of several professional societies (Marsden et al, 2010; Scottish Intercollegiate Guidelines Network, 2013).

Intermediate-dose regimens of pegylated IFNα, which are more convenient to administer and have been evaluated in several clinical trials, demonstrated improved RFS (HR 0.82, $p = 0.011$, 95% confidence interval [CI]: 0.71; 0.96), however there was no effect on DMFS or OS, and toxicity was significant with grade 3 adverse events in approximately 40% of subjects; leading to discontinuation of therapy in about one-third of subjects assigned to the treatment arm (Eggermont et al, 2008; Eggermont et al, 2005).

A recently reported intergroup phase III trial compared a HD IFNα regimen to a 9-week "biochemotherapy" consisting of dacarbazine, vinblastine, cisplatin, intravenous interleukin (IL)-2, and subcutaneous IFNα as adjuvant treatment for patients after

resection of high-risk stage III melanoma. At a median follow-up of 6 years, biochemotherapy improved RFS (HR 0.77, p < 0.02; 90% CI: 0.62-0.96), however there was no difference in OS (HR 1.0, p = 0.49, 90% CI: 0.78-1.27) and same 56% of subjects were alive at 5 years in both arms of the trial. The biochemotherapy regimen was associated with substantial toxicity with grade 3 and 4 adverse events in 36% and 40% of subjects, respectively (Flaherty et al, 2012).

Several meta-analyses have confirmed a significant effect of adjuvant IFNα on RFS and some demonstrated small but significant improvement in OS (Wheatley et al, 2007; Wheatley et al, 2003; Mocellin et al, 2013; Mocellin et al, 2010). In the latest Cochrane meta-analysis that included aggregate patient data from 17 randomized clinical trials comparing adjuvant IFNα to observation, adjuvant IFNα was associated with improved disease-free survival (HR 0.83, p<0.00001, 95% CI: 0.78-0.87) and improved OS (HR 0.91, p<0.003, 95% CI: 0.85-0.97) (Mocellin et al, 2013). The authors concluded that 35 participants needed to be treated in order to prevent 1 subject death of cutaneous stage II-III melanoma (95% CI: 21-108), confirming modest efficacy of adjuvant IFNα (Mocellin et al, 2013).

A variety of whole-cell based and defined antigen-based melanoma vaccines were explored in the adjuvant setting. However, the results of the trials either showed no benefit or could possibly be detrimental compared with observation (Eggermont et al, 2008; Blanchard et al, 2013).

Recently, ipilimumab, a cytotoxic lymphocyte associated antigen 4 (CTLA-4) inhibitor, was approved by the United States Food and Drug Administration for the adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy (Yervoy™, 2015). This approval was based on results of a randomized double-blind phase 3 trial conducted in 951 patients with completely resected stage IIIA (> 1 mm nodal involvement), IIIB, and IIIC melanoma (EORTC Study 18071). Patients with in-transit metastases were excluded. Ipilimumab improved recurrence-free survival (primary endpoint) in this trial from 17.1 months to 26.1 months (HR 0.75; 95% CI 0.64–0.90; p=0.0013). Results of OS and distant metastasis-free survival (secondary endpoints) are pending. Fifty-two percent of patients randomized to the ipilimumab arm discontinued treatment because of toxicity, 5 patients (1%) died because of ipilimumab-related toxicities. Forty-six percent of

patients in the ipilimumab arm experienced grade 3 adverse events (37% immune-related), and 8% grade 4 (6% immune-related) (Eggermont et al, 2015).

Neoadjuvant therapy, the benefit of which has been demonstrated in several operable cancers (Bosset et al, 2006; Rastogi et al, 2008; Vergote et al, 2010), has potential advantages over adjuvant therapy in subjects with locally-advanced disease which include down-sizing of the primary tumor, consequently increasing the probability of negative margin resection, and early systemic exposure to potentially effective therapy through intact blood and lymphatic vessels. Moreover, neoadjuvant therapy allows real-time assessment of antineoplastic effects of the therapy in vivo on tumor cells, tumor microenvironment and the immune system, and permits prospective and sequential collection of tissue samples for biomarker studies.

This investigational approach for preoperative treatment of subjects with locally-advanced melanoma was utilized in several phase 2 trials where the subjects were treated by intravenous high-dose IFNα (Moschos et al, 2006) or by biochemotherapy (Buzaid et al, 1998; Koyanagi et al, 2005; Lewis et al, 2006). Ninety-two subjects with histologically-proven stage III nodal melanoma were enrolled in the phase 2 study to receive 2 cycles of preoperative biochemotherapy followed by surgery and 2 postoperative cycles of biochemotherapy (Lewis et al, 2006). Treatment, which included cisplatin, dacarbazine, vinblastine, and IL-2 and IFNα, was administered in the inpatient setting and included growth factors and blood pressure support. Common adverse events were hematological grade 3 and 4 toxicities, electrolytes grade 3 toxicities, and nausea and vomiting. Nearly 40% of subjects required dose reductions and 40% had treatment delays. Among fifty subjects with measurable disease, complete response (CR) and partial response (PR) rates were 4% and 22%, respectively (assessed by World Health Organization [WHO] criteria [WHO handbook for reporting results of cancer treatment, 1979]). Half of the subjects (50%) had stable disease (SD) and 8% had tumor progression. At the time of surgery, 26% of subjects with measurable disease had pCR. In another neoadjuvant trial, 20 subjects with palpable regional lymph node metastatic melanoma were treated by preoperative high-dose IFN for 4 weeks followed by surgery and postoperative subcutaneous IFN for 48 weeks (Moschos et al, 2006). CR was noted in 1 (5%) subject and 10 subjects (50%) had PR. At the time of surgery, 15% of subjects had pCR. Immunohistochemical analysis of pre-and post-treatment tumor biopsies revealed increases in peritumoral CD4+ T-lymphocytes and endotumoral monocyte-derived dendritic cells after the

treatment with high-dose IFNα. Clinical responders compared with non-responders demonstrated a trend toward greater increases in endotumoral monocyte-derived dendritic cells (Moschos et al, 2006).

Limited clinical experience with neoadjuvant temozolomide administered for 6 weeks for two 8-week cycles to 19 patients, while well tolerated resulted in objective response in 3 patients only (2 had CR and 1 had PR), stable disease in 4 patients, and tumor progression in 12 patients while on treatment (Shah et al, 2010).

2.2 Talimogene Laherparepvec Background

Talimogene laherparepvec is an intralesionally-delivered oncolytic immunotherapy comprised of a genetically engineered herpes simplex virus type 1 (HSV-1) that selectively replicates in tumors (Talimogene Laherparepvec Investigator's Brochure, 2015). The neurovirulence factor ICP34.5 and the ICP47-encoding gene are functionally deleted in the virus, while the gene for human granulocyte macrophage colony-stimulating factor (GM-CSF) is inserted. The ICP34.5 functional deletion allows the virus to replicate selectively in tumors. The role of ICP47 is to block antigen presentation to major histocompatibility complex class I and II molecules by blocking the transporter associated with antigen processing 1 and 2. This deletion also allows the increased expression of the US11 gene. This promotes virus growth in cancer cells without decreasing tumor selectivity.

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

The postulated dual mechanism of action of talimogene laherparepvec comprises:
1) a direct oncolytic effect achieved by infection and replication of the virus in tumor tissue resulting in tumor cell lysis and local release of tumor antigens, and
2) enhancement of a systemic immune response by expression of GM-CSF in the tumor microenvironment to recruit and activate antigen presenting cells. Clinical data currently available have provided evidence of talimogene laherparepvec's efficacy in subjects with

unresectable metastatic melanoma (Talimogene Laherparepvec Investigator's Brochure, 2015). In particular, a high rate of CR was achieved (16%) in the phase 2 study with talimogene laherparepvec in stage IIIC to IV melanoma (Senzer et al, 2009; Talimogene Laherparepvec Investigator's Brochure 2015). Moreover, responses were observed in both injected and uninjected sites, including visceral sites. Responses were seen most often in earlier stage disease, including stage IIIB/C and stage IVM1a, and in disease with lower visceral burden.

In the open-label, randomized, phase 3 study in 436 subjects with stages IIIB, IIIC, and IV unresectable melanoma, intralesional talimogene laherparepvec or subcutaneous GM-CSF were administered at least until week 24, or CR, clinically significant disease progression, intolerable side effects, 12 months of therapy without an objective response, or withdrawal of consent (Study 20110263; OPTiM). If subjects were in response (CR or PR) at 12 months, they were treated in both arms up to 18 months or disease progression (PD), whichever was earlier. The primary endpoint of the OPTiM study was durable response rate (DRR), defined as the rate of subjects with an objective response (CR or PR) by central review lasting continuously for 6 months and starting any time within 12 months of initiating therapy. Secondary endpoints included OS, best response, modified PFS, tumor burden and safety.

Primary analysis of the OPTiM Study showed a statistically significant difference between the DRR 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) (Andtbacka et al, 2013). At the same analysis median modified PFS was 8.2 (95% CI, 6.5, 9.9) months in the talimogene laherparepvec arm versus 2.9 (95% CI, 2.8, 4.0) months in the GM-CSF arm (HR=0.42; 95%CI=0.32, 0.54). An improvement that closely approached statistical significance was seen in the intent-to-treat population in the primary analysis of the secondary endpoint of OS with HR of 0.79 (95% CI: 0.62, 1.00), p = 0.051. Median OS of subjects treated with talimogene laherparepvec was 4.4 months longer than those treated with GM-CSF (23.3. months for talimogene laherparepvec versus 18.9 months for GM-CSF) (Kaufman et al, 2014). Survival at 12, 24, 36 and 48 months in the talimogene laherparepvec arm was estimated to be 74%, 50%, 39% and 33%, respectively, and 69%, 40%, 30% and 21% in the GM-CSF arm, respectively. In exploratory subset analyses, the treatment effect was most pronounced among subjects receiving treatment as first-line therapy (HR=0.50; 95% CI=0.35, 0.73) compared with subjects receiving

treatment as second-line or greater therapy (HR=1.13; 95% CI=0.82, 1.57), and subjects with stage IIIB/C (HR for OS 0.48; 95% CI: 0.29, 0.80, log-rank p-value 0.004) and stage IVM1a (HR 0.67; 95% CI: 0.42, 1.07, log-rank p-value 0.09) melanoma (Kaufman et al, 2014). Similarly, in exploratory subset analyses of DRR, the treatment effect was most pronounced among subjects with stage IIIB/C disease (DRR = 33% in talimogene laherparepvec arm versus 0% in GM-CSF arm), and stage IVM1a disease (DRR = 16% in talimogene laherparepvec arm versus 2% in GM-CSF arm), and these subjects represented > 55% of the study population. DRR was also more pronounced in subjects receiving treatment as first-line therapy (24% versus 0%) than in those receiving treatment as second-line or greater therapy (10% versus 4%) (Kaufman et al, 2013). Serine/threonine protein kinase B-Raf (BRAF) status was known in 31.4% of subjects; the DRR with talimogene laherparepvec was 11% in subjects with or without BRAF mutations.

Median (range) time to response among the 78 subjects in the talimogene laherparepvec arm with a response was 4.1 (1.2 to 16.7) months, whereas among the 8 in the GM-CSF arm with a response, it was 3.7 (1.9 to 9.1) months. Fifty-four percent of talimogene laherparepvec objective responders and 48% of talimogene laherparepvec durable responders exhibited “interval progression”, which is transient locoregional or distant progression including appearance of new lesions, before ultimately achieving response (Kaufman et al, 2013). When investigator-reported response rates (decrease in lesion area: PR, 50 to <100%; CR, 100%) of 3,916 measurable lesions (average 13) in 285 subjects treated by talimogene laherparepvec in the OPTiM Study were analyzed retrospectively, CR and PR rates in injected lesions were 47% and 17%, respectively. CR and PR in non-injected non-visceral lesions were 22% and 12%, respectively. CR and PR in visceral lesions, which were also non-injected, were 9% and 6%, respectively (Andtbacka et al, 2014).

The most common side effects in the OPTiM study were chills (talimogene laherparepvec, 49%; GM-CSF, 9%), pyrexia (43%; 9%), injection-site pain (28%; 6%), nausea (36%; 20%), influenza-like illness (30%; 15%), and fatigue (50%; 36%). Grade ≥ 3 adverse events occurred in 36% of subjects receiving talimogene laherparepvec and 21% of subjects receiving GM-CSF. The only grade 3/4 adverse events occurring in ≥ 5 of subjects was cellulitis (talimogene laherparepvec, n=6 [2.1%]; GM-CSF, n=1 [<1%]). Of 10 fatal adverse events in the talimogene laherparepvec arm, 8 were attributable to disease progression. The remaining 2 fatal adverse events

(sepsis in the setting of salmonella infection; myocardial infarction) were not considered treatment-related per investigator.

Recently, talimogene laherparepvec (Imlygic™) was approved in the USA for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery (with limitation of use: Imlygic has not been shown to improve overall survival or have an effect on visceral metastases) (Imlygic™ Prescribing Information, 2015), in Europe for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (stage IIIB, IIIC, and IVM1a) with no bone, brain, lung or other visceral disease (Imlygic™ Summary of Product Characteristics, 2015), and in Australia as monotherapy for the treatment of melanoma in patients with unresectable cutaneous, subcutaneous, or nodal lesions after initial surgery (Imlygic™ Prescribing Information, 2015).

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

2.3 Rationale

The main purpose of the study is to estimate the ability of talimogene laherparepvec administered prior to surgery to increase RFS in subjects with resectable stage IIIB to IVM1a melanoma.

It is expected that neoadjuvant treatment with talimogene laherparepvec will improve both local and distant control by achieving higher rates of tumor-free (negative) margin surgical resection (R0), and will decrease distant metastasis rate through systemic effects on micrometastatic disease.

Since talimogene laherparepvec is assumed to work via activation of the immune system and infiltrating T cells have also been shown to be prognostic for melanoma (Erdag et al, 2012), it is important to understand whether the number and type of tumor infiltrating and peripheral immune cells impact drug efficacy. Therefore, tumor and blood samples will be collected before and at the end of the talimogene laherparepvec treatment to investigate the relationship between the activities of the immune system, such as cytotoxic CD3+/CD8+ and CD8+/CD45R0 T-lymphocytes, tumor antigen specific T cells, regulatory T cells and myeloid-derived suppressor cells measured both in the tumor and/or in the peripheral blood, and response to the treatment. Additionally, a number of immune-related biomarkers, such as antibodies to melanoma antigens and expression of immune-stimulatory and immune-inhibitory molecules (eg CTLA-4,

program cell death-1 [PD-1], program cell death-1 ligand 1 [PD-L1] and others) in tumors or tumor infiltrating T-cells will be assessed to determine any association with clinical outcomes.

Moreover, tumor biopsy samples will be assessed for mutations effecting viral replication, such as double-stranded RNA-activated protein kinase (PKR) that cells activate to protect themselves from viral infection and whose activity may predict clinical response to treatment with talimogene laherparepvec. Also, safety of talimogene laherparepvec, especially related to postoperative complications will be evaluated.

2.4 Clinical Hypotheses

Formal hypotheses will not be tested in this trial. The study will provide an estimate of the treatment effect, as measured by the difference in RFS of talimogene laherparepvec neoadjuvant therapy followed by surgery compared to surgery alone in subjects with resectable, stage IIIB to IVM1a melanoma.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a phase 2, multicenter, randomized, open-label study to estimate the efficacy of talimogene laherparepvec as a neoadjuvant treatment followed by surgery compared to surgery alone in subjects with resectable stage IIIB, IIIC, or IVM1a melanoma. Approximately 150 subjects with completely resectable melanoma and at least one injectable lesion will be randomized 1:1 to receive the following:

- **Arm 1:** Talimogene laherparepvec for 6 doses followed by surgical resection of melanoma tumor lesion(s).
  - **Talimogene Laherparepvec:**

    Talimogene laherparepvec will be administered by intralesional injection into the injectable cutaneous, subcutaneous, and nodal tumors initially at a dose of 10^6 plaque forming units (PFU)/mL at day 1 of week 1 followed by a dose of 10^8 PFU/mL at day 1 (±3 days) of weeks 4, 6, 8, 10 and 12 or until all injectable tumors have disappeared, or intolerance of study treatment, whichever occurs first. Due to the mechanism of action of talimogene laherparepvec, subjects may experience transient growth in existing tumors or the appearance of new tumors prior to maximal clinical benefit of talimogene laherparepvec. Subjects who experience growth in existing tumors or the appearance of new tumors will be allowed to remain on talimogene laherparepvec treatment until week 12 of therapy unless, in the opinion of the investigator, immediate surgical resection or

any other treatment for melanoma is warranted. If talimogene laherparepvec treatment will end prior to week 12, the investigator or designee should notify the sponsor's medical monitor as soon as possible.

- **Surgical Resection of Melanoma Tumor Lesions(s):**
  For subjects who complete 12 weeks of talimogene laherparepvec treatment, surgical resection of melanoma lesion(s) will be performed at any time during weeks 13 to 18. Subjects who stop talimogene laherparepvec prior to week 12 due to disappearance of all injectable tumor lesions, intolerance to talimogene laherparepvec, or any other reason will undergo adequate surgical resection of melanoma lesion(s) or tissue where melanoma was present before achieving CR, within 1 to 6 weeks after the last dose of talimogene laherparepvec. If surgery will be performed prior to week 12, the investigator or designee should notify the sponsor's medical monitor as soon as possible. Refer to Appendix F for surgery guidelines.

- **Arm 2:** Immediate surgical resection of melanoma tumor lesion(s)
  - Surgical resection of melanoma tumor lesion(s) will be performed after enrolment any time during weeks 1 to 6. Refer to Appendix F for surgery guidelines.

Randomization will be stratified by disease stage (IIIB nodal versus IIIB in-transit versus IIIC nodal versus IIIC in-transit with nodal versus IVM1a), planned adjuvant therapy (adjuvant systemic therapy [eg, INFα, ipilimumab] with or without radiotherapy versus radiotherapy without adjuvant systemic therapy versus none).

Following surgery, adjuvant systemic therapy and/or radiotherapy may be administered at the investigator's discretion and per the institutional standard of care.

Subjects will be followed for safety approximately 30 (+15) days after surgery and for disease recurrence (local, regional, or distant), subsequent anticancer therapy for melanoma, adverse events thought to be potentially related to talimogene laherparepvec, and survival every 3 months (±30 days) for first 3 years after the end of the safety follow-up period and then every 6 months (±30 days) until death, subject withdraws full consent, or up to 5 years after the last subject is randomized, which is first. Thereafter, subjects randomized to Arm 1 who received at least a single dose of talimogene laherparepvec will be followed under an ongoing separate registry protocol (Study 20120139) for the long-term survival follow-up of subjects treated with talimogene laherparepvec. The registry protocol will also monitor for late and long-term adverse events thought to be potentially related to talimogene laherparepvec and use of

subsequent anticancer therapy for melanoma. Subjects who after the long-term follow-up period of this study (Study 20110266) will elect to participate in the registry study must sign new informed consent form before any registry protocol-specific activities.

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 50 sites in Australia, Brazil, Europe, Russia, and USA. Additional sites and countries may be added.

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 150 subjects will be randomized in this study. Refer to Section 10.2 for sample size considerations.

3.4 Replacement of Subjects

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

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

The duration for the study will be approximately 7 years. The duration of screening for each subject will be approximately 28 days. The subject accrual period is planned for approximately 18 months. The duration of treatment will vary by treatment arm. Subjects randomized to Arm 1 of the study will be treated with talimogene laherparepvec for approximately 12 weeks then followed by surgical resection of melanoma lesion(s) any time from week 13 to 18. Subjects randomized to Arm 2 of the study will undergo immediate surgical resection of melanoma lesion(s) any time from week 1 to 6. Subjects will be followed for safety approximately 30 (+15) days after surgery and for disease recurrence (local, regional, or distant), subsequent anticancer therapy for melanoma, adverse events thought to be potentially related to talimogene laherparepvec, and survival every 3 months (±30 days) for first 3 years after the end of the safety follow-up

period and then every 6 months (±30 days) until death, subject withdraws full consent, or up to 5 years after the last subject is randomized, which is first.

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

3.5.2 End of Study

Primary Completion: the time when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary analysis. The primary completion is anticipated to occur at the later time of either the occurrence of approximately 64 events (local, regional, or distant recurrence of melanoma or death) or approximately 2 years after the end of randomization.

End of Trial: the time when the last subject is assessed or receives an intervention for evaluation in the study. The end of trial will occur when the last subject has had the opportunity to complete the long-term follow-up. The end of trial is anticipated to occur approximately 5 years after the end of randomization.

4. SUBJECT ELIGIBILITY

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

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

4.1 Inclusion and Exclusion Criteria

4.1.1 Inclusion Criteria

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

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

103 Disease stage: Subject with histologically-proven stage IIIB, IIIC, or IVM1a eligible for complete surgical resection according to the surgery guidelines in Appendix F

104 Prior systemic, regional, and radiation anticancer therapies for melanoma must have been completed at least 3 months prior to randomization

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

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

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

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

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

108 Serum LDH level ≤ 1.5 x upper limit of normal (ULN) for stages IIIB and IIIC melanoma and ≤ 1.0 x ULN for stage IVM1a melanoma within 28 days prior to randomization

109 Adequate organ function determined within 28 days prior to randomization, defined as follows:

- Hematological
  - white blood cell count ≥ 3000/mm^3
  - absolute neutrophil count (ANC) ≥ 1500/mm^3
  - platelet count ≥ 100,000/mm^3
  - hemoglobin ≥ 10 g/dL without need for hematopoietic growth factor or transfusion support
- Hepatic
  - serum bilirubin ≤ 2.0 x ULN
  - serum albumin ≥ 2.5 g/dL
  - aspartate aminotransferase (AST) ≤ 2.5 x ULN
  - alanine aminotransferase (ALT) ≤ 2.5 x ULN
  - alkaline phosphatase ≤ 2.5 x ULN
- Renal
  - serum creatinine ≤ 1.5 x ULN
- Coagulation
  - prothrombin time (PT) ≤ 1.5 x ULN (or international normalization ratio [INR] ≤ 1.5)
  - partial thromboplastin time (PTT) or activated PTT (aPTT) ≤ 1.5 x ULN

4.1.2 Exclusion Criteria

201. Primary ocular or mucosal melanoma

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

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

- malignancy treated with curative intent and with no known active disease present and has not received chemotherapy for ≤ 3 years before randomization and felt to be at low risk for recurrence by the treating physician
- adequately treated non-melanoma skin cancer without evidence of disease at the time of randomization
- adequately treated cervical carcinoma in situ without evidence of disease at the time of randomization
- adequately treated breast ductal carcinoma in situ without evidence of disease at the time of randomization
- prostatic intraepithelial neoplasia without evidence of prostate cancer at the time of randomization
- adequately treated superficial or in situ carcinoma of the bladder without evidence of disease at the time of randomization

204 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.

205 Evidence of clinically significant immunosuppression such as the following:

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

206 Known to have acute or chronic active hepatitis B infection

207 Known to have acute of chronic active hepatitis C infection

208 Known to have human immunodeficiency virus infection

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

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

211 Prior therapy with talimogene laherparepvec

213 Currently receiving treatment in another investigational device or drug study, or less than 28 days since ending treatment on another investigational device or drug study

214 Other investigational procedures while participating in this study are excluded

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

216 Female subject of childbearing potential who is unwilling to use acceptable method(s) of effective contraception during talimogene laherparepvec treatment and through 3 months after the last dose of talimogene laherparepvec. (Note: women not of childbearing potential are defined as: Any female who is post-menopausal [age ≥ 55 years with cessation of menses for 12 or more months or less than 55 years with postmenopausal status confirmed by follicle-stimulating hormone [FSH] in the postmenopausal range] or who have had a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy).

217 Subject has known sensitivity to talimogene laherparepvec or components to be administered during dosing

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

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

220 Subject previously has entered this study

221 Sexually active subjects and their partners unwilling to use male or female latex condoms 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.**

5. SUBJECT ENROLLMENT

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

Upon confirmation of eligibility, the site staff will use the Interactive Voice Response (IVR) system to randomize a subject. The investigator is to document this decision and

date in the subject's medical record and in/on the enrolment case report form (CRF). A subject is considered enrolled upon randomization in the IVR system.

Each subject who enters into the screening period for the study (defined as the point 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 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 once at the discretion of the investigator. If a subject is being rescreened, he or she may need to reconsent to the study to ensure that the IRB/IEC approved main consent form is signed within 28 days of randomization. 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 be randomized only 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. This number will not necessarily be the same as the randomization number assigned for the study.

5.1 Randomization/Treatment Assignment

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

The IVR system will assign a randomization number. Approximately 150 subjects will be stratified by disease stage (IIIB nodal versus IIIB in-transit versus IIIC nodal versus IIIC in-transit with nodal versus IVM1a), planned adjuvant therapy (adjuvant systemic therapy [eg, INFα, ipilimumab] with or without radiotherapy versus radiotherapy without adjuvant systemic therapy versus none).

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

- Arm 1: Talimogene laherparepvec for 6 doses followed by surgical resection of melanoma tumor lesion(s).
- Arm 2: Surgical resection of melanoma tumor lesion(s)

Following randomization via the IVR system, talimogene laherparepvec treatment must commence within 5 days.

Eligible subjects must be registered as randomized subjects in the IVR system before the administration of protocol specified therapy.

The randomization date is to be documented in the subject's medical record and on the enrollment CRF.

6. TREATMENT PROCEDURES

6.1 Classification of Product

The Amgen Investigational Product used in this study is talimogene laherparepvec. Only subjects randomized to Arm 1 will receive talimogene laherparepvec.

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

6.2 Investigational Product

6.2.1 Amgen Investigational Product Talimogene Laherparepvec

Talimogene laherparepvec will be manufactured and packaged by Amgen Inc and distributed using Amgen clinical study drug distribution procedures. Talimogene laherparepvec is supplied as a sterile frozen liquid in a single-use 2-cc Crystal Zenith (CZ resin) vial with a gray Fluorotec®-coated chlorobutyl elastomer stopper, aluminum seal, and polypropylene cap. Each vial contains a minimum of 1.0 mL talimogene laherparepvec at either 10^6 PFU/mL or 10^8 PFU/mL concentrations. The supply for the 10^6 PFU/mL concentration will be packaged separately from the supply for the 10^8 PFU/mL concentration.

6.2.1.1 Dosage, Administration, and Schedule

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

Talimogene laherparepvec will be administered by intralesional injection only into injectable cutaneous, subcutaneous, and nodal tumors, with or without image ultrasound guidance. Talimogene laherparepvec must not be administered into visceral organ metastases. The initial dose of talimogene laherparepvec is up to 4.0 mL of 10^6 PFU/mL. Subsequent doses of talimogene laherparepvec are up to 4.0 mL of 10^8 PFU/mL.

The first cycle of talimogene laherparepvec will be 21 (+5) days. Subsequent cycles of talimogene laherparepvec will be 14 (±3) days. On day 1 of cycle 1 the first dose of talimogene laherparepvec will be up to 4.0 mL of 10^6 PFU/mL. The second injection up to 4.0 mL of 10^8 PFU/mL, should be administered 21 (+5) days after the initial injection (ie, no sooner than day 22 but should not be delayed more than 5 days after the 21-day time point). Subsequent injections up to 4.0 mL of 10^8 PFU/mL should be given every 14 (±3) days until week 12, all injectable tumors have disappeared, or intolerance of study treatment, whichever occurs first.

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

The recommended volume of talimogene laherparepvec to be injected into the tumor(s) is dependent on the size of the tumor(s) and should be determined according to the injection volume guideline in Table 1. The tumor size assessment for the injection should be done by clinical exam using a ruler or caliper for cutaneous lesions 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

All reasonably injectable lesions (cutaneous, subcutaneous, and nodal disease that can be injected with or without ultrasound guidance) should be injected with the maximum dosing volume available on an individual dosing occasion (Table 1). On each treatment day, prioritization of injections is recommended as follows:

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

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

A subject will be treated with talimogene laherparepvec until week 12, all injectable tumors have disappeared, or intolerance of study treatment, whichever occurs first. Due to the mechanism of action, subjects may experience transient growth in existing tumors or the appearance of new tumors prior to maximal clinical benefit of talimogene laherparepvec. Therefore, subjects will be allowed to remain on talimogene laherparepvec treatment until week 12 of therapy unless, in the opinion of the investigator, immediate surgical resection or any other treatment for melanoma is warranted. If talimogene laherparepvec treatment will end prior to week 12, the investigator or designee should notify the sponsor's medical monitor as soon as possible.

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

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

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

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

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

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

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

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

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

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

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

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

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

  Note: immune-mediated glomerulonephritis, vasculitis, and pneumonitis, and exacerbation of psoriasis have been observed in subjects receiving talimogene laherparepvec in clinical trials. Most of these subjects had a history of other autoimmune disease and/or prior treatment with agents that offered plausible alternative etiologies, however, immune-mediated adverse events can potentially involve any organ system.

- Any other talimogene laherparepvec-related non-hematologic or hematologic toxicities grade 3 or greater occur that, in the opinion of the investigator, would require a dose delay of greater than 4 weeks from the date of the planned dose (ie, approximately 6 weeks from the previous dose).
- The subject develops clinical evidence of any systemic herpes infection (such as encephalitis or disseminated infection).
- A female subject becomes pregnant or fails to use acceptable method(s) of effective contraception (for those subjects who are able to conceive) while on talimogene laherparepvec treatment.
- A female subject-breast feeds a child while on talimogene laherparepvec treatment.
- Concurrent medical illness that, in the judgment of the investigator, would make continued treatment with talimogene laherparepvec dangerous for the subject.

For additional information related to 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

Surgical radical resection of melanoma lesion(s) aimed to achieve both clinically and microscopically tumor-free margins will be performed at any time during weeks 13 to 18 (Arm 1) or weeks 1 to 6 (Arm 2). Subjects randomized to Arm 1 who stop talimogene laherparepvec prior to week 12 due to disappearance of all injectable tumor lesions, intolerance to talimogene laherparepvec, or any other reason will undergo surgical resection of melanoma lesion(s) or tissue where melanoma was present before achieving CR within 1 to 6 weeks after the last dose of talimogene laherparepvec. If surgery will be performed prior to week 12, the investigator or designee should notify the sponsor's medical monitor as soon as possible. Refer to Appendix F for surgery guidelines. Details on handling surgical specimens are provided in the Laboratory Manual.

All other protocol-required therapies including topical anesthetics 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 nonprescription concomitant medication administered up to 28 days prior to randomization, on an ongoing basis at randomization, as well as changes in such concomitant medication, and any new concomitant medication taken while the subject is on study, should be recorded on the appropriate case report form (CRF) until 30 days (+15) days after surgery. The therapy name, indication, dose, unit, frequency, start date, and stop date will be collected. Concomitant medications administered 30 (+15) days after surgery for serious adverse events should for recorded as defined in Section 9.2.

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

6.5 Other Treatment Procedures

Following surgical resection of melanoma lesion(s), adjuvant systemic therapy and/or radiotherapy may be administered at the investigator's discretion and per the institutional standard of care. If adjuvant therapy (systemic and/or radiation therapy; approved or investigational) is planned, this should be reported via IVR during randomization.

If a subject undergoes adjuvant therapy, the investigator or designee should notify the sponsor's medical monitor as soon as possible and the treatment should be recorded in the source document and CRF.

6.6 Medical Devices

Medical devices (eg, syringes, sterile needles, alcohol prep pads), that are commercially available are not usually provided or reimbursed by Amgen (except, 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 any investigational or non-investigational product(s) or device(s).

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

6.8 Excluded Treatments and/or Procedures During Study Period

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

- other investigational agents or procedures
- concurrent experimental or approved antitumor therapies other than study drug
- 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]). Steroids with low systemic absorption [eg, triamcinolone hexacetonide] injected into a joint space are allowed)
- antiherpetic drugs (eg, acyclovir), other than if topically administered > 20 cm from a talimogene laherparepvec injection site
- Subjects must not schedule any elective surgeries during the treatment period and for at least 30 days after surgical resection of melanoma lesion(s). If a subject undergoes any unexpected surgery during the course of the study, talimogene laherparepvec must be withheld and the investigator or designee should notify the sponsor's medical monitor as soon as possible. A subject may be allowed to resume talimogene laherparepvec if both the investigator and the sponsor's medical monitor agree to restart study therapy.

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

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

7. STUDY PROCEDURES

7.1 Schedule of Assessments

For Schedule of Assessments refer to Table 2 and Table 3, respectively.

Table 2. Schedule of Assessments for Arm 1 (Talimogene Laherparepvec Plus Surgery)

	Screening [a]		Treatment Period [b]							Follow-up Period [c]	
	≤ 28 days	≤ 3 days	Week 1	Week 4	Week 6	Week 8	Week 10	Week 12	Week 13 to 18	Safety Follow-up 30 (+15) days	Long-term Follow-up Every 3 months (± 30 days) for 3 years then every 6 months (± 30 days) until 5 years after randomization
GENERAL & SAFETY ASSESSMENTS											
Informed Consent	X										
Review of Medical/Surgical History	X										
Demographic Data (sex, age or date of birth, race, and ethnicity)	X										
Review of Eligibility Criteria	X										
Concomitant Medications	X	→	→	→	→	→	→	→	→	X	
Adverse and Serious Adverse Events	X	→	→	→	→	→	→	→	→	X	
Adverse Events Potentially Related to Treatment with Talimogene Laherparepvec											X
Physical Exam	X		X	X		X			X	X	
Vital Signs	X		X	X		X		X	X	X	
ECOG Performance Status	X			X		X			X	X	
Surgical Safety Evaluation (including wound closure, drain time, and post operation infection)										X	
Subsequent Anticancer Therapy for Melanoma										X	X
Survival											X
LOCAL LABORATORY ASSESSMENTS											
Urine or Serum Pregnancy Test		X								X	
Hematology	X		X		X			X		X	
Chemistry	X		X		X			X		X	
Serum LDH	X										
PT, PTT or aPTT, INR	X										

Footnotes defined on last page of the table

Table 2. Schedule of Assessments for Arm 1 (Talimogene Laherparepvec Plus Surgery)

	Screening [a]		Treatment Period [b]							Follow-up Period [c]	
	≤ 28 days	≤ 3 days	Week 1	Week 4	Week 6	Week 8	Week 10	Week 12	Week 13 to 18	Safety Follow-up 30 (+15) days	Long-term Follow-up Every 3 months (± 30 days) for 3 years then every 6 months (± 30 days) until 5 years after randomization
CENTRAL LABORATORY ASSESSMENTS											
Blood for HSV-1 Antibody			Week 1 (prior to 1st dose)								
Archived Tumor Tissue for Biomarker Analyses			Submit to central laboratory within 28 days after randomization								
Archived Tumor Tissue for $BRAF^{V600}$ Mutation Testing			Submit to central laboratory within 28 days after randomization if $BRAF^{V600}$ mutation status is unknown prior to screening and was not tested at local laboratory								
Tumor Biopsy			X						X		
Blood for Biomarker Development			X		X				X		
Swab of Herpetic Lesion for qPCR			Within 3 days of occurrence of suspected lesion of herpetic origin								
TREATMENT											
Talimogene Laherparepvec Administration			X	X	X	X	X	X			
Surgery									X		
RADIOGRAPHIC IMAGING, CLINICAL, AND HISTOLOGICAL TUMOR ASSESSMENTS											
Radiographic Imaging (CT, PET/CT, MRI)	X							X			X
Clinical Tumor Measurement and Response Assessment	X							X			X
Histological Tumor Assessment of Surgical Specimen[d]									X		

Footnotes defined on next page of the table

Table 2. Schedule of Assessments for Arm 1 (Talimogene Laherparepvec Plus Surgery)

	Screening [a]		Treatment Period [b]							Follow-up Period [c]	
	≤ 28 days	≤ 3 days	Week 1	Week 4	Week 6	Week 8	Week 10	Week 12	Week 13 to 18	Safety Follow-up 30 (+15) days	Long-term Follow-up Every 3 months (± 30 days) for 3 years then every 6 months (± 30 days) until 5 years after randomization
REPORTING EXPOSURE TO TALIMOGENE LAHERPAREPVEC											
Exposure of Subject's Household member or Caregiver			X	→	→	→	→	→	→	X	
Exposure of Subject's Healthcare Provider			X	→	→	→	→	→	→	X	
REPORTING PREGNANCY/LACTATION											
Reporting of Pregnancy or Lactation [e]			X	→	→	→	→	→	→	→	→

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[a] For additional information regarding the procedures performed during screening procedures and the timing of the procedures please refer to Section 7.2.1.
[b] For additional information regarding the procedures performed during treatment and the timing of the procedures please refer to Section 7.2.2.
[c] For additional information regarding the procedures performed during safety follow-up and long-term follow-up and timing of the procedures please refer to Section 7.2.3 and Section 7.2.4, respectively.
[d] Surgical specimens will be assessed for presence of viable tumor and tumor margin status for cutaneous and subcutaneous tumor; please refer to Section 7.2.2.
[e] Reporting of pregnancy or lactation: If a pregnancy occurs in a female subject, or female partner of a male subject, or a lactation case occurs in a female subject while the subject is taking talimogene laherparepvec and through 3 months after the last dose of talimogene laherparepvec, the case must be reported to Amgen as specified in Section 9.3.

Table 3. Schedule of Assessment for Arm 2 (Surgery Alone)

	Screening [a]		Treatment Period [b]	Follow-up Period [c]	
	≤ 28 days	≤ 3 days	At time of Surgery (Week 1 to 6)	Safety Follow-up 30 (+15) days	Long-term Follow-up Every 3 months (± 30 days) for 3 years then every 6 months (± 30 days) until 5 years after randomization
GENERAL & SAFETY ASSESSMENTS					
Informed Consent	X				
Review of Medical/Surgical History	X				
Demographic Data (sex, age or date of birth, race, and ethnicity)	X				
Review of Eligibility Criteria	X				
Concomitant Medications	X		X	X	
Adverse and Serious Adverse Events	X		X	X	
Physical Exam	X			X	
Vital Signs	X		X	X	
ECOG Performance Status	X			X	
Surgical Safety Evaluation (including wound closure, drain time, and post operation infection)				X	
Subsequent Anticancer Therapy for Melanoma				X	X
Survival					X
LOCAL LABORATORY ASSESSMENTS					
Urine or Serum Pregnancy Test		X		X	
Hematology	X			X	
Chemistry	X			X	
Serum LDH	X				
PT, PTT or aPTT, INR	X				

Footnotes defined on next page of the table

Table 3. Schedule of Assessment for Arm 2 (Surgery Alone)

	Screening [a]		Treatment Period [b]	Follow-up Period [c]	
	≤ 28 days	≤ 3 days	At time of Surgery (Week 1 to 6)	Safety Follow-up 30 (+15) days	Long-term Follow-up Every 3 months (± 30 days) for 3 years then every 6 months (± 30 days) until 5 years after randomization
CENTRAL LABORATORY ASSESSMENTS					
Archived Tumor Tissue for Biomarker Analyses			Submit to central laboratory within 28 days after randomization		
Archived Tumor Tissue for $BRAF^{V600}$ Mutation Testing			Submit to central laboratory within 28 days after randomization if $BRAF^{V600}$ mutation status is unknown prior to screening and was not tested at local laboratory		
Tumor Biopsy			X		
Blood for Biomarker Development			X		
TREATMENT					
Surgery			X		
RADIOGRAPHIC IMAGING, CLINICAL, AND HISTOLOGICAL TUMOR ASSESSMENTS					
Radiographic Imaging (CT, PET/CT, MRI)	X				X
Clinical Tumor Measurement and Response Assessment	X				X
Histological Tumor Assessment of Surgical Specimen[d]			X		

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[a] For additional information regarding the procedures performed during screening procedures and the timing of the procedures please refer to Section 7.2.1.
[b] For additional information regarding the procedures performed during treatment and the timing of the procedures please refer to Section 7.2.2.
[c] For additional information regarding the procedures performed during safety follow-up and long-term follow-up and timing of the procedures please refer to Section 7.2.3 and Section 7.2.4, respectively.
[d] Surgical specimens will be assessed for presence of viable tumor and tumor margin status for cutaneous and subcutaneous tumor; please refer to Section 7.2.2.

7.2 General Study Procedures

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

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

The following laboratory analytes in Table 4 will be assessed at various times throughout the study:

Table 4. Laboratory Analytes

Chemistry	Coagulation	Hematology	Other Labs
Sodium	PT or INR	RBC	LDH
Potassium	PTT or aPTT	Hemoglobin	Pregnancy
Chloride		Hematocrit	qPCR for talimogene laherparepvec DNA
Calcium		Platelets	HSV-1 antibody
Magnesium		WBC	$BRAF^{V600}$
Phosphorus		Differential*	Biomarkers
Uric acid		• Neutrophils	• Blood
Total protein		• Eosinophils	• Archived tumor tissue
Albumin		• Basophils	• Fresh tumor biopsy tissue
BUN		• Lymphocytes	
Creatinine		• Monocytes	
Total bilirubin			
Alkaline-phosphatase			
AST			
ALT			
Glucose			

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

All tests (except for real-time polymerase chain reaction [qPCR], HSV-1 antibody and biomarkers) are to be performed at the local laboratory and test results are to be fully and routinely recorded on the CRFs. Serine/threonine protein kinase B-Raf V600 ($BRAF^{V600}$) mutation analysis may be performed at a central laboratory. Missed tests that are not done must be reported as such on the CRFs. The qPCR, HSV-1 antibody

and biomarker tests will be performed at a central laboratory and results will not be recorded on the CRFs.

7.2.1 Screening and Randomization

The following procedures are to be completed during the screening period at time points designated in the Schedule of Assessments (Table 2 and Table 3):

- Confirmation that the Informed Consent Form has been signed
- Demographic data including sex, age or date of birth, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness.
- Medical and surgical history: The Investigator or designee will collect complete medical and surgical history. Medical history will include information on the subject's concurrent medical conditions. Record all findings on the medical history CRF.
- 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 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.
- Physical examination as per standard of care
- Documentation of concomitant medications
- ECOG performance status assessment
- Local Laboratory Assessments
  - within ≤ 28 days prior to randomization
    - hematology panel: hemoglobin, hematocrit, white blood cell (WBC) count with 5-part differential (3-part differential if 5-part unable to be performed), red blood cell (RBC) count, platelets
    - chemistry panel: sodium, potassium, chloride, calcium, magnesium, phosphorous, uric acid, total protein, albumin, blood urea nitrogen (BUN), creatinine, total bilirubin, alkaline phosphatase, AST, ALT, glucose
    - LDH
    - coagulation: PT or INR and PTT or aPTT
  - within ≤ 3 days prior to randomization
    - serum or urine pregnancy test for female subjects of childbearing potential
- Clinical tumor assessments, including clinical measurement of cutaneous, subcutaneous, and palpable nodal tumor lesions by caliper to be used as baseline assessment
- Radiographic tumor imaging (including CT scan, positron emission tomography [PET]/CT scan, magnetic resonance imaging [MRI] or ultrasound) of the chest, abdomen, pelvis, and all other sites of disease, MRI of the brain (required to be completed for all subjects), to be used as baseline imaging

- Recording of serious adverse events that occur after subject signs informed consent. Serious adverse events will be reported to Amgen within 24 hours following the investigator's knowledge of the event
- Review of inclusion and exclusion criteria
- Randomization in IVR system

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 once at the discretion of the investigator. If a subject is being rescreened, he or she may need to reconsent to the study to ensure that the IRB/IEC-approved main consent form is signed within 28 days of randomization. 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 randomized once into this study.

7.2.2 Treatment

Treatment begins when the first dose of protocol-required therapies is administered to a subject (Arm 1) or the subject undergoes surgery (Arm 2).

The following procedures will be completed during the treatment period at the times designated in the Schedule of Assessments (Table 2 and Table 3).

- 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 possible. The position selected for a subject should be the same that is used throughout the study and be documented on the vital signs CRF.
  - Arm 1: prior to talimogene laherparepvec administration on day 1 of weeks 1, 4, 8, 12, and prior to surgery
  - Arm 2: within 3 days prior to surgery
- Physical examination as per standard of care
  - Arm 1: within 3 days prior to talimogene laherparepvec administration on day 1 of week 1 and within 3 days prior to surgery, and prior to talimogene laherparepvec administration on day 1 of weeks 4 and 8
- ECOG performance status
  - Arm 1: prior to talimogene laherparepvec administration on day 1 of weeks 4 and 8 and within 3 days prior to the surgery

- Local laboratory assessments
  - Arm 1: prior to talimogene laherparepvec administration on day 1 of weeks 1, 6, 12. Screening laboratory values may be used for week 1 day 1 assessment if completed within 3 days of study treatment initiation. On treatment tests can be performed within 3 days of the planned visit. Results should be reviewed prior to the administration of study drug
    - Hematology panel: hemoglobin, hematocrit, WBC with 5-part differential (3-part differential if 5-part unable to be performed), RBC, platelet
    - Chemistry panel: sodium, potassium, chloride, calcium, magnesium, phosphorus, uric acid, total protein, albumin, BUN, creatinine, total bilirubin, alkaline phosphatase, AST, ALT, glucose

- Central laboratory assessments:
  - Blood for HSV-1 antibody serostatus
    - Arm 1: within 3 days of day 1 of week 1 (prior to administration of talimogene laherparepvec)
  - Blood for biomarker analysis
    - Arm 1: within 3 days of day 1 of week 1 (prior to administration of talimogene laherparepvec) and week 6 (prior to administration of talimogene laherparepvec) and within 3 days prior to the day of surgery
    - Arm 2: within 3 days prior to the surgery
  - Tumor biopsy for biomarker analysis
    - Arm 1: within 3 days of day 1 of week 1 (prior to talimogene laherparepvec administration) and at the time of surgery. At the time of surgery the tumor biopsy should be marked as injected lesion or non-injected lesion.
    - Arm 2: at the time of surgery
  - Swab of cold sore, vesicles and other lesions suspected to be herpetic in origin (if any) for qPCR testing of talimogene laherparepvec DNA:
    - Arm 1 - 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 to evaluate whether the talimogene laherparepvec DNA is detectable in the sample.
  - Archived formalin-fixed paraffin-embedded tumor tissue (block or unstained tumor slide) from either the primary tumor or a metastatic lesion, and the associated pathology reports, must be submitted to the central laboratory within 28 days after randomization for biomarker analyses

  - $BRAF^{V600}$ mutation testing/status may be obtained in a number of ways as listed below:
    - previously known $BRAF^{V600}$ tumor status: $BRAF^{V600}$ tumor status result, obtained from a local laboratory prior to screening for this study will be acceptable and should be available within 28 days after randomization
    - previously unknown $BRAF^{V600}$ tumor status: Archived formalin-fixed paraffin-embedded tumor tissue (block or unstained tumor slide) from either the primary tumor or a metastatic lesion (as described above) will be analyzed at a local laboratory or submitted to the central laboratory within 28 days after randomization for $BRAF^{V600}$ tumor status determination

- Radiographic tumor imaging assessments
  - Arm 1: day 1 of week 12 (± 2 weeks) or within 2 weeks prior to surgery if a subject ends talimogene laherparepvec prior to week 12
    - Radiographic imaging must include CT scan, PET/CT, MRI, or ultrasound of the chest, abdomen, and pelvis and all other sites of disease. In addition, CT scan or MRI of the brain will only be performed if symptoms or signs suggestive of CNS metastasis are present. The imaging modality selected (eg, CT or MRI) should remain constant for any individual subject.

- Clinical tumor assessments (clinical measurement of cutaneous, subcutaneous, or palpable nodal tumor measurement by caliper)
  - Arm 1: day 1 of week 12 (± 2 weeks) or within 1 week prior to surgery if a subject ends talimogene laherparepvec prior to week 12

- Response assessment per modified WHO response criteria (Appendix D)
  - Arm 1: day 1 of week 12 (± 2 weeks) or within 2 weeks prior to surgery if a subject ends talimogene laherparepvec prior to week 12

- Histological tumor assessment of the surgical specimens. Surgical specimens will be assessed for presence of viable tumor and tumor margin status for cutaneous and subcutaneous tumor.
  - Tumor-free margins (negative margins, R0) resection is defined by pathologist as absence of ink on the tumor. All other resections of viable tumor are described as tumor positive margins resections, and are defined as
    - R1 resection - complete resection with no grossly visible tumor left behind as defined by the surgeon, or
    - R2 resection - partial resection with grossly visible tumor left behind as defined by the surgeon.
  - A pathological complete response (pCR) in Arm 1 is defined as no evidence of viable tumor cells on complete pathological evaluation of the surgical specimen per institutional standards of care

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

- Documentation of concomitant medications at each visit
- Arm 1 - Reporting pregnancy in a female subject or a female partner of a male subject while the subject is taking talimogene laherparepvec treatment and through 3 months after end of treatment (Section 9.3)
- Arm 1 - Reporting lactation case in a female subject while the subject is taking talimogene laherparepvec treatment and through 3 months after end of treatment (Section 9.3)
- Talimogene laherparepvec administration
  - Arm 1: day 1 of weeks 1, 4, 6, 8, 10, and 12 or until all injectable tumors have disappeared, intolerance of study treatment, whichever occurs first. Subjects who experience growth in existing tumors or the appearance of new tumors will be allowed to remain on talimogene laherparepvec treatment until week 12 of therapy unless, in the opinion of the investigator and in consultation with the sponsor's medical monitor, immediate surgical resection or any other treatment for melanoma is warranted.
- Surgery
  - Arm 1: For subjects who complete 12 weeks of talimogene laherparepvec treatment, surgical resection of melanoma lesion(s) will be performed at any time during weeks 13 to 18. Subjects who stop talimogene laherparepvec prior to week 12 due to disappearance of all injectable tumor lesions, intolerance to talimogene laherparepvec, or any other reason will undergo surgical resection of melanoma lesion(s) or tissue where melanoma was present before CR within 1 to 6 weeks after the last dose of talimogene laherparepvec.
    Refer to Appendix F for surgery guidelines.
  - Arm 2: Surgical resection of melanoma tumor lesion(s) will be performed after randomization any time during weeks 1 to 6. Refer to Appendix F for surgery guidelines.

7.2.3 Safety Follow-up Visit

Upon permanent discontinuation from the study treatment for any reason, the following procedures will be performed 30 (+15) days after the surgery:

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

- Central laboratory assessments:
  - Arm 1: swabs of cold sores, vesicles, and other lesions suspected to be herpetic in origin (if any) for qPCR testing:
    - Subject should return to clinic within 3 days of the occurrence of a reportable lesion suspected to be herpetic in origin such as cold sores or vesicles. The lesion should be evaluated by the investigator and swabbed if HSV infection is suspected. A qPCR analysis will be performed on the swab sample to evaluate whether the talimogene laherparepvec DNA is detectable in the sample.
- Recording of adverse events
- Recording of serious adverse events. Serious adverse events will be reported to Amgen within 24 hours following the investigator's knowledge of the event.
- Documentation of concomitant medications
- Documentation of subsequent anticancer therapy for melanoma (including local, regional, or systemic therapy)
- Surgical safety evaluation (including wound closure, drain time and post operational infection)
- Arm 1 - Reporting pregnancy in a female subject or a female partner of a male subject through 3 months after end of talimogene laherparepvec treatment (Section 9.3)
- Arm 1 - Reporting lactation case in a female subject through 3 months after end of talimogene laherparepvec treatment (Section 9.3)

7.2.4 Long-term Follow-up

All randomized subjects will be contacted by telephone, or clinic visit, to assess survival status, collect adverse events deemed by the investigator to be potentially related to talimogene laherparepvec (Arm 1 only), and, if applicable, commencement of any subsequent anticancer melanoma therapy. Follow-up will occur every 3 months (±30 days) for 3 years following the safety follow-up visit and then every 6 months (±30 days) until death, subject withdraws full consent, or up to 5 years after the last subject is randomized, which is first.

Radiographic tumor imaging, clinical tumor assessments, and tumor response assessments, will be performed as documented in Section 7.2.2 every 3 months (±30 days) for 3 years following the safety follow-up visit and then every 6 months (±30 days) until distant disease recurrence, death, subject withdraws full consent, or up to 5 years after the last subject is randomized, whichever is first. Local and regional recurrences will be reported until appearance of distant recurrence, or end of study, whichever is first. Local recurrence is defined as histologically or cytologically confirmed reappearance of melanoma in the area of up to 2 cm from the scar from the surgical

excision or at the edge of the skin graft if that was used for closure. Regional recurrence (excludes local recurrence) is defined as histologically, cytologically, or radiographically confirmed reappearance of melanoma in the regional lymph node basin. New in-transit melanoma metastases in the regional lymphatic drainage will be reported as regional recurrence. Histological or cytological confirmation of new in-transit metastases is recommended but is not required. Distant metastases exclude local and regional recurrence and will include distant cutaneous/subcutaneous metastases, distant nodal metastases, or visceral, central nervous system, brain, or bone metastases.

After the long-term follow-up period of this study has ended, subjects randomized to Arm 1 who received at least a single dose of talimogene laherparepvec and who end the study for any reason other than death or withdrawal of full consent will be followed for survival under an ongoing separate registry protocol (Study 20120139) that is in place for the long-term follow-up of all subjects treated with talimogene laherparepvec in clinical trials. The registry protocol will also monitor for late and long-term adverse events thought to be potentially related to talimogene laherparepvec and use of subsequent anticancer therapy for melanoma. Subjects who after the long-term follow-up period of this study (20110266) will elect to participate in the registry study must sign new informed consent form before any registry protocol-specific activities.

7.2.5 Reporting Exposure to Talimogene Laherparepvec

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

7.3 Biomarker Development

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

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

7.3.1 Blood Samples

Blood samples are to be collected for biomarker development at time points designated in the Schedule of Assessments (Table 2 and Table 3) and as described in Section 7.2.2.

Blood samples (both cells and plasma) will be analyzed for changes in the immune system before and during treatment that correlate with clinical response. Tumor antigen-specific cytotoxic T cells will be enumerated in blood samples by assays which count T cells that bind or secrete cytokines in response to tumor antigen specific peptides such as the enzyme-linked immunosorbent spot (ELISPOT) or tetramer assay. Changes in circulating immune cells will be characterized by flow cytometry to enumerate the number of immune cell subsets such as T cells, B cells and NK cells. T cell subsets will also be characterized for activation markers such as HLA-DR and CD25. Additional assays which may be performed on blood samples include measuring antibody responses to melanoma antigens, changes in circulating cytokine levels before and during treatment, and RNA transcript profiling of circulating blood cells.

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

7.3.2 Tumor Tissue Samples

Archived Tumor Tissue Sample:

A block of formalin-fixed paraffin-embedded tumor tissue collected prior to the study is to be sent to the central laboratory along with the corresponding pathology report as described in the Schedule of Assessments (Table 2 and Table 3) and in Section 7.2.2.

The tumor block is to be carefully selected by a pathologist or a skilled experienced histology associate to include generous tumor tissue using the Pathology Report as a guide. In the event that multiple tumor blocks with generous tumor tissue are available, the most recent block should be submitted. In lieu of a block, approximately 20 unstained sections on charged slides from the same block can be submitted. Analyses of tumor-specific mutations or epigenetic changes may be performed (eg, somatic mutations) on tumor tissues.

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

Tumor Biopsy Samples:

On-study biopsies will be collected, as described in the Schedule of Assessments (Table 2 and Table 3) and in Section 7.2.2, to characterize the mechanism of systemic action of talimogene laherparepvec. Refer to the Laboratory Manual for specific instructions on tumor biopsy procedures.

Immunohistochemistry at a central laboratory will be used to measure the number of infiltrating CD8+ T cells in tumor biopsy samples collected before and after treatment as well as in archival tumor samples. Tissue slides will be stained for CD8+ cells and scanned to create a digital image. Image analysis software will be used to exclude areas of adjacent normal tissue, necrotic tissue and large blood vessels and to define the region of interested which will be measured in square millimeters (mm2). Within the region of interest, the image analysis software will measure the number of CD8+ T cells and report the number of CD8+ T cells per square millimeter (#CD8+ cells/mm2). In addition to CD8+ cells, a variety of other tumor infiltrating immune cell markers may be explored by immunohistochemistry such as CTLA-4, FoxP3, PD-1, PD-L1, IDO, granzyme, and others. The tumor samples will also be analyzed for mutations or other changes within the PKR pathway, that could make tumor cells more susceptible to talimogene laherparepvec viral replication.

7.4 Pharmacogenetic Studies

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

7.5 Sample Storage and Destruction

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

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

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

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

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

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information,

discoveries, or derivative materials gained or produced from the sample.

See Section 11.3 for subject confidentiality.

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw

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

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments (Table 2 and Table 3) and collection of data, including endpoints and adverse events. The investigator must document the change to the Schedule of Assessments (Table 2 and Table 3) 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, publicly 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.

8.2.1 Reasons for Removal From Treatment

Reasons for removal from protocol-required investigational product 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
- protocol-specified criteria (see Sections 6.2.1.2)
- pregnancy
- death
- lost to follow-up
- decision by sponsor (other than subject request, safety concern, lost to follow-up)
- disease progression requiring immediate surgical resection

8.2.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

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

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Adverse Events

9.1.1 Definition of Adverse Events

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

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

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

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

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

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

9.1.2 Definition of Serious Adverse Events

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

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

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

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

The criteria for grade 4 in the CTCAE grading scale differs from the regulatory criteria for serious adverse events. It is left to the investigator's judgment to report these grade 4 abnormalities as serious adverse events.

9.2 Reporting of Adverse Events

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

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after randomization through the safety follow-up visit (ie, 30 [+15] days after surgery) are reported using the applicable CRF (eg, Adverse Event Summary).

The investigator must assign the following adverse event attributes:

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

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

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

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

clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

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

9.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through the safety follow-up (ie, 30 [+15] days after surgery) are recorded in the subject's medical record and are submitted to Amgen. All serious adverse events must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the applicable CRF.

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

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

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

The investigator must assess whether the serious adverse event is possibly related to any study-mandated activity or procedure. This relationship is indicated by a "yes" or

"no" response to the question: "Is there a reasonable possibility that the event may have been caused by a study activity/procedure"?

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

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

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

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

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

9.3 Pregnancy and Lactation Reporting

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

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

The pregnancy should be reported to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C).

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

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

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

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 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 (+15) days after the last dose of talimogene laherparepvec.

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

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

10.1.1.1 Primary Endpoint

- Recurrence-free Survival (RFS): RFS is defined as time from randomization to the date of the first of local, regional, or distant recurrence of melanoma or death due to any cause.

10.1.1.2 Secondary Endpoint

Efficacy Endpoints:

- **1-year,** 2-year, 3-year, 5-year RFS: The Kaplan-Meier (K-M) estimate of RFS rate at **1-year,** 2 years, 3 years and 5 years
- Rate of histopathology tumor-free margin (R0) surgical resection
- Rate of pathological complete response (pCR)
- Local recurrence-free survival (LRFS): Time from randomization to the date of the first of local disease recurrence or death due to any cause. Local recurrence is defined as histologically or cytologically confirmed reappearance of melanoma in the in the area of up to 2 cm from the scar from the surgical excision or at the edge of the skin graft if that was used for closure
- Regional recurrence-free survival (RRFS): Time from randomization to the date of the first of regional disease recurrence or death due to any cause. Regional recurrence excludes local recurrence and is defined as histologically, cytologically, or radiographically confirmed reappearance of melanoma in the regional lymph node basin. New in-transit melanoma metastases in the regional lymphatic drainage will be reported as regional recurrence. Histological or cytological confirmation of new in-transit metastases is recommended but is not required.
- Distant metastases free survival (DMFS): Time from randomization to the date of the first of distant metastases or death due to any cause. Distant metastases exclude local and regional recurrence and will include distant cutaneous/subcutaneous metastases, distant nodal metastases, or visceral, central nervous system, brain, or bone metastases.
- Overall survival (OS): Time from randomization to death due to any cause
- **1-year,** 2-year, 3-year and 5-year survival: The Kaplan-Meier (K-M) estimate of the survival rate at **1-year,** 2 years, 3 years and 5 years
- Overall tumor response and tumor response in injected and uninjected lesions (Arm 1 only): The tumor response is evaluated up to the surgical resection. The overall tumor response is per the modified WHO (Appendix D). For tumor response in injected and uninjected lesions both subject-level and lesion-level response will be assessed. The subject-level injected and uninjected responses will be based on the tumor burden of only injected index lesions including injected new measurable lesions, or the tumor burden of only uninjected index lesions including uninjected new measurable lesions, respectively. The lesion-level response will evaluate the change of the area of each individual lesion. For the tumor response based on the tumor burden of a subset of lesions (injected/uninjected lesions) or individual lesions, a response is achieved if the percentage of tumor burden reduction from baseline is at least 50%. The related endpoints, such as time to response, may also be evaluated if appropriate.

Safety Endpoints:

- Subject incidence of treatment-emergent and treatment-related adverse events

10.1.1.3 Exploratory Endpoints

- Correlation between baseline intratumoral CD8+ cell density and clinical outcomes
- Correlation between changes in an intratumoral CD8+ cell density during talimogene laherparepvec treatment and clinical outcomes
- Correlation between the changes in the population of tumor-specific cytotoxic T-cells during treatment and clinical outcomes
- Assessment of blood and tumor for potential biomarkers which correlate with or predict clinical outcomes to talimogene laherparepvec

10.1.2 Analysis Sets

Intent to Treat Analysis Set

The primary analysis of all efficacy endpoints of the study will be conducted on the intent to treat analysis set defined as all randomized subjects who were randomized to either treatment arm. All subjects will be analyzed according to their treatment randomization.

Safety Analysis Set

The safety analysis set will include all subjects who received talimogene laherparepvec or surgical resection of melanoma tumor lesion(s). The safety analyses will be performed by treatment received.

Efficacy Analysis Set

The efficacy analysis set will include all subjects in Arm 1 who received at least one dose of talimogene laherparepvec and surgical resection of melanoma tumor lesion(s) and all the subjects in Arm 2 who received surgical resection of melanoma tumor lesion(s). In addition, all subjects in the efficacy analysis set must have achieved histopathologic tumor-free margin (R0) status after surgery and should not have any important protocol deviations which may affect the efficacy endpoints. The efficacy analysis set may be used for sensitivity analysis of efficacy endpoints if needed.

10.1.3 Covariates and Subgroups

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

- Region, if applicable (USA or non-USA)
- Age at baseline: < 50, ≥ 50; < 65, ≥ 65; < 75, ≥ 75 years
- Number of measurable tumors at baseline
- Presence of uninjected tumors at baseline and during the treatment: yes vs no
- The sum of the products of the two largest perpendicular diameters of baseline measurable lesions

- Baseline absolute lymphocyte count: ≤ 1000 vs > 1000
- Recurrent disease ≥1 year from primary diagnosis vs recurrent disease <1 year from primary diagnosis vs no prior melanoma

10.2 Sample Size Considerations

All analyses will be descriptive with no formal hypothesis testing. The primary objective of the study is to estimate the treatment effect, as measured by the hazard ratio of RFS, of talimogene laherparepvec neoadjuvant therapy followed by surgery (Arm 1) compared to surgery alone (Arm 2) in subjects with resectable, stage IIIB to IVM1a melanoma.

Approximately 150 subjects will be randomized 1:1 to receive Arm 1 vs Arm 2 stratified by: (i) disease stage (IIIB nodal vs IIIB in-transit vs IIIC nodal vs IIIC in-transit with nodal vs IVM1a), and (ii) planned adjuvant therapy (adjuvant systemic therapy [eg, INFα, ipilimumab] with or without radiotherapy vs radiotherapy without adjuvant systemic therapy vs none).

Primary efficacy analysis of RFS will be based on the Intent to Treat Analysis Set. An overall between-group difference in RFS will be evaluated with a log-rank test and corresponding proportional hazard model without stratification. The Kaplan-Meier (KM) method will be used to estimate **1-year,** 2-year, 3-year, 5-year, and overall RFS. Subjects who are not confirmed to be disease-free post-surgery (ie, who do not have an R0 surgical outcome) or who withdraw prior to surgery will be considered a failure a day after randomization for RFS.

The primary analysis for the primary endpoint will occur at the later time of either the occurrence of approximately 64 events (local, regional, or distant recurrence of melanoma or death) or approximately 2 years after the end of randomization. An 80% CI will be estimated for the hazard ratio of RFS. In addition, an 80% CI will also be estimated for the between-arm difference (Arm 2 – Arm 1) in 2-year RFS, ie, Δ 2-year RFS. It is assumed that: (i) RFS is exponential over the first 2 years, (ii) the 2-year RFS for Arm 1 is about 0.60 (Eggermont et al, 2008), and that there will be a 10% exponential probability of drop-out by the primary analysis. Simulations were used to evaluate the following parameters assuming possible true Δ 2-year RFS values of 0.05, 0.10, and 0.15: (i) the average Δ 2-year RFS 80% CI and its width, (ii) the probability that the Δ 2-year RFS 80% CI is above 0, and (iii) the average number of events at the primary analysis. The possible true Δ 2-year RFS values were translated to a RFS hazard ratio (HR) (Arm 2 relative to Arm 1) and the HR 80% CI and the probability of it being

< 1 were calculated based on the simulated average number of events. The average width of the Δ 2-year RFS 80% CI was 0.20 (Table 5).

Table 5. Study Design Characteristics

2-year RFS			RFS	Ave. Δ 80% CI			Prob. Δ 80%	Ave. HR 80% CI		Prob. HR 80%	Ave.
Arm 1	Arm 2	Δ	HR	LL	UL	Width	CI > 0	LL	UL	CI < 1	Events
0.70	0.60	0.100	0.70	0.00	0.20	0.20	0.51	0.51	0.96	0.56	64
0.725		0.125	0.63	0.02	0.22	0.20	0.62	0.45	0.87	0.71	62
0.750		0.150	0.56	0.05	0.25	0.20	0.74	0.40	0.78	0.83	60

RFS, Recurrence-free Survival; HR, Hazard Ratio; CI, Confidence Interval; LL, Lower Limit; UL, Upper Limit; Ave, Average; Prob., Probability; Δ = Arm 2 – Arm 1 2-year RFS

10.3 Access to Individual Subject Treatment Assignments by Amgen or Designees

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

10.4 Planned Analyses

10.4.1 Interim Analyses

Two interim analyses with no formal stopping rules are planned to evaluate safety when approximately 40 and 75 subjects randomized to talimogene laherparepvec have had the opportunity to complete the safety follow-up visit. A Data Review Team (DRT) independent of the talimogene laherparepvec product team will review the first interim analysis (see Section 10.4.2). The DRT will also review some efficacy endpoints (eg, R0 resection rate, pCR rate, response to neoadjuvant treatment).

The talimogene laherparepvec product team will review the second interim analysis because it will occur after all subjects have been already treated, have completed safety follow-up, and no additional interventions that may influence safety or efficacy of the investigational product are planned after this time point. The talimogene laherparepvec product team will also review some efficacy endpoints (eg, R0 resection rate, pCR rate, response to neoadjuvant treatment).

An additional third interim analysis with no formal stopping rule is planned to evaluate RFS approximately 1 year after the end of randomization. This analysis will be conducted by the Amgen study team.

Ad hoc analyses for safety or some efficacy endpoints (eg, response to neoadjuvant treatment, R0 resection rate, pCR rate) may be conducted before the planned primary and/or final analyses if interim data are required for submission to regulatory authorities. These ad hoc analyses will be executed by the talimogene laherparepvec product team.

10.4.2 Data Review Team (DRT)

The DRT will consist of one Amgen biostatistician and two Amgen clinicians *(*one from Clinical Development and one from Global Safety) who collectively have experience in oncology clinical research and in the conduct and monitoring of randomized clinical trials. In addition, the DRT may include one or more external clinical expert(s) (eg, a surgical oncologist in melanoma) not directly involved in the conduct of the study. The DRT will be supported by a statistician internal to Amgen but independent of the talimogene laherparepvec product team. The DRT will review unblinded safety data at the first interim analysis. This independent DRT will be governed by a study-specific DRT charter.

10.4.3 Primary Analysis

The primary analyses for RFS will occur at the later time of either the occurrence of approximately 64 events (local, regional, or distant recurrence of melanoma or death) or approximately 2 years after end of randomization. The primary analysis for certain secondary endpoints will be performed using the data from the second interim analysis (eg, response to neoadjuvant treatment, R0 resection, pCR, exploratory correlative endpoints related to neoadjuvant treatment outcomes, and safety).

10.4.4 Final Analysis

The final analyses will occur approximately 5 years after end of randomization.

10.4.5 Additional Analysis

An additional analysis will also occur approximately 3 years after end of randomization.

10.5 Planned Methods of Analysis

10.5.1 General Considerations

All analyses will be descriptive with no formal hypothesis testing.

In principle, mean, standard deviation, median, first and third quartiles, minimum and maximum will be calculated for continuous variables; frequency and percent will be

calculated for binary and categorical variables. Graphical summaries of the data may also be presented.

Analyses of tumor tissue or serum biomarkers may be performed after collection of all samples during the conduct of the study and therefore may be reported after the primary analysis of efficacy endpoint.

The primary analysis for efficacy endpoints will be performed on the Intent to Treat Analysis Set by randomized treatment. Some of the analysis will be repeated on the Efficacy Analysis Set by treatment actually received. Safety analyses will be conducted on the Safety Analysis Set.

10.5.2 Primary Efficacy Endpoint

An overall between-group difference in RFS will be evaluated with a log-rank test and corresponding proportional hazards model without stratification. A log-rank test and proportional hazards model with stratification by the two randomization factors will be also conducted. If warranted due to actual adjuvant therapy, these analyses will be repeated stratifying on actual rather than planned adjuvant therapy and/or adjuvant therapy containing selected types of immunotherapy. Multivariate proportional hazards models may be used to explore the prognostic and/or predictive value of baseline factors.

10.5.3 Secondary Efficacy Endpoints

KM estimates will be calculated for RFS, LRFS, RRFS, DMFS, OS landmarks (**1-,** 2-, 3- and 5-year rates) and quartiles. Greenwood's formula (Kalbfleisch and Prentice, 1980) for standard error will be used to calculate CIs for each group and between-group differences in landmark KM rate estimates. CIs for quartiles of each group will be estimated per Brookmeyer and Crowley (Brookmeyer and Crowley, 1982) and bootstrap methods will be used to estimate CIs for between-group differences. For each group the equal-precision band method will be used to calculate a simultaneous confidence band for RFS, LRFS, RRFS, and DMFS over the interval from **1** to 5 years (Nair, 1984). An overall between-group difference in RFS, LRFS, RRFS, DMFS, and OS will be evaluated with a log-rank test and corresponding proportional hazard model with or without stratification by the two randomization factors. If warranted due to actual adjuvant therapy, these analyses will be repeated stratifying on actual rather than planned adjuvant therapy and/or adjuvant therapy containing selected types of immunotherapy. Multivariate proportional hazards models may be used to explore the prognostic and/or predictive value of baseline factors.

The Clopper-Pearson method (Clopper and Pearson, 1934) will be used to calculate exact CIs for binary endpoints (eg, overall tumor response, response in injected and uninjected lesions, R0 rate, pCR). Wilson's score method with continuity correction (Newcombe, 1998) will be used to calculate an approximate exact CI for between-group differences in binary rates. Multivariate logistic models may be used to explore the prognostic and/or predictive value of baseline factors.

10.5.4 Safety Endpoints

Subject incidence rates of treatment-emergent adverse events (including all adverse events, grade ≥ 3 adverse events, fatal adverse events, serious adverse events, adverse events of interest and events requiring the discontinuation of study drug, local effects on the tumor [ie, pain, inflammation and ulceration]) will be summarized. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code adverse events to a system organ class (SOC) and a preferred term within the SOC. The CTCAE version 3.0 will be used to grade severity of adverse events. In addition, clinically significant laboratory changes and clinically significant changes in vital signs will be summarized with descriptive statistics. Summary statistics will also be provided for concomitant medications, adjuvant therapy, dose delay, study drug discontinuation, overall exposure, and changes in ECOG performance status. Tables and/or narratives of deaths through 30 days after the latter of the last dose of talimogene laherparepvec or surgery will be provided. The incidence of subjects with herpetic lesions found to be positive for talimogene laherparepvec DNA per qPCR in swab samples collected from lesions suspected to be herpetic in origin and the rate of positive lesions (if any) will be calculated. 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.

When appropriate, the safety data during the talimogene laherparepvec monotherapy period before surgical resection will be summarized separately from the safety data after surgical section, which will be summarized by treatment actually received.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Amgen clinical study manager to the

investigator. The written informed consent document is to be prepared in the language(s) of the potential patient population.

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

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

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

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

11.2 Independent Ethics Committee

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

The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent

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

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

11.3 Subject Confidentiality

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

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

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

11.4 Investigator Signatory Obligations

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

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

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

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

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

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

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

12.2 Study Documentation and Archive

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

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

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

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 IRB/IEC and Amgen
- Investigational product-related correspondence including Proof of Receipts, Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable.

In addition, all original source documents supporting entries in the 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 function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study-related records will occur to evaluate

the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the CRFs must be maintained and readily available.
- Updates to CRFs will be automatically documented through the software's "audit trail".
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review is performed on subject data received at Amgen. During this review, subject data are checked for consistency, omissions, and any apparent discrepancies. In addition, the data are reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, and/or 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 electronic data capture study. This signature indicates that investigator inspected or reviewed the data on the CRF, and 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 and Table 3), 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

CRFs must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language. Consult the country-specific language requirements.

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

12.6 Publication Policy

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

Authorship of any publications resulting from this study will be determined on the basis of the Recommendations for Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (International Committee of Medical Journal Editors).

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) is available at the following location:

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

Appendix B. Sample Serious Adverse Event Report Form

Completion Instructions - Electronic Adverse Event Contingency Report Form
(For use for clinical trial studies using Electronic Data Capture [EDC])

NOTE: This form is to be used under restricted conditions outlined on page 1 below. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

General Instructions

The protocol will provide instruction on what types of events to report for the study. This form is to be used ONLY to report events that must be captured in the Amgen safety database. *Indicates a mandatory field.

Types of Events to be reported on this form

- **Serious Adverse Events (regardless of causal relationship to IP)**

1. **Site Information**

   Site Number* – Enter your assigned site number for this study

   Investigator*, Country*, Reporter*, Phone No., and Fax No. – Enter information requested

2. **Subject Information**

   Subject ID Number* – Enter the entire number assigned to the subject

   Age at event onset, Sex, and Race – Enter the subject's demographic information

   End of Study date – If the subject has already completed the study or terminated the study early, enter the End of Study date

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

3. **Serious Adverse Event**

   Provide the date the Investigator became aware of this Information

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

   Date Started* – Enter date the adverse event first started (not the date on which the event met serious criteria)rather than the date of diagnosis or hospitalizion. . **This is a mandatory field.**

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

   If event occurred before the first dose of Investigational Product (IP)/drug under study, add a check mark in the corresponding box.

   Is event serious?* – Indicate Yes or No. This is a mandatory field.

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

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

   Relationship to Amgen device* – The Investigator must determine and enter the relationship of the event to the Amgen device (e.g. prefilled syringe, auto-injector) at the time the event is initially reported. **If the study involves an Amgen device, this is a mandatory field. This question does not apply to non-Amgen devices used in the study (e.g. heating pads, infusion pumps)**

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

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

4. **Hospitalization**

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

Completion Instructions - Electronic Adverse Event Contingency Report Form (for use for Studies using Electronic Data Capture [EDC])

Note, this form is to be used under restricted conditions outlined on page 1 of the form. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

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

5. **IP Administration including Lot # and Serial # when known / available.**
   Blinded or open-label – If applicable, indicate whether the investigational product is blinded or open-label
   Initial Start Date – Enter date the product was first administered, regardless of dose.
   Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.
   Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.
   Action Taken with Product – Enter the status of the product administration.
6. **Concomitant Medications**
   Indicate if there are any medications.
   Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.
   Co-suspect – Indicate if the medication is co-suspect in the event
   Continuing – Indicate if the subject is still taking the medication
   Event Treatment – Indicate if the medication was used to treat the event
7. **Relevant Medical History**
   Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.
8. **Relevant Laboratory Tests**
   Indicate if there are any relevant laboratory values.
   For each test type, enter the test name, units, date the test was run and the results.
9. **Other Relevant Tests**
   Indicate if there are any tests, including any diagnostics or procedures.
   For each test type, enter the date, name, results and units (if applicable).

At the top of Page 3, provide your Site Number and the Subject ID Number in the designated section.

10. **Case Description**
    Describe Event – Enter summary of the event. Provide narrative details of the events listed in section 3. Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in section 6). If necessary, provide additional pages to Amgen.

Complete the signature section at the bottom of page 3 and fax the form to Amgen. *If the reporter is not the investigator, designee must be identified on the Delegation of Authority form.*

AMGEN Study 20110266 Talimogene Laherparepvec	**Electronic Serious 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

<<For completion by COM 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. SERIOUS ADVERSE EVENT

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

Serious 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 eeath. 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	**Is event serious?**	**If serious, enter Serious Criteria code** *(see codes below)*	**Relationship** Is there a reasonable possibility that theEvent may have been caused by IP or an Amgen device used to administer the IP?								**Outcome of Event** ·Resolved ·Not resolved ·Fatal ·Unknown	Check only if event is related to study procedure eg, biopsy
						T-Vec		Device		<IP/device>		<IP/device>			
						No✓	Yes✓	No✓	Yes✓	No✓	Yes✓	No✓	Yes✓		
				☐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

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

		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 #**
IP/Amgen Device:								
Talimogene Laherparepvec	☐blinded ☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<<IP/Device>>	☐blinded ☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable /

AMGEN Study 20110266 Talimogene Laherparepvec	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

								Unknown

	Site Number	Subject ID Number	

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

AMGEN Study 20110266 Talimogene Laherparepvec	**Electronic Serious 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

Appendix C. Pregnancy and Lactation Notification Worksheets

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: _____

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Pregnancy Information

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

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

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

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

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

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

****

Effective Date: March 27, 2011

Page **1** of **1**

Print Form

AMGEN® Lactation Notification Worksheet

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

1. Case Administrative Information

Protocol/Study Number: _____

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

****

Effective Date: 03 April 2012, version 2.

Page **1** of **1**

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

A modified version of the World Health Organization (WHO) response criteria (WHO handbook for reporting results of cancer treatment, 1979) will be employed in this study. Because cutaneous melanoma lesions may be irregularly shaped, WHO criteria using longest perpendicular diameters rather than Response Evaluation Criteria in Solid Tumors (RECIST) using single dimension measurement are preferred for evaluating tumor response.

Method of Measurement of Melanoma Tumor Lesions

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

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

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

Positron Emission Tomography (PET)/CT Scans: If a combined PET/CT scan is performed at the discretion of the investigator, the CT portion of that exam should not be substituted for the dedicated CT exams required by this protocol. The PET portion of the

CT may introduce additional data which may bias the investigator assessment of response if it is not routinely or serially performed. However, if the investigator or the site radiologist can document that the CT performed as part of a PET/CT is of identical diagnostic quality to a diagnostic CT (with intravenous and oral contrast) then the CT portion of the PET/CT can be used for tumor measurements.

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

Measureable Disease

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

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

Definitions of Measurable and Nonmeasurable:

At baseline (the last assessment on or prior to the first dose of talimogene laherparepvec [Arm 1] or prior to surgery [Arm 2]), tumor lesions will be categorized as follows:

- measurable or
- nonmeasurable but evaluable

Measurable Lesions:

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

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

Nonmeasurable Lesions:

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

Lesions with Prior Local Treatment:

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

Coalescing or Splitting Lesions:

Coalescing lesions: When two or more lesions merge and at least one is an index lesion, the largest index lesion prior to merging should be measured and reported during the tumor response assessment. All other merged lesions should be reported as 0 mm x 0 mm (for lesions previously reported as Index or New Measurable Lesions) or absent (for lesions previously reported as Non-Index or New Non-Measurable Lesions). If two or more non-index lesions merge, the apparently larger lesion should be reported as present, and smaller lesion(-s) should be reported as absent. The indication that the lesion coalesced with the specified lesion(-s) should be provided for each merged lesion.

Splitting lesions: When an index lesion splits into two or more lesions the largest measurable part of the split lesion will be measured for the current assessment with the indication that the lesion split from the specified lesion, and followed for future assessments. The remaining lesions will be measured as new lesions with an indication that the lesion split from the specified lesion. In this case, appearance of a new lesion from a previous lesion that split will not be considered disease progression solely due to appearance of a new lesion (may be considered 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).

When an non-index lesion splits into two or more lesions, the apparently larger lesion will be reported as a non-index lesion. All other smaller lesions will be reported as new non-index lesions with an indication that the lesion split from the specified lesion. In this case, appearance of a new lesion from a previous lesion that split will not be considered

disease progression solely due to appearance of a new lesion (may be considered disease progression due to > 25% increase in the sum of the products of the perpendicular diameters of all index tumors since baseline, or the unequivocal appearance of a new tumor, other than the product of the split tumor, since the last response assessment time point).

Measureable Tumor Assessment/Burden:

Baseline Documentation of "Index Lesions":

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

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 largest perpendicular diameters of all index lesions will be calculated and reported.

If a subject has multiple small superficial cutaneous melanoma lesions at baseline (each lesions is less than 10 mm in at least 2 dimensions) which in aggregate have a total diameter of ≥ 10 mm in at least 2 dimensions, up to 10 largest lesions that were included in this measurement will be reported as "Index Lesions", and the sum of the products of the two largest perpendicular diameters of these lesions will be calculated and reported for tumor response assessments.

Baseline Documentation of "Nonindex Lesions":

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

Follow-up "Index Lesions":

At each subsequent tumor assessment, the sum of the products of the two largest perpendicular diameters 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".

Follow-up "New Lesions":

At tumor assessment, if new measurable lesions have appeared they should be added to sum of the products of the two largest perpendicular diameters of the index lesions to provide the total tumor burden. For nonmeasurable new lesion they should be followed as nonindex lesion as "present", "absent", or in rare cases "unequivocal progression". If a new lesion(s) that appears in between scheduled tumor response assessments disappear(s) before the next scheduled assessment, there is no need to include this lesion for tumor response evaluation.

Response Criteria

Evaluation of Objective Response:

The subject response will be assessed based on the response of the index lesions and nonindex lesion, and presence or absence of new lesions. Confirmation of complete or partial response is not required. The overall response is derived from time point response assessments as described in Table 1, Table 2, and Table 3.

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

Complete Response (CR):	Complete disappearance of all index lesions, including any new measurable tumor lesions which might have appeared.
Partial Response (PR):	Achieving a 50% or greater reduction in the sum of the products of the two largest perpendicular diameters of all index lesions and new measurable lesions, if applicable, at the time of assessment as compared to the sum of the products of the perpendicular diameters of all index lesions at baseline.
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 measurable lesion since the last response assessment time point.
Stable Disease (SD):	Neither sufficient tumor shrinkage of index lesion to qualify for response (PR or CR) nor sufficient tumor increase of index lesion to qualify for PD.
Unable to Evaluate (UE):	Any index lesion present at baseline which was not assessed or was unable to be evaluated leading to an inability to determine the status of that particular tumor for that time point.
Not Done (ND)	Radiographic image or clinical measurement were not performed at this time point to evaluate the index lesions

Table 2. Definition of Nonindex Lesion Tumor Response Including New Nonmeasurable Lesions

Complete Response (CR):	Disappearance of all nonindex lesions, including any new nonmeasurable tumor lesions which might have appeared.
Incomplete Response/Stable Disease (SD):	Persistence of one or more nonindex tumor(s).
Disease Progression (PD):	Unequivocal progression of one or more nonindex lesions or the unequivocal appearance of a new nonmeasurable tumor lesion since the last response assessment time point
Unable to Evaluate (UE):	Any nonindex lesion present at baseline which was not assessed or was unable to be evaluated leading to an inability to determine the status of that particular tumor for that time point.
Not Applicable (NA)	No nonindex lesions were identified at baseline
Not Done (ND)	Radiographic image or clinical measurement were not performed at this time point to evaluate the nonindex lesions

CR = complete response; SD = stable disease; PD = disease progression; UE = unable to evaluate; NA = not applicable; ND = not done.

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

Index Lesion Response Including New Measurable Lesions	Nonindex Lesion Response Including New Nonmeasurable Lesions	Overall Response
CR	CR	CR
	SD	PR
	PD	PD
	NA	CR
	UE/ND	UE
PR	CR/SD	PR
	PD	PD
	NA	PR
	UE/ND	UE
SD	CR	SD
	SD	SD
	PD	PD
	NA	SD
	UE/ND	UE
PD	Any	PD
UE/ND	CR/SD/ NA/UE/ND	UE
	PD	PD

CR = complete response; PR = partial response; SD = stable disease; PD = disease progression; UE = unable to evaluate; NA = not applicable; ND = not done.

Appendix E. Eastern Cooperative Oncology Group Performance Status Scale

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

Appendix F. Surgery Guidelines

The decision to perform surgery on subjects with stage IIIB, IIIC or IV M1a melanoma (dermal, subcutaneous or non-regional lymph node metastases) is a complex clinical decision making process that must be based on good clinical judgment that may include consulting with other relevant medical specialities, and considering patient's preferences. Eligible subjects for surgical resection must have metastatic disease that in the judgment of the investigator is deemed completely surgically resectable Eligible subjects may either present with a primary melanoma and evidence of concurrent dermal, subcutaneous or clinically palpable lymph node metastasis, or may have previously had a primary melanoma and subsequently develop recurrence. Subjects who present with metastasis from an unknown primary melanoma are also eligible to participate.

1) Definition of IIIB or IIIC Metastasis: Eligible subjects with stage IIIB or IIIC melanoma have histopathologically confirmed melanoma metastasis in:

   a) the dermis or subcutaneous tissue at, or close to the site of a primary cutaneous melanoma, and/or

   b) the lymphatic channels (satellite, in-transit, or intralymphatic metastasis) draining a primary cutaneous melanoma site, and/or

   c) the regional lymph nodes draining a primary cutaneous melanoma site

2) Definition of IVM1a Metastasis: IVM1a means metastasis to distant skin, subcutaneous tissues, or lymph nodes. Subjects eligible for the protocol must have melanoma metastasis to a skin or soft tissue site beyond the potential lymph drainage basins of the primary site, or to lymph nodes beyond the potential lymph drainage pathways regional to the primary site.

3) Surgical Margins: The goal of surgery is to completely resect all metastases with adequate margins to avoid local recurrence. The surgeon should always attempt to get negative margins and be well beyond the palpable tumor. In subjects with dermal or subcutaneous metastasis, wide margin resection beyond 2 cm is usually not indicated, but the surgeons should always consider appropriate margins of resection to achieve both a clinically and microscopically negative resection. If the metastasis is in the subcutaneous tissue, the underlying fascia should be excised with the specimen. If the margins are found to be positive on pathological examination during the surgery, an additional resection, if feasible, of skin and subcutaneous tissue should be performed. Debulking surgery in which the tumor is shelled out invariably leads to prompt recurrence and is of little benefit to the subject.

4) Handling of Surgical Specimen(s): It is recommended that surgeon will mark the lesion(s) (or the area if CR was achieved) with the suture that was injected with talimogene laherparepvec. Complete surgery report and surgical pathology report have to be recorded in CRF. For additional information on handling of surgical specimens refer to Laboratory Manual.

Guidelines for Lymphadenectomy

1) Axillary Dissection: A complete axillary lymph node dissection should include all three levels of node-bearing axillary tissue. The borders of dissection include superior along the axillary vein from the thoracic inlet (Halsted's ligament) to the latissimus dorsi tendon. The medial border is the intercostal and serratus anterior muscles on the chest wall. The lateral border is the edge of the latissimus dorsi muscle, and the inferior border is the fourth intercostal space. The dissection should extend to the subscapular muscle. All fat and lymphatic tissue should be resected from the axilla and the long thoracic and thoracodorsal neurovascular bundle should be preserved unless involved with tumor. The pectoral minor muscle may be transected or removed if necessary to assure complete dissection of Level III nodes. Drainage of the resection bed with a closed suction drain is recommended. The minimum number of nodes assessed from the axillary region is 15.

2) Inguinal Dissection: Borders of dissection should be superior: along the lower abdomen 5 cm above and parallel to the inguinal ligament, inferior to the apex of the femoral triangle, medially along the medial border of the adductor magnus muscle, and laterally along the lateral border of the sartorius muscle. The fatty tissue and lymphatic tissue overlying the femoral vessels and nerve are removed up to the inguinal ligament. Removal of the node of Cloquet is recommended. Drainage of the resection bed with a closed suction drain is recommended. The minimum number of nodes assessed from the superficial inguinal region is 8. A deep groin dissection is required if inguinal nodes are (a) clinically positive (palpable) and there are 3 or more positive inguinal nodes, (b) positive matted nodes or (c) the node of Cloquet is microscopically positive by either hematoxylin and eosin staining or immunohistochemistry. A deep groin dissection of the common and external iliac, hypogastric, and obturator nodes should be performed by entering the retroperitoneal space either through a separate incision through the abdominal musculature above and parallel to the inguinal ligament, or by transecting the inguinal ligament. Drainage of the resection bed with a closed suction drain is recommended. The minimum number of nodes assessed from the deep groin region is 4.

3) Popliteal Region: The popliteal fossa lymph node dissection should contain the lymph nodes bordered laterally and superiorly by the biceps femoris muscle and medially and superiorly by the semimembranous and semitendinosus muscles. The inferior margins are the lateral and medial heads of the gastrocnemius muscles. The roof of the fossa is bordered by the popliteal surface of the femur and popliteus muscle and the floor is bordered by the fascia lata, superficial fascia and skin. Usually ligation of the lesser saphenous vein is necessary for complete excision of the lymph nodes in this site. Drainage of the resection bed with a closed suction drain is recommended. The minimum number of nodes assessed from the popliteal region is 3.

4) Neck Dissection: Either a classic radical or modified neck dissection preserving the spinal accessory nerve and sternocleidomastoid muscle are acceptable. In subjects who present with a primary melanoma on the anterior scalp, face or ear and concurrent palpable biopsy proven neck lymph node metastasis, a lymphoscintigraphy is recommended to assess possible drainage to the superficial parotid gland. If there is evidence of drainage to parotid lymph nodes, a superficial parotidectomy is required to remove the parotid nodes along with the neck lymph nodes. The borders of the neck dissection are inferior to the clavicle, superior to the mandible, mastoid and tail of the parotid gland, posterior to the anterior border of the of the trapezius muscle, and anterior to the strap muscles. Contents of the digastric triangles should be resected and the spinal accessory nerve preserved as long as there are no metastases in the upper jugular nodes. Drainage of the resection bed with a closed suction drain is recommended. The minimum numbers of nodes assessed from the neck region are as follows: (a) anterior cervical, including suprahyoid, jugulardigastric is 15; (b) posterior cervical, including supraclavicular is 15. Selected neck dissection could be considered in some circumstances, such as metastasis to submental nodes or very low cervical nodes from a medial shoulder primary melanoma.

For resected lymph nodes, refer to Table 4 below.

Table 4. Quantitative/Qualitative Reporting of Fully Resected Lymph Nodes

Lymph Node Type/Presence	Contained cancer under pathology evaluation?	Quantitative/qualitative reporting
Target lymph node previously present	Yes/Unknown	If measurement available: Actual short axis
		If measurement not available: 10mm short axis
	No	If measurement available: Actual short axis
		If measurement not available: 9mm short axis
Non-target lymph node previously present	Yes/Unknown	Present
	No	Absent
Lymph node not previously present	Yes/Unknown	If measurement available and short axis < 15mm: New non-measureable lymph node*
		If measurement available and short axis >/= 15mm: Enter available measurement
		If measurement not available: New non-measurable lymph node*
	No	Not to be recorded as target or non-target lesion. Instead to be reported on Procedures eCRF.

**The initial dimension of a new measurable lymph node or presence of a new non-measurable lymph node should be reported at all subsequent assessments.*

Amendment 3

Protocol Title: A Phase 2, Multicenter, Randomized, Open-label Trial Assessing the Efficacy and Safety of Talimogene Laherparepvec Neoadjuvant Treatment Plus Surgery Versus Surgery Alone for Resectable, Stage IIIB to IVM1a Melanoma

Amgen Protocol Number (Talimogene Laherparepvec) 20110266

Amendment Date: 23 March 2018

Rationale:

This protocol is being amended to:

- Add a third interim analysis to the protocol 1 year after the end of randomization in order to help inform Amgen regarding future potential clinical trials and data collection in this setting.
- Update the time points for assessment of secondary objectives to start at first year.
- Update the exclusion criteria for sexually active subjects and their partners with allergy by providing option for alternative condom type.
- Provide guidance to sites on how to report data for fully resected lymph nodes after surgery with specific qualitative and quantitative features.
- Make minor corrections and clarifications throughout the document, including administrative, typographical, and formatting errors.

Description of Changes

Section: Global

Change: Update protocol amendment dates throughout document from 22 April 2016 to **23 March 2018**.

Section: Global

Change: Make editorial corrections (including typographical, grammatical, and formatting errors) throughout the document.

Section: Title page

Add:

Amgen Protocol Number (Talimogene Laherparepvec) 20110266

EudraCT number 2014-001146-13

NCT02211131

Section: Title page

Replace:

Key Sponsor Contacts:	[redacted] MD Clinical Research Medical Director One Amgen Center Drive Thousand Oaks, CA 91320-1799 Telephone: [redacted] Email address: [redacted] [redacted] Clinical Research Study Manager Amgen Limited 1 Sanderson Road (Uxbridge Business Park) Uxbridge, UB8 1DH Telephone: [redacted] Email: [redacted]
Date:	23 May 2014
Amendment 1 Date:	09 June 2014
Amendment 2 Date:	31 March 2016
Superseding Amendment 2 Date:	22 April 2016

With:

Key Sponsor Contacts:	[redacted] MD Clinical Research Medical Director One Amgen Center Drive Thousand Oaks, CA 91320-1799 Telephone: [redacted] Email address: [redacted] [redacted] **PhD** **Senior Manager, Global Clinical Program Management** Amgen Limited 1 Sanderson Road (Uxbridge Business Park) Uxbridge, UB8 1DH Telephone: [redacted] Email: [redacted]
Date:	23 May 2014
Amendment 1 Date:	09 June 2014
Amendment 2 Date:	31 March 2016
Superseding Amendment 2 Date:	22 April 2016
Amendment 3 Date:	**23 March 2018**

Section: Protocol Synopsis, Secondary Objectives, Bullet points 1 and 5.

Add:

- To estimate the effect of neoadjuvant talimogene laherparepvec plus surgery compared to surgery alone on **1-year,** 2-year, 3-year, and 5-year RFS
- To estimate the effect of neoadjuvant talimogene laherparepvec plus surgery compared to surgery alone on **1-year,** 2-year, 3-year, 5-year, and overall survival (OS)

Section: Protocol Synopsis, Secondary Endpoints, Bullet points 1 and 7.

Add:

- **1-year,** 2-year, 3-year, and 5-year RFS
- **1-year,** 2-year, 3-year**,** and 5-year, and overall survival

Section: Protocol Synopsis, Statistical Considerations, Paragraphs 3 and 7

Add:

An additional third interim analysis with no formal stopping rule is planned to evaluate RFS approximately 1 year after the end of randomization. This analysis will be conducted by the Amgen study team.

All efficacy analyses will be descriptive with no formal hypothesis testing. Kaplan-Meier (KM) estimates and CI will be calculated for RFS, LRFS, RRFS, DMFS, OS landmarks (**1-,** 2-, 3- and 5-year rates) and quartiles.

Section: 1.2. Secondary, Bullet points 1 and 5.

Add:

- To estimate the effect of neoadjuvant talimogene laherparepvec plus surgery compared to surgery alone on **1-year,** 2-year, 3-year, and 5-year RFS
- To estimate the effect of neoadjuvant talimogene laherparepvec plus surgery compared to surgery alone on **1-year,** 2-year, 3-year, 5-year, and overall survival (OS)

Section: 4.1.2. Exclusion criteria, 221.

Add:

221 Sexually active subjects and their partners unwilling to use male or female latex condoms 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.**

Section: 10.1.1.2. Secondary Endpoint, Efficacy Endpoints, Bullet points 1 and 8

Add:

- **1-year,** 2-year, 3-year, 5-year RFS: The Kaplan-Meier (K-M) estimate of RFS rate at **1-year,** 2 years, 3 years and 5 years
- **1-year,** 2-year, 3-year and 5-year survival: The Kaplan-Meier (K-M) estimate of the survival rate at **1-year,** 2 years, 3 years and 5 years

Section: 10.2. Sample Size Considerations, Paragraph 3

Add:

The Kaplan-Meier (KM) method will be used to estimate **1-year,** 2-year, 3-year, 5-year, and overall RFS.

Section: 10.4.1. Interim Analyses, Paragraph 3

Add:

An additional third interim analysis with no formal stopping rule is planned to evaluate RFS approximately 1 year after the end of randomization. This analysis will be conducted by the Amgen study team.

Section: 10.5.3. Secondary Efficacy Endpoints, Paragraph 1

Add:

KM estimates will be calculated for RFS, LRFS, RRFS, DMFS, OS landmarks (**1-,** 2-, 3- and 5-year rates) and quartiles.

Section: 10.5.3. Secondary Efficacy Endpoints, Paragraph 1

Replace:

For each group the equal precision band method will be used to calculate a simultaneous confidence band for RFS, LRFS, RRFS, and DMFS over the interval from 2 to 5 years (Nair, 1984).

With

For each group the equal-precision band method will be used to calculate a simultaneous confidence band for RFS, LRFS, RRFS, and DMFS over the interval from **1** to 5 years (Nair, 1984).

Section: Appendix F. Surgery Guidelines

Add:

For resected lymph nodes, refer to Table 4 below.

Table 4. Quantitative/Qualitative Reporting of Fully Resected Lymph Nodes

Lymph Node Type/Presence	Contained cancer under pathology evaluation?	Quantitative/qualitative reporting
Target lymph node previously present	Yes/Unknown	If measurement available: Actual short axis
		If measurement not available: 10mm short axis
	No	If measurement available: Actual short axis
		If measurement not available: 9mm short axis
Non-target lymph node previously present	Yes/Unknown	Present
	No	Absent
Lymph node not previously present	Yes/Unknown	If measurement available and short axis < 15mm: New non-measureable lymph node*
		If measurement available and short axis >/= 15mm: Enter available measurement
		If measurement not available: New non-measurable lymph node*
	No	Not to be recorded as target or non-target lesion. Instead to be reported on Procedures eCRF.

**The initial dimension of a new measurable lymph node or presence of a new non-measurable lymph node should be reported at all subsequent assessments.*

Superseding Amendment 2

Protocol Title: A Phase 2, Multicenter, Randomized, Open-label Trial Assessing the Efficacy and Safety of Talimogene Laherparepvec Neoadjuvant Treatment Plus Surgery Versus Surgery Alone for Resectable, Stage IIIB to IVM1a Melanoma

Amgen Protocol Number 20110266

Amendment Date: 22 April 2016

Rationale:

The Superseding Amendment 2 was written to:

- Correct the numbering of the exclusion criteria in Amendment 2
- Update sponsor contact

The key protocol changes are:

- **Secondary objective**

An objective of regional recurrence-free survival (RRFS) was added to the following secondary objective "To estimate the effect of neoadjuvant talimogene laherparepvec plus surgery compared to surgery alone on local recurrence-free survival (LRFS) and distant metastases-free survival (DMFS)" to better characterize patterns of recurrences of melanoma, which include not only local and distant, but also regional recurrences.

- **Secondary endpoint**

Regional recurrence-free survival was added to the secondary endpoints in parallel to this addition to the secondary objective.

- **Distant metastases free survival**

The efficacy endpoint of DMFS was clarified by specifying what DMFS includes and excludes.

- **Adjuvant ipilimumab information**

Information on adjuvant ipilimumab use was added to the Introduction because ipilimumab was recently approved by the United States Food and Drug Administration (FDA) for the adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy.

- **Marketing information on talimogene laherparepvec**

Marketing information on talimogene laherparepvec (Imlygic™) was added to the Introduction to update the background section because it was recently approved by regulatory authorities for specified indications in the US, Europe, and Australia.

- **Randomization stratification**

Stratification by adjuvant interferon use was replaced with adjuvant systemic therapy to include interferon alpha (INFα) and ipilimumab since ipilimumab has been FDA approved to reduce the risk of melanoma returning after surgery and other systemically active therapy may also be approved for this indication.

- **Number of sites**

The number of sites was changed from 40 to 50 to achieve the enrollment goal.

- **Safety follow-up**

The 30-day safety follow-up was modified to specify that subjects will be followed for local, regional, and distant disease recurrence and for melanoma and adverse events thought to be potentially related to talimogene laherparepvec to align with the schedule of assessment in the Registry Study 20120139. The protocol was also changed to specify that subjects who participate in 20120139 must sign a new informed consent form.

- **Measurable disease inclusion criterion**

Inclusion criterion 106 was clarified to specify that the measurement of the lesion diameter “in at least 2 dimensions” is ≥ 10 mm to align with other talimogene laherparepvec studies. Also, measurement using ultrasound for superficial lymph nodes and subcutaneous lesions was added.

- **Serum lactate dehydrogenase (LDH) level inclusion criterion**

Inclusion criterion 108 was changed as follows: Serum LDH level ≤ 1.**5** x upper limit of normal (ULN) **for stages IIIB and IIIC melanoma and ≤ 1.0 x ULN for Stage IVM1a melanoma** within 28 days prior to randomization, since LDH is not a staging component for Stage III melanoma.

- **Serum albumin inclusion criterion**

Inclusion criterion 109 was modified to include serum albumin ≥ 2.5 g/dL to align with other talimogene laherparepvec studies.

- **Autoimmune disease exclusion criterion**

Exclusion criterion 204 was expanded to clarify symptomatic autoimmune disease to align with the same criterion in other talimogene laherparepvec monotherapy studies.

- **Clinically significant immunosuppression**

The definition of clinically significant immunosuppression was updated in exclusion criterion 205 to align with other talimogene laherparepvec monotherapy studies.

- **Tumor vaccine exclusion criterion**

Exclusion criterion 212 (prior therapy with tumor vaccine) was deleted to align with other talimogene laherparepvec monotherapy studies.

- **Viral transmission during sexual contact exclusion criterion**

The criterion (216) to exclude sexually active subjects and their partners unwilling to use male or female latex condoms to avoid potential viral transmission during sexual contact was added as a condition of marketing approval and to align with other talimogene laherparepvec studies.

- **Talimogene laherparepvec vials**

Each vial contains a minimum of 1.0 mL talimogene laherparepvec at either 10^6 PFU/mL or 10^8 PFU/mL concentrations. The description of the two vial concentrations as green cap and blue cap, respectively, were deleted since they no longer apply.

- **Treatment procedures**

The following statement was added to stress the need to report adjuvant therapies, if planned, via Interactive Voice Response (IVR): If adjuvant therapy (systemic and/or radiation therapy; approved or investigational) is planned, this should be reported via IVR at randomization.

- **Reporting of potentially talimogene laherparepvec related adverse events during long-term follow-up**

Adverse events deemed by the investigator to be potentially related to talimogene laherparepvec (Arm 1 only) and use of subsequent anticancer therapy for melanoma will be collected during long-term follow-up to align this protocol with all other talimogene laherparepvec studies.

- **Activated PTT**

Activated thromboplastin time was added as an alternative to PTT in screening laboratory tests because it may be an alternative test of choice for testing coagulation.

- **Physical examination and ECOG performance status**

Required physical examination and ECOG performance status was added at weeks 4 and 8 to report any change in a patient's performance status.

- **Oral and genital swabbing after surgery**

Oral and genital swabbing for real-time polymerase chain reaction (qPCR) and 50% Tissue Culture Infective Dose (TCID50) assay testing was removed from the safety follow-up visit because identical information is currently being collected in Study 20120324.

- **Safety Follow-up procedures**

Surgical safety evaluation and recording of subsequent anticancer therapy for melanoma were added to safety follow-up procedures to align the schedule of assessment in the Registry Study 20120139.

- **Pregnancy and lactation reporting**

Reference to Amgen's global Pregnancy and Lactation Surveillance Programs was deleted and replaced by Amgen Global Patient Safety to align with current company practice.

- **Statistical considerations**

RRFS analysis was added to meet the addition of RRFS to the secondary objectives.

The protocol was modified to clarify that a DRT will review the first interim analysis and the talimogene laherparepvec product team will review the second interim analysis, since the second analysis will be performed after all subjects in Arm 1 have been enrolled. The DRT and talimogene laherparepvec product team will also review some efficacy endpoints (eg, R0 resection rate, pCR rate, response to neoadjuvant treatment).

Ad hoc analyses, executed by the talimogene laherparepvec product team, for safety or some efficacy endpoints may be conducted before the planned primary or final analyses if interim data are required for submission to regulatory authorities.

- **Sample size**

In the statement regarding subjects who are not confirmed to be disease-free post-surgery or who withdraw prior to surgery, failure was changed from at randomization to "a day after randomization" for RFS. With this change, the number of subjects at risk at the earliest possible time (randomization +1 day) would not change

due to non-melanoma subjects, and would reduce the impact on the Cox model, Kaplan-Meier, and log-rank test results.

- **Trial integrity document**

The mention of using a Trial Integrity Document was deleted to comply with current standard operating procedures.

- **Index lesions**

Language was added to Appendix D (documentation of index lesions) to clarify the recording of aggregate lesions and to align with other talimogene laherparepvec monotherapy studies.

- **Definition of progressive disease for measurable disease**

The definition of progressive disease (PD) was changed to clarify that PD includes the unequivocal appearance of a new measurable lesion since the last response assessment time point, to align with other talimogene laherparepvec studies.

- **Appendix F**

Appendix F was modified to state that the decision to perform surgery may include consulting with other relevant medical specialties and consideration of a patient's preferences, to provide guidance on the decision making process of resection of melanoma.

- **Administrative**

Minor text clarifications, additions, and corrections as well as typographical and formatting changes were made throughout the protocol. The key sponsor contact information was updated to align with current personnel and the talimogene laherparepvec Investigator Brochure reference was updated to the current version. New references were added as needed for newly added text.

Description of Changes (all changes to the Protocol are indicated in bold text)

Section:	All applicable sections and header
Replace:	09 June 2014
With:	**22 April 2016**
Replace:	end point
With:	**Endpoint**
Replace:	arm 1, arm 2
With:	**A**rm 1, **A**rm 2
Replace:	(Talimogene Laherparepvec Investigator's Brochure, 2014)
With:	(Talimogene Laherparepvec Investigator's Brochure, 201**5**)
Section	Cover page
Replace:	[redacted] PhD, MD Clinical Research Senior Medical Scientist Telephone: [redacted] Email address: [redacted]
With:	[redacted] **MD** Clinical Research Medical **Director** Telephone: [redacted] Email address: [redacted]
Replace:	[redacted] Clinical Research Study Manager Amgen Limited 1 Sanderson Road (Uxbridge Business Park) Uxbridge, UB8 1DH Telephone: [redacted] Email: [redacted]
With:	[redacted] Clinical Research Study Manager Amgen Limited 1 Sanderson Road (Uxbridge Business Park) Uxbridge, UB8 1DH Telephone: [redacted] Email: [redacted]
Add:	**Superseding Amendment 2 Date 22 April 2016**

Section: Protocol Synopsis, Secondary Objectives, bullet 4

Add:
- To estimate the effect of neoadjuvant talimogene laherparepvec plus surgery compared to surgery alone on local recurrence-free survival (LRFS)**, regional recurrence-free survival (RRFS),** and distant metastases-free survival (DMFS)

Section: Protocol Synopsis, Secondary Endpoints, bullet 5

Add:
- **RRFS**

Section: Synopsis, Study Design

Replace: Randomization will be stratified by disease stage (IIIB nodal versus IIIB in-transit versus IIIC nodal versus IIIC in-transit with nodal versus IVM1a), planned adjuvant therapy (interferon alpha [INFα] with or without radiotherapy versus radiotherapy without INFα versus none).

With: Randomization will be stratified by disease stage (IIIB nodal versus IIIB in-transit versus IIIC nodal versus IIIC in-transit with nodal versus IVM1a), planned adjuvant therapy (**adjuvant systemic therapy [eg,** interferon alpha (INFα**), ipilimumab]** with or without radiotherapy versus radiotherapy without **adjuvant systemic therapy** versus none).

Add: Subjects will be followed for safety approximately 30 (+15) days after surgery and for disease recurrence **(local, regional, or distant)**, subsequent anticancer therapy **for melanoma, adverse events thought to be potentially related to talimogene laherparepvec (Arm 1 only),** and survival every 3 months (±30 days) for first 3 years after the end of the safety follow-up period and then every 6 months (±30 days) until death, subject withdraws full consent, or up to 5 years after the last subject is randomized. Thereafter, subjects randomized to **A**rm 1 who received at least a single dose of talimogene laherparepvec will be followed under an ongoing separate registry protocol **(Study 20120139)** for the long-term survival follow-up of subjects treated with talimogene laherparepvec. The registry protocol will also monitor for late and long-term adverse events thought to be potentially related to talimogene laherparepvec **and use of subsequent anticancer therapy for melanoma**. **Subjects who after the long-term follow-up period of this study (Study 20110266) will elect to participate in the registry study must sign new informed consent form before any registry protocol-specific activities.**

Section: Synopsis, Key Inclusion Criteria

Replace: Also, subject must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and must have a serum lactate dehydrogenase (LDH) ≤ 1.0 X upper limit of normal and adequate hematologic, hepatic, renal, and coagulation organ function.

With:	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 **(ULN) for stages IIIB/C melanoma and LDH ≤1.0 x ULN for stage IVM1a melanoma** and adequate hematologic, hepatic, renal, and coagulation organ function**s**.
Section:	Synopsis, Key Exclusion Criteria
Replace:	Subject must not have history or evidence of symptomatic autoimmune pneumonitis, glomerulonephritis, vasculitis, or other symptomatic autoimmune disease.
With:	Subject must not have 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**.
Delete:	Subject must not have been treated previously with talimogene laherparepvec ~~or tumor vaccine~~.
Section:	Synopsis, Procedures, Screening, bullets 3 and 4
Delete:	demographics, ~~physical examination,~~ vital signs, and ECOG performance status assessment
Add:	local laboratory tests including, hematology panel, chemistry panel, serum LDH, prothrombin time (PT) (or international normalization ratio [INR]) and partial thromboplastin time (PTT) **(or activated PTT)**, and serum or urine pregnancy test for female subjects of childbearing potential
Section:	Synopsis, Procedures, Treatment, bullets 2, 3, and 8
Add:	• **ECOG performance status**
Add:	• **physical examination**
Add:	histological tumor assessment of the surgical specimen**, including assessment for tumor-free margins (R0 resection for negative margins, R1 or R2 resections for tumor positive margins) and pathological complete response (in Arm 1 only)**
Section:	Synopsis, Procedures, Safety Follow-up Visit, bullets 2, 3, and 5
Add:	• **surgical safety evaluation**

Add:
- **documentation of subsequent anticancer therapy for melanoma (including local, regional, or systemic therapy)**

Replace:
- central laboratory tests including blood and urine for qPCR, oral mucosa swabs and genital swabs (if study drug is injected into a melanoma lesion below the waist) for qPCR and 50% Tissue Culture Infective Dose (TCID50) assay testing, and swabs of cold sores, vesicles, and other lesions suspected to be herpetic in origin (if any) for qPCR testing within 24 hours following the investigator's knowledge of the event

With:
- central laboratory tests **of** swabs of cold sores, vesicles, and other lesions suspected to be herpetic in origin (if any) for qPCR testing **of talimogene laherparepvec DNA** within 24 hours following the investigator's knowledge of the event

Section: Synopsis, Procedures, Long-term Follow-up, paragraphs 1, 2, and 3

Add: All randomized subjects will be contacted by telephone, or clinic visit, to assess survival status**, collect adverse events deemed by the investigator to be potentially related to talimogene laherparepvec (Arm 1 only),** and, if applicable, commencement of any subsequent anticancer melanoma therapy **(including local, regional, or systemic therapy for melanoma)**.

Add: every 3 months (±30 days) for 3 years following the safety follow-up visit and then every 6 months (±30 days) until **distant** disease recurrence, death,

Add: After the long-term follow-up period of this study has ended, subjects **randomized to Arm 1 who received at least a single dose of talimogene laherparepvec and** who end the study for any reason other than death or withdrawal of full consent will be followed for survival under an

Add: The registry protocol will also monitor for late and long-term adverse events thought to be potentially related to talimogene laherparepvec **and use of subsequent anticancer therapy for melanoma**. **Subjects who after the long-term follow-up period of this study (Study 20110266) will elect to participate in the registry study must sign new informed consent form before any registry protocol-specific activities.**

Section: Synopsis, Statistical Considerations paragraphs 1, 2, 3, 5, and 6

Add: The primary analysis for the primary endpoint will occur at the later time of either the occurrence of approximately 64 events (local, **regional,** or distant recurrence of melanoma or death) or approximately 2 years after the end of randomization.

Replace:	Two interim analyses with no formal stopping rules are planned to evaluate safety when approximately 40 and 75 subjects randomized to talimogene laherparepvec have had the opportunity to complete the safety follow-up visit. The primary analysis for certain secondary endpoints will be performed using the data from the second interim analysis.
With:	Two interim analyses with no formal stopping rules are planned to evaluate safety **and some efficacy endpoints (eg, R0 resection rate, pCR rate, response to neoadjuvant treatment)** when approximately 40 and 75 subjects randomized to talimogene laherparepvec have had the opportunity to complete the safety follow-up visit. The primary analysis for certain secondary endpoints **(eg, response to neoadjuvant treatment, R0 resection rate, pCR rate, and safety)** will be performed using the data from the second interim analysis.
Add:	**The primary analyses for RFS will occur at the later time of either the occurrence of approximately 64 events (local, regional, or distant recurrence of melanoma or death) or approximately 2 years after end of randomization.**
Add:	**Ad hoc analyses for safety or some efficacy endpoints (eg, response to neoadjuvant treatment, R0 resection rate, pCR rate) may be conducted before the planned primary and/or final analyses if interim data are required for submission to regulatory authorities.**
Add:	All efficacy analyses will be descriptive with no formal hypothesis testing. Kaplan-Meier (KM) estimates and CI will be calculated for RFS, LRFS, **RRFS,** DMFS, OS landmarks (2-, 3- and 5-year rates) and quartiles. Estimates and CIs for between-group differences will also be calculated. An overall between-group difference in RFS, LRFS, **RRFS,** DMFS, and OS will be
Section:	Study Glossary, definition of end of study (primary completion)
Add:	The primary completion is anticipated to occur at the later time of either occurrence of approximately 64 events (local**, regional,** or distant recurrence of melanoma or death) or approximately 2 years after the end of randomization
Add:	**RRFS - regional recurrence-free survival**
Delete:	~~TCID50 - 50% Tissue Culture Infective Dose~~ ~~TID - Trial Integrity Document~~ ~~SPD - the sum of the products of the two largest perpendicular diameters~~

Section: 1.2 Secondary, bullet 4

Add:
- To estimate the effect of neoadjuvant talimogene laherparepvec plus surgery compared to surgery alone on local recurrence-free survival (LRFS)**, regional recurrence-free survival (RRFS),** and distant metastases-free survival (DMFS)

Section: 2.1 Melanoma and Adjuvant and Neoadjuvant Therapy for Melanoma, paragraphs 2, 7, and 10

Delete: While radical resection is a cornerstone of treatment for subjects with stage~~s~~ III melanoma

Add: The biochemotherapy regimen was associated with substantial toxicity with grade 3 and 4 adverse events in 36% and 40% **of** subjects, respectively (Flaherty et al, 2012).

Add: **Recently, ipilimumab, a a cytotoxic lymphocyte associated antigen 4 (CTLA-4 inhibitor), was approved by the United States Food and Drug Administration for the adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy (Yervoy™, 2015). This approval was based on results of a randomized double-blind phase 3 trial conducted in 951 patients with completely resected stage IIIA (> 1 mm nodal involvement), IIIB, and IIIC melanoma (EORTC 18071). Patients with in-transit metastases were excluded. Ipilimumab improved recurrence-free survival (primary endpoint) in this trial from 17.1 months to 26.1 months (HR 0.75; 95% CI 0.64–0.90; p=0.0013). Results of OS and distant metastasis-free survival (secondary endpoints) are pending. Fifty-two percent of patients randomized to the ipilimumab arm discontinued treatment because of toxicity, 5 patients (1%) died because of ipilimumab-related toxicities. Forty-six percent of patients in the ipilimumab arm experienced grade 3 adverse events (37% immune-related), and 8% grade 4 (6% immune-related) (Eggermont et al, 2015).**

Section: 2.2 Talimogene Laherparepvec Background, paragraphs 8 and 9

Replace: Clinical data currently available have provided evidence of talimogene laherparepvec's efficacy in subjects with regionally and distantly metastatic melanoma

With: Clinical data currently available have provided evidence of talimogene laherparepvec's efficacy in subjects with **unresectable** metastatic melanoma

Add: **Recently, talimogene laherparepvec (Imlygic™) was approved in the USA for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery (with limitation of use: Imlygic has not been shown to improve overall survival or have an effect on visceral metastases) (Imlygic™ Prescribing Information, 2015), in Europe for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (stage IIIB, IIIC, and IVM1a) with no bone, brain, lung or other visceral disease (Imlygic™ Summary of Product Characteristics, 2015), and in Australia as monotherapy for the treatment of melanoma in patients with unresectable cutaneous, subcutaneous, or nodal lesions after initial surgery (Imlygic™ Prescribing Information, 2015).**

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

Section: 2.3 Rationale, paragraph 3

Delete: Additionally, a number of immune-related biomarkers, such as antibodies to melanoma antigens and expression of immune-stimulatory and immune-inhibitory molecules (eg ~~cytotoxic lymphocyte associated antigen 4 [~~CTLA-4~~]~~, program cell death-1 **[**PD-1], program cell death-1 ligand 1 [PD-L1] and others) in tumors or tumor infiltrating T-cells will be assessed to determine any association with clinical outcomes.

Section: 3.1 Study Design, paragraphs 5 and 7

Replace: Randomization will be stratified by disease stage (IIIB nodal versus IIIB in-transit versus IIIC nodal versus IIIC in-transit with nodal versus IVM1a) and planned adjuvant therapy (INFα with or without radiotherapy versus radiotherapy without INFα versus none).

With: Randomization will be stratified by disease stage (IIIB nodal versus IIIB in-transit versus IIIC nodal versus IIIC in-transit with nodal versus IVM1a), planned adjuvant therapy (**adjuvant systemic therapy [eg, INFα, ipilimumab**] with or without radiotherapy versus radiotherapy without **adjuvant systemic therapy** versus none).

Add: Subjects will be followed for safety approximately 30 (+15) days after surgery and for disease recurrence **(local, regional, or distant)**, subsequent anticancer therapy **for melanoma, adverse events thought to be potentially related to talimogene laherparepvec,** and survival every 3 months (±30 days) for first 3 years after the end of the safety follow-up

Add: laherparepvec will be followed under an ongoing separate registry protocol **(Study 20120139)** for the long-term survival follow-up of subjects treated with talimogene

Add: The registry protocol will also monitor for late and long-term adverse events thought to be potentially related to talimogene laherparepvec **and use of subsequent anticancer therapy for melanoma**. **Subjects who after the long-term follow-up period of this study (Study 20110266) will elect to participate in the registry study must sign new informed consent form before any registry protocol-specific activities.**

Section: 3.2 Number of Sites, paragraph 1

Replace: The study will be conducted at approximately 40 sites in Australia, Brazil, United Kingdom, Russia, and USA. Additional sites and countries may be added.

With: The study will be conducted at approximately **5**0 sites in Australia, Brazil, **Europe,** Russia, and USA. Additional sites and countries may be added.

Section: 3.5.1 Study Duration for Subjects

Add: Subjects will be followed for safety approximately 30 (+15) days after surgery and for disease recurrence **(local, regional, or distant)**, subsequent anticancer therapy **for melanoma, adverse events thought to be potentially related to talimogene laherparepvec**, and survival

Section: 3.5.2 End of Study

Add: The primary completion is anticipated to occur at the later time of either the occurrence of approximately 64 events (local**, regional,** or distant recurrence of melanoma or death) or approximately 2 years after the end of randomization.

Section: 4.1.1 Inclusion Criterion, No. 106

Replace: 106 Measurable disease defined as one or more of the following:

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

With: 106 Measurable disease defined as one or more of the following:

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

Section: 4.1.1 Inclusion Criterion, No. 108

Replace: 108 Serum LDH level ≤ 1.0 upper limit of normal (ULN) within 28 days prior to randomization

With: 108 Serum LDH level ≤ 1.**5 x** upper limit of normal (ULN) **for stages IIIB and IIIC melanoma and ≤ 1.0 x ULN for stage IVM1a melanoma** within 28 days prior to randomization

Section: 4.1.1 Inclusion Criterion, No. 109

Add:

- Hepatic
  - serum bilirubin ≤ 2.0 x ULN
  - **serum albumin ≥ 2.5 g/dL**
  - aspartate aminotransferase (AST) ≤ 2.5 x ULN
-

Section: 4.1.2 Exclusion Criterion, No. 204

Replace: 204 History or evidence of symptomatic autoimmune pneumonitis, glomerulonephritis, vasculitis, or other symptomatic autoimmune disease

With: 204 History or evidence of symptomatic autoimmune **disease (such as** pneumonitis, glomerulonephritis, vasculitis, or other**), or history of** autoimmune disease **that required systemic treatment (ie, use of corticosteroids, immunosuppressive drugs or biological agents used for treatment of autoimmune diseases) in past 2 months prior to enrollment. Replacement therapy (eg, thyroxine for hypothyroidism, insulin for diabetes mellitus) is not considered a form of systemic treatment for autoimmune disease.**

Section: 4.1.2 Exclusion Criterion, No. 205

Replace:

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

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

Section: 4.1.2 Exclusion Criterion, No. 212

Delete: ~~212 Prior therapy with tumor vaccine~~

Section: 4.1.2 Exclusion Criterion, No. 216

Add: **216 Sexually active subjects and their partners unwilling to use male or female latex condoms to avoid potential viral transmission during sexual contact while on treatment and within 30 days after treatment with talimogene laherparepvec**

Section: 5.1 Randomization/Treatment Assignment

Replace: The IVR system will assign a randomization number. Approximately 150 subjects will be stratified by disease stage (IIIB nodal versus IIIB in-transit versus IIIC nodal versus IIIC in-transit with nodal versus IVM1a) and planned adjuvant therapy (INFα with or without radiotherapy versus radiotherapy without INFα versus none).

With: The IVR system will assign a randomization number. Approximately 150 subjects will be stratified by disease stage (IIIB nodal versus IIIB in-transit versus IIIC nodal versus IIIC in-transit with nodal versus IVM1a) and planned adjuvant therapy (**adjuvant systemic therapy [eg, INFα, ipilimumab]** with or without radiotherapy versus radiotherapy without **adjuvant systemic therapy** versus none).

Section: 6.2.1 Amgen Investigational Product Talimogene Laherparepvec

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

Section: 6.5 Other Treatment Procedures

Add: **If adjuvant therapy (systemic and/or radiation therapy; approved or investigational) is planned, this should be reported via IVR at randomization.**

Section: 7.1 Table 2. Schedule of Assessments for Arm 1 (Talimogene Laherparepvec Plus Surgery)

Add: **Adverse Events Potentially Related to Treatment with Talimogene Laherparepvec**
X under Long-term Follow-up

Add: **X** under week 1, week 4, and week 8 for physical exam

Add: **X** under week 4 and week 8 for ECOG performance status

Add:	Subsequent **A**nticancer **T**herapy **for melanoma**
Delete:	~~Blood and urine for qPCR~~
Delete:	~~Oral Mucosa Swab for qPCR and TCID50 Assay~~
Delete:	~~Genital Swab for qPCR and TCID50 Assay~~ [d]
Delete:	[d]~~Genital swab sample is required if talimogene laherparepvec is injected into a melanoma lesion below the waist~~.
Add:	[d]**Surgical specimens will be assessed for presence of viable tumor and tumor margin status for cutaneous and subcutaneous tumor; please refer to Section 7.2.2.**
Section:	7.1 Table 3. Schedule of Assessment for Arm 2 (Surgery Alone)
Add:	Subsequent **A**nticancer **T**herapy **for Melanoma**
Add:	[d] **Surgical specimens will be assessed for presence of viable tumor and tumor margin status for cutaneous and subcutaneous tumor; please refer to Section 7.2.2..**
Section:	7.2 Table 4. Laboratory Analytes
Delete:	~~TCID50 assay for talimogene laherparepvec viral infectivity~~
Section:	7.2.1 Screening and Randomization, bullet 10
Delete:	~~and CT scan or~~
Section:	7.2.2 Treatment
Add:	• Physical examination as per standard of care Arm 1: within 3 days prior to talimogene laherparepvec administration on day 1 of week 1 and within 3 days prior to surgery, **and prior to talimogene laherparepvec administration on day 1 of weeks 4 and 8**
Add:	• ECOG performance status – Arm 1: **prior to talimogene laherparepvec administration on day 1 of weeks 4 and 8 and** within 3 days prior to the surgery
Add:	– A pathological complete response (pCR) **in Arm 1** is defined as no evidence of viable tumor cells on complete pathological evaluation of the surgical specimen per institutional standards of care

Section: 7.2.3 Safety Follow-up Visit

Delete:

- Central laboratory assessments:
  - ~~Arm 1: blood and urine samples for qPCR analysis~~
  - ~~Arm 1: swab of oral mucosa for qPCR and 50% Tissue Culture Infective Dose (TCID50) assay testing:~~
    - ~~Initially, a qPCR analysis will be performed on the swab sample to evaluate whether the talimogene laherparepvec DNA is detectable in the sample:~~
      - ~~i. If result of the qPCR testing is negative, TCID50 assay testing is not required~~
      - ~~ii. If the result of the qPCR testing is positive, then a TCID50 assay will be performed on the swab sample to assess viral infectivity~~
  - ~~Arm 1: genital swabs for qPCR and TCID50 assay testing is required if talimogene laherparepvec is injected into a melanoma lesion below the waist:~~
    - ~~Initially, a qPCR analysis will be performed on the swab sample to evaluate whether the talimogene laherparepvec DNA is detectable in the sample:~~
      - ~~i. If result of the qPCR testing is negative, TCID50 assay testing is not required~~
      - ~~ii. If the result of the qPCR testing is positive, then a TCID50 assay will be performed on the swab sample to assess viral infectivity~~

Add:

- Documentation of subsequent anticancer therapy **for melanoma (including local, regional, or systemic therapy)**

Section: 7.2.4 Long-term Follow-up

Add: All randomized subjects will be contacted by telephone, or clinic visit, to assess survival status**, collect adverse events deemed by the investigator to be potentially related to** t**alimogene laherparepvec (Arm 1 only),** and, if applicable, commencement of any subsequent anticancer melanoma therapy.

Add: Radiographic tumor imaging, clinical tumor assessments, and tumor response assessments, will be performed as documented in Section 7.2.2 every 3 months (±30 days) for 3 years following the safety follow-up visit and then every 6 months (±30 days) until **distant** disease recurrence, death, subject withdraws full consent, or up to 5 years after the last subject is randomized, whichever is first. **Local and regional recurrences will be reported until appearance of distant recurrence, or end of study, whichever is first. Local recurrence is defined as histologically or cytologically confirmed reappearance of melanoma in the area of up to 2 cm from the scar from the surgical excision or at the edge of the skin graft if that was used for closure. Regional recurrence (excludes local recurrence) is defined as histologically, cytologically, or radiographically confirmed reappearance of melanoma in the regional lymph node basin. New in-transit melanoma metastases**

in the regional lymphatic drainage will be reported as regional recurrence. Histological or cytological confirmation of new in-transit metastases is recommended but is not required. Distant metastases exclude local and regional recurrence and will include distant cutaneous/subcutaneous metastases, distant nodal metastases, or visceral, central nervous system, brain, or bone metastases.

Add: After the long-term follow-up period of this study has ended, subjects **randomized to Arm 1 who received at least a single dose of talimogene laherparepvec and** who end the study for any reason other than death or withdrawal of full consent will be followed for survival under an ongoing separate registry protocol (Study 20120139) that is in place for the long-term follow-up of all subjects treated with talimogene laherparepvec in clinical trials.

Add: The registry protocol will also monitor for late and long-term adverse events thought to be potentially related to talimogene laherparepvec **and use of subsequent anticancer therapy for melanoma**. **Subjects who after the long-term follow-up period of this study (20110266) will elect to participate in the registry study must sign new informed consent form before any registry protocol-specific activities.**

Section: 7.3.1 Blood Samples

Add: Blood samples are to be collected for biomarker development at time points designated in the Schedule of Assessments (Table 2 **and Table 3**) and as described in Section 7.2.2.

Section: 9.3 Pregnancy and Lactation Reporting

Replace: The pregnancy should be reported to Amgen's global Pregnancy Surveillance Program within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C). The Pregnancy Surveillance Program will seek to follow the pregnant woman throughout her pregnancy and her baby up to 12 months after birth.

With: The pregnancy should be reported to Amgen **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).

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

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

Section: 10.1.1.1 Primary Endpoint

Add:
- Recurrence-Free Survival (RFS): RFS is defined as time from randomization to the date of the first of local**, regional,** or distant recurrence of melanoma or death due to any cause.

Section: 10.1.1.2 Secondary Endpoint, bullets 1, 4, 5, and 6

Add:
- 2-year, 3-year, 5-year RFS: The Kaplan-Meier (K-M) estimate of RFS rate at 2 **years**, 3 years and 5 years

Add: Local recurrence is defined as histologically or cytologically confirmed reappearance of melanoma in the **in the area of up to 2 cm from the** scar from the surgical excision

Add:
- **Regional recurrence-free survival (RRFS): Time from randomization to the date of the first of regional disease recurrence or death due to any cause. Regional recurrence excludes local recurrence and is defined as histologically, cytologically, or radiographically confirmed reappearance of melanoma in the regional lymph node basin. New in-transit melanoma metastases in the regional lymphatic drainage will be reported as regional recurrence. Histological or cytological confirmation of new in-transit metastases is recommended but is not required.**

Add:
- Distant metastases free survival (DMFS): Time from randomization to the date of the first of distant metastases or death due to any cause. **Distant metastases exclude local and regional recurrence and will include distant cutaneous/subcutaneous metastases, distant nodal metastases, or visceral, central nervous system, brain, or bone metastases.**

Section: 10.1.3 Covariates and Subgroups, bullet 5

Delete:
- The sum of the products of the two largest perpendicular diameters of baseline measurable lesions ~~(SPD)~~

Section: 10.2 Sample Size Considerations, paragraphs 2, 3, and 4

Replace: Approximately 150 subjects will be randomized 1:1 to receive arm 1 vs arm 2 stratified by: (i) disease stage (IIIB nodal vs IIIB in-transit vs IIIC nodal vs IIIC in-transit with nodal vs IVM1a), and (ii) planned adjuvant therapy (INFα with or without radiotherapy vs radiotherapy without INFα vs none).

With:	Approximately 150 subjects will be randomized 1:1 to receive **A**rm 1 vs **A**rm 2 stratified by: (i) disease stage (IIIB nodal vs IIIB in-transit vs IIIC nodal vs IIIC in-transit with nodal vs IVM1a), and (ii) planned adjuvant therapy (**adjuvant systemic therapy [eg, INFα, ipilimumab] with or without radiotherapy vs radiotherapy without adjuvant systemic therapy vs none.**
Add:	Subjects who are not confirmed to be disease-free post-surgery (ie, who do not have an R0 surgical outcome) or who withdraw prior to surgery will be considered a failure a~~t~~ **day after** randomization for RFS.
Add:	The primary analysis for the primary endpoint will occur at the later time of either the occurrence of approximately 64 events (local**, regional,** or distant recurrence of
Section:	Table 5. Study Design Characteristics, 2-year RFS, Arm 1
Replace:	0.60
With:	**0.70**
Add:	**0.725, 0.750**
Section:	Table 5. Study Design Characteristics, 2-year RFS, Arm 2
Replace:	0.70
With:	**0.60**
Delete:	~~0.725, 0.750~~
Section:	10.3 Access to Individual Subject Treatment Assignments by Amgen or Designees
Delete:	~~To guard against actual or perceived bias due to subjective decisions made by Amgen or designees in light of the treatment knowledge and data captured during the study, Amgen will implement a Trial Integrity Document (TID). The TID will include study-specific guidelines to restrict access to aggregate postbaseline data by randomized or received treatment until the primary analysis. Details of which sponsor staff or designees can access the data and their level of access will be provided in the TID. Amgen will finalize the TID before the first subject is randomized in the study.~~

Section: 10.4.1 Interim Analyses

Add: **A Data Review Team (DRT) independent of the talimogene laherparepvec product team will review the first interim analysis (see Section10.4.2). The DRT will also review some efficacy endpoints (eg, R0 resection rate, pCR rate, response to neoadjuvant treatment).**

The talimogene laherparepvec product team will review the second interim analysis because it will occur after all subjects have been already treated, have completed safety follow-up, and no additional interventions that may influence safety or efficacy of the investigational product are planned after this time point. The talimogene laherparepvec product team will also review some efficacy endpoints (eg, R0 resection rate, pCR rate, response to neoadjuvant treatment).

Ad hoc analyses for safety or some efficacy endpoints (eg, response to neoadjuvant treatment, R0 resection rate, pCR rate) may be conducted before the planned primary and/or final analyses if interim data are required for submission to regulatory authorities. These ad hoc analyses will be executed by the talimogene laherparepvec product team.

Section: 10.4.2 Data Review Team (DRT)

Delete: ~~A Data Review Team (DRT) independent of the talimogene laherparepvec product team will be formed.~~

Add: **The DRT will be supported by a statistician internal to Amgen but independent of the talimogene laherparepvec product team.** ~~This team~~The **DRT** will review unblinded safety data at the **first** interim analys**i**s.

Section: 10.4.3 Primary Analysis

Add: The primary analyses for RFS will occur at the later time of either the occurrence of approximately 64 events (local**, regional,** or distant recurrence of melanoma or death) or

Section: 10.5.3 Secondary Efficacy Endpoints

Add: KM estimates will be calculated for RFS, LRFS, **RRFS,** DMFS, OS landmarks (2-, 3- and 5-year rates) and quartiles.

Add: For each group the equal-precision band method will be used to calculate a simultaneous confidence band for RFS, LRFS, **RRFS**, and DMFS over the interval from 2 to 5 years (Nair, 1984). An overall between-group difference in **RFS,** LRFS, **RRFS,** DMFS, and OS will be

Section:	10.5.4 Safety Endpoints
Delete:	~~The incidence of subjects with positive qPCR analysis result of talimogene laherparepvec DNA in blood and urine samples will be calculated. The incidence of subjects with positive qPCR analysis result of talimogene laherparepvec DNA and positive TCID50 assay analysis result of talimogene laherparepvec viral infectivity in oral mucosa and genital swab samples, respectively, will be calculated.~~
Section:	13 References
Add:	**Eggermont AMM, Chiarion-Sileni V, Grob JJ, et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomized, double-blind, phase 3 trial. *Lancet Oncol.* 2015;16:522-530.**
Add:	**Imlygic™ (talimogene laherparepvec) Prescribing Information, Amgen Europe B.V, 2015.**
Add:	**Summary of Imlygic™ Product Characteristics, Amgen Europe B.V, 2015.**
Replace:	Talimogene Laherparepvec Investigator's Brochure, Edition 10.0. Woburn, MA. BioVEX (a wholly owned subsidiary of Amgen); 17 January 2014.
With:	Talimogene Laherparepvec Investigator's Brochure, Edition 1**3**. Woburn, MA. BioVEX (a wholly owned subsidiary of Amgen); 201**5**.
Add:	**Yervoy™ (ipilimumab) Prescribing Information, Bristol-Myers Squibb, 2015.**
Section:	Appendix D World Health Organization (WHO) Response Criteria
Add:	**Modified** World Health Organization (WHO) Response Criteria
Replace:	(Note: When a lesion can be evaluated by both, clinical examination and imaging, radiographic imaging evaluations should be undertaken since it is more objective).
With:	(Note: When a lesion can be evaluated by both, clinical examination and imaging, radiographic imaging evaluations should be **preferred** since it is more objective).
Add:	Measurable Lesions: Measurable lesions are defined at baseline as lesions that can be accurately and serially measured in at least 2 dimensions and for which the longest diameter **in at least 2 dimensions** is:

Add: Coalescing or Splitting Lesions:

Coalescing lesions: When two or more lesions merge and at least one is an index lesion, the largest index lesion prior to merging should be measured and reported during the tumor response assessment. All other merged lesions should be reported as 0 mm x 0 mm (for lesions previously reported as Index or New Measurable Lesions) or absent (for lesions previously reported as Non-Index or New Non-Measurable Lesions). If two or more non-index lesions merge, the apparently larger lesion should be reported as present, and smaller lesion(-s) should be reported as absent. The indication that the lesion coalesced with the specified lesion(-s) should be provided for each merged lesion.

Splitting lesions: When an index lesion splits into two or more lesions the largest measurable part of the split lesion will be measured for the current assessment with the indication that the lesion split from the specified lesion, and followed for future assessments. The remaining lesions will be measured as new lesions with an indication that the lesion split from the specified lesion. In this case, appearance of a new lesion from a previous lesion that split will not be considered disease progression solely due to appearance of a new lesion (may be considered 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).

When an non-index lesion splits into two or more lesions, the apparently larger lesion will be reported as a non-index lesion. All other smaller lesions will be reported as new non-index lesions with an indication that the lesion split from the specified lesion. In this case, appearance of a new lesion from a previous lesion that split will not be considered disease progression solely due to appearance of a new lesion (may be considered disease progression due to > 25% increase in the sum of the products of the perpendicular diameters of all index tumors since baseline, or the unequivocal appearance of a new tumor, other than the product of the split tumor, since the last response assessment time point).

Section: Baseline Documentation of "Index Lesions":

Add: **The sum of the products of the largest perpendicular diameters of all index lesions will be calculated and reported.**

If a subject has multiple small superficial cutaneous melanoma lesions at baseline (each lesions is less than 10 mm in at least 2 dimensions) which in aggregate have a total diameter of ≥ 10 mm in at least 2 dimensions, up to 10 largest lesions that were included in this measurement will be reported as "Index Lesions", and the sum of the products of the two largest perpendicular diameters of these lesions will be calculated and reported for tumor response assessments.

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

Section: **Follow-up "Index Lesions":**

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

With: At each subsequent tumor assessment, the **sum of the products of the two largest perpendicular diameters** of the index lesions are added together to provide the total tumor burden.

Section: **Follow-up "New Lesions":**

Delete: At ~~each subsequent~~ tumor assessment, if new measurable lesions have appeared they

Add: At tumor assessment, if new measurable lesions have appeared they should be added to **sum of the products of the two largest perpendicular diameters** ~~SPD~~ of the index lesions to provide the total tumor burden. For nonmeasurable new lesion they should be followed as nonindex lesion as "present", "absent", or in rare cases "unequivocal progression". **If a new lesion(s) that appears in between scheduled tumor response assessments disappear(s) before the next scheduled assessment, there is no need to include this lesion for tumor response evaluation.**

Section: Appendix D, Table 1 Definition of Index Lesion Tumor Response Including New Measurable Lesions

Replace: Achieving a 50% or greater reduction in the SPD of the perpendicular diameters of all index lesions and new measurable lesions, if applicable, at the time of assessment as compared to the sum of the products of the perpendicular diameters of all index lesions at baseline.

With:	Achieving a 50% or greater reduction in the **sum of the products of the two largest perpendicular diameters** of all index lesions and new measurable lesions, if applicable, at the time of assessment as compared to the sum of the products of the perpendicular diameters of all index lesions at baseline.
Replace:	A > 25% increase in the sum of the products of the perpendicular diameters of all index tumors and new measurable lesions, if applicable, since baseline.
With:	**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 measurable lesion since the last response assessment time point.**
Section:	Appendix D, Table 2 Definition of Nonindex Lesion Tumor Response Including New Nonmeasurable Lesions, footnote
Add:	**CR = complete response; SD = stable disease; PD = disease progression; UE = unable to evaluate; NA = not applicable; ND = not done.**
Section:	Appendix D, Table 3 Matrix for Determining the Overall Response at Each Assessment Point, footnote
Delete:	~~PD = disease progression~~
Section:	Appendix F Surgery Guidelines
Add:	The decision~~s~~ to perform surgery on subjects with stage IIIB, IIIC or IV M1a melanoma (dermal, subcutaneous or non-regional lymph node metastases) **is a complex clinical decision making process that** must be based on good clinical judgment **that may include consulting with other relevant medical specialities, and considering patient's preferences**.

Amendment 2

Protocol Title: A Phase 2, Multicenter, Randomized, Open-label Trial Assessing the Efficacy and Safety of Talimogene Laherparepvec Neoadjuvant Treatment Plus Surgery Versus Surgery Alone for Resectable, Stage IIIB to IVM1a Melanoma

Amgen Protocol Number 20110266

Amendment Date: 31 March 2016

Rationale:

The key protocol changes are:

- **Secondary objective**

An objective of regional recurrence-free survival (RRFS) was added to the following secondary objective "To estimate the effect of neoadjuvant talimogene laherparepvec plus surgery compared to surgery alone on local recurrence-free survival (LRFS) and distant metastases-free survival (DMFS)" to better characterize patterns of recurrences of melanoma, which include not only local and distant, but also regional recurrences.

- **Secondary endpoint**

Regional recurrence-free survival was added to the secondary endpoints in parallel to this addition to the secondary objective.

- **Distant metastases free survival**

The efficacy endpoint of DMFS was clarified by specifying what DMFS includes and excludes.

- **Adjuvant ipilimumab information**

Information on adjuvant ipilimumab use was added to the Introduction because ipilimumab was recently approved by the United States Food and Drug Administration (FDA) for the adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy.

- **Marketing information on talimogene laherparepvec**

Marketing information on talimogene laherparepvec (Imlygic™) was added to the Introduction to update the background section because it was recently approved by regulatory authorities for specified indications in the US, Europe, and Australia.

- **Randomization stratification**

Stratification by adjuvant interferon use was replaced with adjuvant systemic therapy to include interferon alpha (INFα) and ipilimumab since ipilimumab has been FDA approved to reduce the risk of melanoma returning after surgery and other systemically active therapy may also be approved for this indication.

- **Number of sites**

The number of sites was changed from 40 to 50 to achieve the enrollment goal.

- **Safety follow-up**

The 30-day safety follow-up was modified to specify that subjects will be followed for local, regional, and distant disease recurrence and for melanoma and adverse events thought to be potentially related to talimogene laherparepvec to align with the schedule of assessment in the Registry Study 20120139. The protocol was also changed to specify that subjects who participate in 20120139 must sign a new informed consent form.

- **Measurable disease inclusion criterion**

Inclusion criterion 106 was clarified to specify that the measurement of the lesion diameter "in at least 2 dimensions" is ≥ 10 mm to align with other talimogene laherparepvec studies. Also, measurement using ultrasound for superficial lymph nodes and subcutaneous lesions was added.

- **Serum lactate dehydrogenase (LDH) level inclusion criterion**

Inclusion criterion 108 was changed as follows: Serum LDH level ≤ 1.**5** x upper limit of normal (ULN) **for stages IIIB and IIIC melanoma and ≤ 1.0 x ULN for Stage IVM1a melanoma** within 28 days prior to randomization, since LDH is not a staging component for Stage III melanoma.

- **Serum albumin inclusion criterion**

Inclusion criterion 109 was modified to include serum albumin ≥ 2.5 g/dL to align with other talimogene laherparepvec studies.

- **Autoimmune disease exclusion criterion**

Exclusion criterion 204 was expanded to clarify symptomatic autoimmune disease to align with the same criterion in other talimogene laherparepvec monotherapy studies.

- **Clinically significant immunosuppression**

The definition of clinically significant immunosuppression was updated in exclusion criterion 205 to align with other talimogene laherparepvec monotherapy studies.

- **Tumor vaccine exclusion criterion**

Exclusion criterion 212 (prior therapy with tumor vaccine) was deleted to align with other talimogene laherparepvec monotherapy studies.

- **Viral transmission during sexual contact exclusion criterion**

The criterion (216) to exclude sexually active subjects and their partners unwilling to use male or female latex condoms to avoid potential viral transmission during sexual contact was added as a condition of marketing approval and to align with other talimogene laherparepvec studies.

- **Talimogene laherparepvec vials**

Each vial contains a minimum of 1.0 mL talimogene laherparepvec at either 10^6 PFU/mL or 10^8 PFU/mL concentrations. The description of the two vial concentrations as green cap and blue cap, respectively, were deleted since they no longer apply.

- **Treatment procedures**

The following statement was added to stress the need to report adjuvant therapies, if planned, via Interactive Voice Response (IVR): If adjuvant therapy (systemic and/or radiation therapy; approved or investigational) is planned, this should be reported via IVR at randomization.

- **Reporting of potentially talimogene laherparepvec related adverse events during long-term follow-up**

Adverse events deemed by the investigator to be potentially related to talimogene laherparepvec (Arm 1 only) and use of subsequent anticancer therapy for melanoma will be collected during long-term follow-up to align this protocol with all other talimogene laherparepvec studies.

- **Activated PTT**

Activated thromboplastin time was added as an alternative to PTT in screening laboratory tests because it may be an alternative test of choice for testing coagulation.

- **Physical examination and ECOG performance status**

Required physical examination and ECOG performance status was added at weeks 4 and 8 to report any change in a patient's performance status.

- **Oral and genital swabbing after surgery**

Oral and genital swabbing for real-time polymerase chain reaction (qPCR) and 50% Tissue Culture Infective Dose (TCID50) assay testing was removed from the safety

follow-up visit because identical information is currently being collected in Study 20120324.

- **Safety Follow-up procedures**

Surgical safety evaluation and recording of subsequent anticancer therapy for melanoma were added to safety follow-up procedures to align the schedule of assessment in the Registry Study 20120139.

- **Pregnancy and lactation reporting**

Reference to Amgen's global Pregnancy and Lactation Surveillance Programs was deleted and replaced by Amgen Global Patient Safety to align with current company practice.

- **Statistical considerations**

RRFS analysis was added to meet the addition of RRFS to the secondary objectives.

The protocol was modified to clarify that a DRT will review the first interim analysis and the talimogene laherparepvec product team will review the second interim analysis, since the second analysis will be performed after all subjects in Arm 1 have been enrolled. The DRT and talimogene laherparepvec product team will also review some efficacy endpoints (eg, R0 resection rate, pCR rate, response to neoadjuvant treatment).

Ad hoc analyses, executed by the talimogene laherparepvec product team, for safety or some efficacy endpoints may be conducted before the planned primary or final analyses if interim data are required for submission to regulatory authorities.

- **Sample size**

In the statement regarding subjects who are not confirmed to be disease-free post-surgery or who withdraw prior to surgery, failure was changed from at randomization to "a day after randomization" for RFS. With this change, the number of subjects at risk at the earliest possible time (randomization +1 day) would not change due to non-melanoma subjects, and would reduce the impact on the Cox model, Kaplan-Meier, and log-rank test results.

- **Trial integrity document**

The mention of using a Trial Integrity Document was deleted to comply with current standard operating procedures.

- **Index lesions**

Language was added to Appendix D (documentation of index lesions) to clarify the recording of aggregate lesions and to align with other talimogene laherparepvec monotherapy studies.

- **Definition of progressive disease for measurable disease**

The definition of progressive disease (PD) was changed to clarify that PD includes the unequivocal appearance of a new measurable lesion since the last response assessment time point, to align with other talimogene laherparepvec studies.

- **Appendix F**

Appendix F was modified to state that the decision to perform surgery may include consulting with other relevant medical specialties and consideration of a patient's preferences, to provide guidance on the decision making process of resection of melanoma.

- **Administrative**

Minor text clarifications, additions, and corrections as well as typographical and formatting changes were made throughout the protocol. The key sponsor contact information was updated to align with current personnel and the talimogene laherparepvec Investigator Brochure reference was updated to the current version. New references were added as needed for newly added text.

Description of Changes (all changes to the Protocol are indicated in bold text)

Section:	All applicable sections and header
Replace:	09 June 2014
With:	**31 March 2016**
Replace:	end point
With:	**endpoint**
Replace:	arm 1, arm 2
With:	**A**rm 1, **A**rm 2
Replace:	(Talimogene Laherparepvec Investigator's Brochure, 2014)
With:	(Talimogene Laherparepvec Investigator's Brochure, 201**5**)
Section	Cover page
Replace:	[redacted] PhD, MD Clinical Research Senior Medical Scientist
With:	[redacted] **MD,** PhD Clinical Research Medical **Director**
Replace:	[redacted] Clinical Research Study Manager Amgen Limited 1 Sanderson Road (Uxbridge Business Park) Uxbridge, UB8 1DH Telephone [redacted] Email: [redacted]
With:	[redacted] Clinical Research Study Manager Amgen Limited 1 Sanderson Road (Uxbridge Business Park) Uxbridge, UB8 1DH Telephone: [redacted] Email: [redacted]
Add:	**Amendment 2 Date 31 March 2016**
Section:	Protocol Synopsis, Secondary Objectives, bullet 4
Add:	• To estimate the effect of neoadjuvant talimogene laherparepvec plus surgery compared to surgery alone on local recurrence-free survival (LRFS)**, regional recurrence-free survival (RRFS),** and distant metastases-free survival (DMFS)

Section: Protocol Synopsis, Secondary Endpoints, bullet 5

Add:
- **RRFS**

Section: Synopsis, Study Design

Replace: Randomization will be stratified by disease stage (IIIB nodal versus IIIB in-transit versus IIIC nodal versus IIIC in-transit with nodal versus IVM1a), planned adjuvant therapy (interferon alpha [INFα] with or without radiotherapy versus radiotherapy without INFα versus none).

With: Randomization will be stratified by disease stage (IIIB nodal versus IIIB in-transit versus IIIC nodal versus IIIC in-transit with nodal versus IVM1a), planned adjuvant therapy (**adjuvant systemic therapy [eg,** interferon alpha (INFα**), ipilimumab]** with or without radiotherapy versus radiotherapy without **adjuvant systemic therapy** versus none).

Add: Subjects will be followed for safety approximately 30 (+15) days after surgery and for disease recurrence **(local, regional, or distant)**, subsequent anticancer therapy **for melanoma, adverse events thought to be potentially related to talimogene laherparepvec (Arm 1 only),** and survival every 3 months (±30 days) for first 3 years after the end of the safety follow-up period and then every 6 months (±30 days) until death, subject withdraws full consent, or up to 5 years after the last subject is randomized. Thereafter, subjects randomized to **A**rm 1 who received at least a single dose of talimogene laherparepvec will be followed under an ongoing separate registry protocol **(Study 20120139)** for the long-term survival follow-up of subjects treated with talimogene laherparepvec. The registry protocol will also monitor for late and long-term adverse events thought to be potentially related to talimogene laherparepvec **and use of subsequent anticancer therapy for melanoma**. **Subjects who after the long-term follow-up period of this study (Study 20110266) will elect to participate in the registry study must sign new informed consent form before any registry protocol-specific activities.**

Section: Synopsis, Key Inclusion Criteria

Replace: Also, subject must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and must have a serum lactate dehydrogenase (LDH) ≤ 1.0 X upper limit of normal and adequate hematologic, hepatic, renal, and coagulation organ function.

With: 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 **(ULN) for stages IIIB/C melanoma and LDH ≤1.0 x ULN for stage IVM1a melanoma** and adequate hematologic, hepatic, renal, and coagulation organ function**s**.

Section:	Synopsis, Key Exclusion Criteria
Replace:	Subject must not have history or evidence of symptomatic autoimmune pneumonitis, glomerulonephritis, vasculitis, or other symptomatic autoimmune disease.
With:	Subject must not have 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**.
Delete:	Subject must not have been treated previously with talimogene laherparepvec ~~or tumor vaccine~~.
Section:	Synopsis, Procedures, Screening, bullets 3 and 4
Delete:	demographics, ~~physical examination,~~ vital signs, and ECOG performance status assessment
Add:	local laboratory tests including, hematology panel, chemistry panel, serum LDH, prothrombin time (PT) (or international normalization ratio [INR]) and partial thromboplastin time (PTT) **(or activated PTT)**, and serum or urine pregnancy test for female subjects of childbearing potential
Section:	Synopsis, Procedures, Treatment, bullets 2, 3, and 8
Add:	• **ECOG performance status**
Add:	• **physical examination**
Add:	histological tumor assessment of the surgical specimen**, including assessment for tumor-free margins (R0 resection for negative margins, R1 or R2 resections for tumor positive margins) and pathological complete response (in Arm 1 only)**
Section:	Synopsis, Procedures, Safety Follow-up Visit, bullets 2, 3, and 5
Add:	• **surgical safety evaluation**
Add:	• **documentation of subsequent anticancer therapy for melanoma (including local, regional, or systemic therapy)**

Replace:	• central laboratory tests including blood and urine for qPCR, oral mucosa swabs and genital swabs (if study drug is injected into a melanoma lesion below the waist) for qPCR and 50% Tissue Culture Infective Dose (TCID50) assay testing, and swabs of cold sores, vesicles, and other lesions suspected to be herpetic in origin (if any) for qPCR testing within 24 hours following the investigator's knowledge of the event
With:	• central laboratory tests **of** swabs of cold sores, vesicles, and other lesions suspected to be herpetic in origin (if any) for qPCR testing **of talimogene laherparepvec DNA** within 24 hours following the investigator's knowledge of the event
Section:	Synopsis, Procedures, Long-term Follow-up, paragraphs 1, 2, and 3
Add:	All randomized subjects will be contacted by telephone, or clinic visit, to assess survival status**, collect adverse events deemed by the investigator to be potentially related to talimogene laherparepvec (Arm 1 only),** and, if applicable, commencement of any subsequent anticancer melanoma therapy **(including local, regional, or systemic therapy for melanoma)**.
Add:	every 3 months (±30 days) for 3 years following the safety follow-up visit and then every 6 months (±30 days) until **distant** disease recurrence, death,
Add:	After the long-term follow-up period of this study has ended, subjects **randomized to Arm 1 who received at least a single dose of talimogene laherparepvec and** who end the study for any reason other than death or withdrawal of full consent will be followed for survival under an
Add:	The registry protocol will also monitor for late and long-term adverse events thought to be potentially related to talimogene laherparepvec **and use of subsequent anticancer therapy for melanoma**. **Subjects who after the long-term follow-up period of this study (Study 20110266) will elect to participate in the registry study must sign new informed consent form before any registry protocol-specific activities.**
Section:	Synopsis, Statistical Considerations paragraphs 1, 2, 3, 5, and 6
Add:	The primary analysis for the primary endpoint will occur at the later time of either the occurrence of approximately 64 events (local, **regional,** or distant recurrence of melanoma or death) or approximately 2 years after the end of randomization.

Replace:	Two interim analyses with no formal stopping rules are planned to evaluate safety when approximately 40 and 75 subjects randomized to talimogene laherparepvec have had the opportunity to complete the safety follow-up visit. The primary analysis for certain secondary endpoints will be performed using the data from the second interim analysis.
With:	Two interim analyses with no formal stopping rules are planned to evaluate safety **and some efficacy endpoints (eg, R0 resection rate, pCR rate, response to neoadjuvant treatment)** when approximately 40 and 75 subjects randomized to talimogene laherparepvec have had the opportunity to complete the safety follow-up visit. The primary analysis for certain secondary endpoints **(eg, response to neoadjuvant treatment, R0 resection rate, pCR rate, and safety)** will be performed using the data from the second interim analysis.
Add:	**The primary analyses for RFS will occur at the later time of either the occurrence of approximately 64 events (local, regional, or distant recurrence of melanoma or death) or approximately 2 years after end of randomization.**
Add:	**Ad hoc analyses for safety or some efficacy endpoints (eg, response to neoadjuvant treatment, R0 resection rate, pCR rate) may be conducted before the planned primary and/or final analyses if interim data are required for submission to regulatory authorities.**
Add:	All efficacy analyses will be descriptive with no formal hypothesis testing. Kaplan-Meier (KM) estimates and CI will be calculated for RFS, LRFS, **RRFS,** DMFS, OS landmarks (2-, 3- and 5-year rates) and quartiles. Estimates and CIs for between-group differences will also be calculated. An overall between-group difference in RFS, LRFS, **RRFS,** DMFS, and OS will be
Section:	Study Glossary, definition of end of study (primary completion)
Add:	The primary completion is anticipated to occur at the later time of either occurrence of approximately 64 events (local**, regional,** or distant recurrence of melanoma or death) or approximately 2 years after the end of randomization
Add:	**RRFS - regional recurrence-free survival**
Delete:	~~TCID50 - 50% Tissue Culture Infective Dose~~ ~~TID - Trial Integrity Document~~ ~~SPD - the sum of the products of the two largest perpendicular diameters~~

Section: 1.2 Secondary, bullet 4

Add:
- To estimate the effect of neoadjuvant talimogene laherparepvec plus surgery compared to surgery alone on local recurrence-free survival (LRFS)**, regional recurrence-free survival (RRFS),** and distant metastases-free survival (DMFS)

Section: 2.1 Melanoma and Adjuvant and Neoadjuvant Therapy for Melanoma, paragraphs 2, 7, and 10

Delete: While radical resection is a cornerstone of treatment for subjects with stage~~s~~ III melanoma

Add: The biochemotherapy regimen was associated with substantial toxicity with grade 3 and 4 adverse events in 36% and 40% **of** subjects, respectively (Flaherty et al, 2012).

Add: **Recently, ipilimumab, a a cytotoxic lymphocyte associated antigen 4 (CTLA-4 inhibitor), was approved by the United States Food and Drug Administration for the adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy (Yervoy™, 2015). This approval was based on results of a randomized double-blind phase 3 trial conducted in 951 patients with completely resected stage IIIA (> 1 mm nodal involvement), IIIB, and IIIC melanoma (EORTC 18071). Patients with in-transit metastases were excluded. Ipilimumab improved recurrence-free survival (primary endpoint) in this trial from 17.1 months to 26.1 months (HR 0.75; 95% CI 0.64–0.90; p=0.0013). Results of OS and distant metastasis-free survival (secondary endpoints) are pending. Fifty-two percent of patients randomized to the ipilimumab arm discontinued treatment because of toxicity, 5 patients (1%) died because of ipilimumab-related toxicities. Forty-six percent of patients in the ipilimumab arm experienced grade 3 adverse events (37% immune-related), and 8% grade 4 (6% immune-related) (Eggermont et al, 2015).**

Section: 2.2 Talimogene Laherparepvec Background, paragraphs 8 and 9

Replace: Clinical data currently available have provided evidence of talimogene laherparepvec's efficacy in subjects with regionally and distantly metastatic melanoma

With: Clinical data currently available have provided evidence of talimogene laherparepvec's efficacy in subjects with **unresectable** metastatic melanoma

Add: **Recently, talimogene laherparepvec (Imlygic™) was approved in the USA for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery (with limitation of use: Imlygic has not been shown to improve overall survival or have an effect on visceral metastases) (Imlygic™ Prescribing Information, 2015), in Europe for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (stage IIIB, IIIC, and IVM1a) with no bone, brain, lung or other visceral disease (Imlygic™ Summary of Product Characteristics, 2015), and in Australia as monotherapy for the treatment of melanoma in patients with unresectable cutaneous, subcutaneous, or nodal lesions after initial surgery (Imlygic™ Prescribing Information, 2015).**

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

Section: 2.3 Rationale, paragraph 3

Delete: Additionally, a number of immune-related biomarkers, such as antibodies to melanoma antigens and expression of immune-stimulatory and immune-inhibitory molecules (eg ~~cytotoxic lymphocyte associated antigen 4 [~~CTLA-4~~]~~, program cell death-1 **[**PD-1], program cell death-1 ligand 1 [PD-L1] and others) in tumors or tumor infiltrating T-cells will be assessed to determine any association with clinical outcomes.

Section: 3.1 Study Design, paragraphs 5 and 7

Replace: Randomization will be stratified by disease stage (IIIB nodal versus IIIB in-transit versus IIIC nodal versus IIIC in-transit with nodal versus IVM1a) and planned adjuvant therapy (INFα with or without radiotherapy versus radiotherapy without INFα versus none).

With: Randomization will be stratified by disease stage (IIIB nodal versus IIIB in-transit versus IIIC nodal versus IIIC in-transit with nodal versus IVM1a), planned adjuvant therapy (**adjuvant systemic therapy [eg, INFα, ipilimumab**] with or without radiotherapy versus radiotherapy without **adjuvant systemic therapy** versus none).

Add: Subjects will be followed for safety approximately 30 (+15) days after surgery and for disease recurrence **(local, regional, or distant)**, subsequent anticancer therapy **for melanoma, adverse events thought to be potentially related to talimogene laherparepvec,** and survival every 3 months (±30 days) for first 3 years after the end of the safety follow-up

Add: laherparepvec will be followed under an ongoing separate registry protocol **(Study 20120139)** for the long-term survival follow-up of subjects treated with talimogene

Add: The registry protocol will also monitor for late and long-term adverse events thought to be potentially related to talimogene laherparepvec **and use of subsequent anticancer therapy for melanoma**. **Subjects who after the long-term follow-up period of this study (Study 20110266) will elect to participate in the registry study must sign new informed consent form before any registry protocol-specific activities.**

Section: 3.2 Number of Sites, paragraph 1

Replace: The study will be conducted at approximately 40 sites in Australia, Brazil, United Kingdom, Russia, and USA. Additional sites and countries may be added.

With: The study will be conducted at approximately **5**0 sites in Australia, Brazil, **Europe,** Russia, and USA. Additional sites and countries may be added.

Section: 3.5.1 Study Duration for Subjects

Add: Subjects will be followed for safety approximately 30 (+15) days after surgery and for disease recurrence **(local, regional, or distant)**, subsequent anticancer therapy **for melanoma, adverse events thought to be potentially related to talimogene laherparepvec**, and survival

Section: 3.5.2 End of Study

Add: The primary completion is anticipated to occur at the later time of either the occurrence of approximately 64 events (local**, regional,** or distant recurrence of melanoma or death) or approximately 2 years after the end of randomization.

Section: 4.1.1 Inclusion Criterion, No. 106

Replace: 106 Measurable disease defined as one or more of the following:

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

With: 106 Measurable disease defined as one or more of the following:

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

Section: 4.1.1 Inclusion Criterion, No. 108

Replace: 108 Serum LDH level ≤ 1.0 upper limit of normal (ULN) within 28 days prior to randomization

With: 108 Serum LDH level ≤ 1.**5 x** upper limit of normal (ULN) **for stages IIIB and IIIC melanoma and ≤ 1.0 x ULN for stage IVM1a melanoma** within 28 days prior to randomization

Section: 4.1.1 Inclusion Criterion, No. 109

Add:

- Hepatic
  - serum bilirubin ≤ 2.0 x ULN
  - **serum albumin ≥ 2.5 g/dL**
  - aspartate aminotransferase (AST) ≤ 2.5 x ULN
-

Section: 4.1.2 Exclusion Criterion, No. 204

Replace: 204 History or evidence of symptomatic autoimmune pneumonitis, glomerulonephritis, vasculitis, or other symptomatic autoimmune disease

With: 204 History or evidence of symptomatic autoimmune **disease (such as** pneumonitis, glomerulonephritis, vasculitis, or other**), or history of** autoimmune disease **that required systemic treatment (ie, use of corticosteroids, immunosuppressive drugs or biological agents used for treatment of autoimmune diseases) in past 2 months prior to enrollment. Replacement therapy (eg, thyroxine for hypothyroidism, insulin for diabetes mellitus) is not considered a form of systemic treatment for autoimmune disease.**

Section: 4.1.2 Exclusion Criterion, No. 205

Replace:

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

With:

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

Section: 4.1.2 Exclusion Criterion, No. 212

Delete: ~~212 Prior therapy with tumor vaccine~~

Section: 4.1.2 Exclusion Criterion, No. 216

Add: **216 Sexually active subjects and their partners unwilling to use male or female latex condoms to avoid potential viral transmission during sexual contact while on treatment and within 30 days after treatment with talimogene laherparepvec**

Section: 5.1 Randomization/Treatment Assignment

Replace: The IVR system will assign a randomization number. Approximately 150 subjects will be stratified by disease stage (IIIB nodal versus IIIB in-transit versus IIIC nodal versus IIIC in-transit with nodal versus IVM1a) and planned adjuvant therapy (INFα with or without radiotherapy versus radiotherapy without INFα versus none).

With: The IVR system will assign a randomization number. Approximately 150 subjects will be stratified by disease stage (IIIB nodal versus IIIB in-transit versus IIIC nodal versus IIIC in-transit with nodal versus IVM1a) and planned adjuvant therapy (**adjuvant systemic therapy [eg, INFα, ipilimumab]** with or without radiotherapy versus radiotherapy without **adjuvant systemic therapy** versus none).

Section: 6.2.1 Amgen Investigational Product Talimogene Laherparepvec

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

Section: 6.5 Other Treatment Procedures

Add: **If adjuvant therapy (systemic and/or radiation therapy; approved or investigational) is planned, this should be reported via IVR at randomization.**

Section: 7.1 Table 2. Schedule of Assessments for Arm 1 (Talimogene Laherparepvec Plus Surgery)

Add: **Adverse Events Potentially Related to Treatment with Talimogene Laherparepvec**
X under Long-term Follow-up

Add: **X** under week 1, week 4, and week 8 for physical exam

Add: **X** under week 4 and week 8 for ECOG performance status

Add:	Subsequent **A**nticancer **T**herapy **for melanoma**
Delete:	~~Blood and urine for qPCR~~
Delete:	~~Oral Mucosa Swab for qPCR and TCID50 Assay~~
Delete:	~~Genital Swab for qPCR and TCID50 Assay~~ [d]
Delete:	[d]~~Genital swab sample is required if talimogene laherparepvec is injected into a melanoma lesion below the waist~~.
Add:	[d]**Surgical specimens will be assessed for presence of viable tumor and tumor margin status for cutaneous and subcutaneous tumor; please refer to Section 7.2.2.**
Section:	7.1 Table 3. Schedule of Assessment for Arm 2 (Surgery Alone)
Add:	Subsequent **A**nticancer **T**herapy **for Melanoma**
Add:	[d] **Surgical specimens will be assessed for presence of viable tumor and tumor margin status for cutaneous and subcutaneous tumor; please refer to Section 7.2.2..**
Section:	7.2 Table 4. Laboratory Analytes
Delete:	~~TCID50 assay for talimogene laherparepvec viral infectivity~~
Section:	7.2.1 Screening and Randomization, bullet 10
Delete:	~~and CT scan or~~
Section:	7.2.2 Treatment
Add:	• Physical examination as per standard of care Arm 1: within 3 days prior to talimogene laherparepvec administration on day 1 of week 1 and within 3 days prior to surgery, **and prior to talimogene laherparepvec administration on day 1 of weeks 4 and 8**
Add:	• ECOG performance status – Arm 1: **prior to talimogene laherparepvec administration on day 1 of weeks 4 and 8 and** within 3 days prior to the surgery
Add:	– A pathological complete response (pCR) **in Arm 1** is defined as no evidence of viable tumor cells on complete pathological evaluation of the surgical specimen per institutional standards of care

Section: 7.2.3 Safety Follow-up Visit

Delete:

- Central laboratory assessments:
  - ~~Arm 1: blood and urine samples for qPCR analysis~~
  - ~~Arm 1: swab of oral mucosa for qPCR and 50% Tissue Culture Infective Dose (TCID50) assay testing:~~
    - ~~Initially, a qPCR analysis will be performed on the swab sample to evaluate whether the talimogene laherparepvec DNA is detectable in the sample:~~
      - ~~i. If result of the qPCR testing is negative, TCID50 assay testing is not required~~
      - ~~ii. If the result of the qPCR testing is positive, then a TCID50 assay will be performed on the swab sample to assess viral infectivity~~
  - ~~Arm 1: genital swabs for qPCR and TCID50 assay testing is required if talimogene laherparepvec is injected into a melanoma lesion below the waist:~~
    - ~~Initially, a qPCR analysis will be performed on the swab sample to evaluate whether the talimogene laherparepvec DNA is detectable in the sample:~~
      - ~~i. If result of the qPCR testing is negative, TCID50 assay testing is not required~~
      - ~~ii. If the result of the qPCR testing is positive, then a TCID50 assay will be performed on the swab sample to assess viral infectivity~~

Add:

- Documentation of subsequent anticancer therapy **for melanoma (including local, regional, or systemic therapy)**

Section: 7.2.4 Long-term Follow-up

Add: All randomized subjects will be contacted by telephone, or clinic visit, to assess survival status**, collect adverse events deemed by the investigator to be potentially related to** t**alimogene laherparepvec (Arm 1 only),** and, if applicable, commencement of any subsequent anticancer melanoma therapy.

Add: Radiographic tumor imaging, clinical tumor assessments, and tumor response assessments, will be performed as documented in Section 7.2.2 every 3 months (±30 days) for 3 years following the safety follow-up visit and then every 6 months (±30 days) until **distant** disease recurrence, death, subject withdraws full consent, or up to 5 years after the last subject is randomized, whichever is first. **Local and regional recurrences will be reported until appearance of distant recurrence, or end of study, whichever is first. Local recurrence is defined as histologically or cytologically confirmed reappearance of melanoma in the area of up to 2 cm from the scar from the surgical excision or at the edge of the skin graft if that was used for closure. Regional recurrence (excludes local recurrence) is defined as histologically, cytologically, or radiographically confirmed reappearance of melanoma in the regional lymph node basin. New in-transit melanoma metastases**

in the regional lymphatic drainage will be reported as regional recurrence. Histological or cytological confirmation of new in-transit metastases is recommended but is not required. Distant metastases exclude local and regional recurrence and will include distant cutaneous/subcutaneous metastases, distant nodal metastases, or visceral, central nervous system, brain, or bone metastases.

Add: After the long-term follow-up period of this study has ended, subjects **randomized to Arm 1 who received at least a single dose of talimogene laherparepvec and** who end the study for any reason other than death or withdrawal of full consent will be followed for survival under an ongoing separate registry protocol (Study 20120139) that is in place for the long-term follow-up of all subjects treated with talimogene laherparepvec in clinical trials.

Add: The registry protocol will also monitor for late and long-term adverse events thought to be potentially related to talimogene laherparepvec **and use of subsequent anticancer therapy for melanoma**. **Subjects who after the long-term follow-up period of this study (20110266) will elect to participate in the registry study must sign new informed consent form before any registry protocol-specific activities.**

Section: 7.3.1 Blood Samples

Add: Blood samples are to be collected for biomarker development at time points designated in the Schedule of Assessments (Table 2 **and Table 3**) and as described in Section 7.2.2.

Section: 9.3 Pregnancy and Lactation Reporting

Replace: The pregnancy should be reported to Amgen's global Pregnancy Surveillance Program within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C). The Pregnancy Surveillance Program will seek to follow the pregnant woman throughout her pregnancy and her baby up to 12 months after birth.

With: The pregnancy should be reported to Amgen **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).

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

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

Section: 10.1.1.1 Primary Endpoint

Add:
- Recurrence-Free Survival (RFS): RFS is defined as time from randomization to the date of the first of local**, regional,** or distant recurrence of melanoma or death due to any cause.

Section: 10.1.1.2 Secondary Endpoint, bullets 1, 4, 5, and 6

Add:
- 2-year, 3-year, 5-year RFS: The Kaplan-Meier (K-M) estimate of RFS rate at 2 **years**, 3 years and 5 years

Add: Local recurrence is defined as histologically or cytologically confirmed reappearance of melanoma in the **in the area of up to 2 cm from the** scar from the surgical excision

Add:
- **Regional recurrence-free survival (RRFS): Time from randomization to the date of the first of regional disease recurrence or death due to any cause. Regional recurrence excludes local recurrence and is defined as histologically, cytologically, or radiographically confirmed reappearance of melanoma in the regional lymph node basin. New in-transit melanoma metastases in the regional lymphatic drainage will be reported as regional recurrence. Histological or cytological confirmation of new in-transit metastases is recommended but is not required.**

Add:
- Distant metastases free survival (DMFS): Time from randomization to the date of the first of distant metastases or death due to any cause. **Distant metastases exclude local and regional recurrence and will include distant cutaneous/subcutaneous metastases, distant nodal metastases, or visceral, central nervous system, brain, or bone metastases.**

Section: 10.1.3 Covariates and Subgroups, bullet 5

Delete:
- The sum of the products of the two largest perpendicular diameters of baseline measurable lesions ~~(SPD)~~

Section: 10.2 Sample Size Considerations, paragraphs 2, 3, and 4

Replace: Approximately 150 subjects will be randomized 1:1 to receive arm 1 vs arm 2 stratified by: (i) disease stage (IIIB nodal vs IIIB in-transit vs IIIC nodal vs IIIC in-transit with nodal vs IVM1a), and (ii) planned adjuvant therapy (INFα with or without radiotherapy vs radiotherapy without INFα vs none).

With:	Approximately 150 subjects will be randomized 1:1 to receive **A**rm 1 vs **A**rm 2 stratified by: (i) disease stage (IIIB nodal vs IIIB in-transit vs IIIC nodal vs IIIC in-transit with nodal vs IVM1a), and (ii) planned adjuvant therapy (**adjuvant systemic therapy [eg, INFα, ipilimumab] with or without radiotherapy vs radiotherapy without adjuvant systemic therapy vs none.**
Add:	Subjects who are not confirmed to be disease-free post-surgery (ie, who do not have an R0 surgical outcome) or who withdraw prior to surgery will be considered a failure at~~t~~ **day after** randomization for RFS.
Add:	The primary analysis for the primary endpoint will occur at the later time of either the occurrence of approximately 64 events (local**, regional,** or distant recurrence of
Section:	Table 5. Study Design Characteristics, 2-year RFS, Arm 1
Replace:	0.60
With:	**0.70**
Add:	**0.725, 0.750**
Section:	Table 5. Study Design Characteristics, 2-year RFS, Arm 2
Replace:	0.70
With:	**0.60**
Delete:	~~0.725, 0.750~~
Section:	10.3 Access to Individual Subject Treatment Assignments by Amgen or Designees
Delete:	~~To guard against actual or perceived bias due to subjective decisions made by Amgen or designees in light of the treatment knowledge and data captured during the study, Amgen will implement a Trial Integrity Document (TID). The TID will include study-specific guidelines to restrict access to aggregate postbaseline data by randomized or received treatment until the primary analysis. Details of which sponsor staff or designees can access the data and their level of access will be provided in the TID. Amgen will finalize the TID before the first subject is randomized in the study.~~

Section: 10.4.1 Interim Analyses

Add: **A Data Review Team (DRT) independent of the talimogene laherparepvec product team will review the first interim analysis (see Section10.4.2). The DRT will also review some efficacy endpoints (eg, R0 resection rate, pCR rate, response to neoadjuvant treatment).**

The talimogene laherparepvec product team will review the second interim analysis because it will occur after all subjects have been already treated, have completed safety follow-up, and no additional interventions that may influence safety or efficacy of the investigational product are planned after this time point. The talimogene laherparepvec product team will also review some efficacy endpoints (eg, R0 resection rate, pCR rate, response to neoadjuvant treatment).

Ad hoc analyses for safety or some efficacy endpoints (eg, response to neoadjuvant treatment, R0 resection rate, pCR rate) may be conducted before the planned primary and/or final analyses if interim data are required for submission to regulatory authorities. These ad hoc analyses will be executed by the talimogene laherparepvec product team.

Section: 10.4.2 Data Review Team (DRT)

Delete: ~~A Data Review Team (DRT) independent of the talimogene laherparepvec product team will be formed.~~

Add: **The DRT will be supported by a statistician internal to Amgen but independent of the talimogene laherparepvec product team.** ~~This team~~The **DRT** will review unblinded safety data at the **first** interim analys**i**s.

Section: 10.4.3 Primary Analysis

Add: The primary analyses for RFS will occur at the later time of either the occurrence of approximately 64 events (local**, regional,** or distant recurrence of melanoma or death) or

Section: 10.5.3 Secondary Efficacy Endpoints

Add: KM estimates will be calculated for RFS, LRFS, **RRFS,** DMFS, OS landmarks (2-, 3- and 5-year rates) and quartiles.

Add: For each group the equal-precision band method will be used to calculate a simultaneous confidence band for RFS, LRFS, **RRFS**, and DMFS over the interval from 2 to 5 years (Nair, 1984). An overall between-group difference in **RFS,** LRFS, **RRFS,** DMFS, and OS will be

Section:	10.5.4 Safety Endpoints
Delete:	~~The incidence of subjects with positive qPCR analysis result of talimogene laherparepvec DNA in blood and urine samples will be calculated. The incidence of subjects with positive qPCR analysis result of talimogene laherparepvec DNA and positive TCID50 assay analysis result of talimogene laherparepvec viral infectivity in oral mucosa and genital swab samples, respectively, will be calculated.~~
Section:	13 References
Add:	**Eggermont AMM, Chiarion-Sileni V, Grob JJ, et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomized, double-blind, phase 3 trial. *Lancet Oncol.* 2015;16:522-530.**
Add:	**Imlygic™ (talimogene laherparepvec) Prescribing Information, Amgen Europe B.V, 2015.**
Add:	**Summary of Imlygic™ Product Characteristics, Amgen Europe B.V, 2015.**
Replace:	Talimogene Laherparepvec Investigator's Brochure, Edition 10.0. Woburn, MA. BioVEX (a wholly owned subsidiary of Amgen); 17 January 2014.
With:	Talimogene Laherparepvec Investigator's Brochure, Edition 1**3**. Woburn, MA. BioVEX (a wholly owned subsidiary of Amgen); 201**5**.
Add:	**Yervoy™ (ipilimumab) Prescribing Information, Bristol-Myers Squibb, 2015.**
Section:	Appendix D World Health Organization (WHO) Response Criteria
Add:	**Modified** World Health Organization (WHO) Response Criteria
Replace:	(Note: When a lesion can be evaluated by both, clinical examination and imaging, radiographic imaging evaluations should be undertaken since it is more objective).
With:	(Note: When a lesion can be evaluated by both, clinical examination and imaging, radiographic imaging evaluations should be **preferred** since it is more objective).
Add:	Measurable Lesions: Measurable lesions are defined at baseline as lesions that can be accurately and serially measured in at least 2 dimensions and for which the longest diameter **in at least 2 dimensions** is:

Add: Coalescing or Splitting Lesions:

Coalescing lesions: When two or more lesions merge and at least one is an index lesion, the largest index lesion prior to merging should be measured and reported during the tumor response assessment. All other merged lesions should be reported as 0 mm x 0 mm (for lesions previously reported as Index or New Measurable Lesions) or absent (for lesions previously reported as Non-Index or New Non-Measurable Lesions). If two or more non-index lesions merge, the apparently larger lesion should be reported as present, and smaller lesion(-s) should be reported as absent. The indication that the lesion coalesced with the specified lesion(-s) should be provided for each merged lesion.

Splitting lesions: When an index lesion splits into two or more lesions the largest measurable part of the split lesion will be measured for the current assessment with the indication that the lesion split from the specified lesion, and followed for future assessments. The remaining lesions will be measured as new lesions with an indication that the lesion split from the specified lesion. In this case, appearance of a new lesion from a previous lesion that split will not be considered disease progression solely due to appearance of a new lesion (may be considered 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).

When an non-index lesion splits into two or more lesions, the apparently larger lesion will be reported as a non-index lesion. All other smaller lesions will be reported as new non-index lesions with an indication that the lesion split from the specified lesion. In this case, appearance of a new lesion from a previous lesion that split will not be considered disease progression solely due to appearance of a new lesion (may be considered disease progression due to > 25% increase in the sum of the products of the perpendicular diameters of all index tumors since baseline, or the unequivocal appearance of a new tumor, other than the product of the split tumor, since the last response assessment time point).

Section:	Baseline Documentation of "Index Lesions":
Add:	**The sum of the products of the largest perpendicular diameters of all index lesions will be calculated and reported.** **If a subject has multiple small superficial cutaneous melanoma lesions at baseline (each lesions is less than 10 mm in at least 2 dimensions) which in aggregate have a total diameter of ≥ 10 mm in at least 2 dimensions, up to 10 largest lesions that were included in this measurement will be reported as "Index Lesions", and the sum of the products of the two largest perpendicular diameters of these lesions will be calculated and reported for tumor response assessments.**
Delete:	~~The sum of the products of the two largest of perpendicular diameters (SPD) of all index lesions will be calculated and reported~~.
Section:	**Follow-up "Index Lesions":**
Replace:	At each subsequent tumor assessment, the SPD of the index lesions are added together to provide the total tumor burden.
With:	At each subsequent tumor assessment, the **sum of the products of the two largest perpendicular diameters** of the index lesions are added together to provide the total tumor burden.
Section:	**Follow-up "New Lesions":**
Delete:	At ~~each subsequent~~ tumor assessment, if new measurable lesions have appeared they
Add:	At tumor assessment, if new measurable lesions have appeared they should be added to **sum of the products of the two largest perpendicular diameters** ~~SPD~~ of the index lesions to provide the total tumor burden. For nonmeasurable new lesion they should be followed as nonindex lesion as "present", "absent", or in rare cases "unequivocal progression". **If a new lesion(s) that appears in between scheduled tumor response assessments disappear(s) before the next scheduled assessment, there is no need to include this lesion for tumor response evaluation.**
Section:	Appendix D, Table 1 Definition of Index Lesion Tumor Response Including New Measurable Lesions
Replace:	Achieving a 50% or greater reduction in the SPD of the perpendicular diameters of all index lesions and new measurable lesions, if applicable, at the time of assessment as compared to the sum of the products of the perpendicular diameters of all index lesions at baseline.

With:	Achieving a 50% or greater reduction in the **sum of the products of the two largest perpendicular diameters** of all index lesions and new measurable lesions, if applicable, at the time of assessment as compared to the sum of the products of the perpendicular diameters of all index lesions at baseline.
Replace:	A > 25% increase in the sum of the products of the perpendicular diameters of all index tumors and new measurable lesions, if applicable, since baseline.
With:	**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 measurable lesion since the last response assessment time point.**
Section:	Appendix D, Table 2 Definition of Nonindex Lesion Tumor Response Including New Nonmeasurable Lesions, footnote
Add:	**CR = complete response; SD = stable disease; PD = disease progression; UE = unable to evaluate; NA = not applicable; ND = not done.**
Section:	Appendix D, Table 3 Matrix for Determining the Overall Response at Each Assessment Point, footnote
Delete:	~~PD = disease progression~~
Section:	Appendix F Surgery Guidelines
Add:	The decision~~s~~ to perform surgery on subjects with stage IIIB, IIIC or IV M1a melanoma (dermal, subcutaneous or non-regional lymph node metastases) **is a complex clinical decision making process that** must be based on good clinical judgment **that may include consulting with other relevant medical specialities, and considering patient's preferences**.

Amendment 1

Protocol Title: A Phase 2, Multicenter, Randomized, Open-label Trial Assessing the Efficacy and Safety of Talimogene Laherparepvec Neoadjuvant Treatment Plus Surgery Versus Surgery Alone for Resectable, Stage IIIB to IVM1a Melanoma

Amgen Protocol Number (Talimogene Laherparepvec) 20110266

Amendment Date: 09 June 2014

Rationale: The protocol was updated due to discrepancy noted in Section 10.4.2 (Data Review Team [DRT]) concerning the inclusion of external clinical expert to serve as a DRT member.

Description of Changes:

Section: Header

Protocol date

From:

23 May 2014

To:

09 June 2014

Section: Protocol Title Page

Add:

Amendment 1 Date: 09 June 2014

Section: Investigator's Agreement

From:

I have read the attached protocol entitled A Phase 2, Multicenter, Randomized, Open-label Trial Assessing the Efficacy and Safety of Talimogene Laherparepvec Neoadjuvant Treatment Plus Surgery Versus Surgery Alone for Resectable, Stage IIIB to IVM1a Melanoma, dated 23 May 2014, and agree to abide by all provisions set forth therein.

To:

I have read the attached protocol entitled A Phase 2, Multicenter, Randomized, Open-label Trial Assessing the Efficacy and Safety of Talimogene Laherparepvec Neoadjuvant Treatment Plus Surgery Versus Surgery Alone for Resectable, Stage IIIB to IVM1a Melanoma, dated **09 June 2014**, and agree to abide by all provisions set forth therein.

Section 10.4.2: Data Review Team (DRT)

Sentence 3

From:

In addition the DRT will also include one or more external clinical expert(s) (a surgical oncologist in melanoma and a clinical virologist) who are not directly involved in the conduct of the study.

To:

In addition, the DRT **may** include one or more external clinical expert(s) (**eg**, a surgical oncologist in melanoma) not directly involved in the conduct of the study.