Title Page

Protocol Title:		Phase 2 Study of Talimogene Laherparepvec in Combination With Pembrolizumab in Subjects With Unresectable/Metastatic Stage IIIB-IVM1d Melanoma Who Have Progressed on Prior Anti-PD-1 Based Therapy
Short Protocol Title:		MASTERKEY-115
Protocol Number:		20180115
Investigational Product:		Talimogene Laherparepvec (T-VEC)
Trade Name:		Imlygic®
Sponsor	**Name of Sponsor:**	Amgen Inc.
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	Function:	Global Development
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EudraCT Number:		2019-001906-61
NCT Number:		NCT04068181
Protocol Date:		**Document Version** — **Date** Original — 17 May 2019 Amendment 1 — 24 July 2019 Amendment 2 — 10 March 2020 **Amendment 3 — 09 June 2021**
Version/Date:		**Data Element Standards Version** 6.2

Confidentiality Notice

This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures. **This format and content of this protocol is aligned with Good Clinical Practice: Consolidated Guidance (ICH E6).**

Investigator's Agreement:

I have read the attached protocol entitled Phase 2 Study of Talimogene Laherparepvec in Combination With Pembrolizumab in Subjects with Unresectable/Metastatic Stage IIIB-IVM1d Melanoma Who Have Progressed on Prior Anti-PD-1 Based Therapy, dated **09 June 2021**, and agree to abide by all provisions set forth therein.

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

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

_____
Signature

_____ _____
Name of Investigator Date (DD Month YYYY)

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1. Protocol Synopsis

Protocol Title: Phase 2 Study of Talimogene Laherparepvec in Combination With Pembrolizumab in Subjects with Unresectable/Metastatic Stage IIIB-IVM1d Melanoma Who Have Progressed on Prior Anti-PD-1 Based Therapy

Short Protocol Title: MASTERKEY-115

Study Phase: Phase 2

Indication: Unresectable/Metastatic Stage IIIB-IVM1d Melanoma

Rationale

Anti-programmed cell death-1 (PD-1) therapies, pembrolizumab and nivolumab, are currently considered the standard of care for advanced melanoma in the first line metastatic setting. For patients who fail anti-PD-1 therapy, treatment options are limited in advanced melanoma following disease progression during or after anti-PD-1 therapy, thus it is considered an unmet medical need. In patients with advanced metastatic melanoma who harbor a BRAF V600 mutation, both immunotherapy and targeted therapy are recommended as first line treatment in the metastatic setting (ESMO, 2019; NCCN, 2019). National Comprehensive Cancer Network (NCCN) guidelines recommend that targeted therapy is preferred when a rapid clinical response is desired, and treatment continue until maximum clinical benefit is reached. Additionally, for those treated with a BRAF target therapy who have achieved maximum clinical benefit (but not complete remission) a switch to immune checkpoint inhibitor therapy may be considered. Therefore, this protocol allows prior BRAF/MEK inhibitor therapy if clinically indicated but does not mandate prior progression on BRAF/MEK inhibitor. If these patients progress on or after anti-PD-1 therapy, they are also considered an unmet medical need. Additionally, with the recent availability of checkpoint inhibitors in the adjuvant setting, it remains to be understood how patients will be treated upon progression to metastatic disease. The purpose of this study is to explore the safety and efficacy of the talimogene laherparepvec and pembrolizumab combination in patients with unresectable, injectable metastatic IIIB-IVM1d melanoma who have progressed following PD-1 therapy.

The combination of talimogene laherparepvec and pembrolizumab in the first line metastatic setting is being investigated in the MASTERKEY-265 phase 1b/3 study in subjects with unresectable/metastatic IIIB-IVM1c melanoma. The phase 1b portion of the study enrolled 21 subjects who received talimogene laherparepvec and pembrolizumab in combination to establish the safety of the combination. There were no

unanticipated safety signals observed with the combination of talimogene laherparepvec and pembrolizumab. At the time of the phase 1b 6-month primary analysis, the confirmed objective response rate (ORR) and complete response rate (CRR) were 57.1% and 23.8%, respectively, per immune-related Response Criteria (irRC). Median PFS was not reached, with 71% of subjects progression free at 6 months (Long et al, 2016).

Baseline and on therapy biopsies of talimogene laherparepvec injected lesions showed that the combination of talimogene laherparepvec and pembrolizumab changed the tumor microenvironment by increasing the CD8+ T cell infiltration. The response was independent of the baseline CD8+ T cell density. Of the 13 patients with CD8+ density < 1,000 cells/mm^2 at baseline, 9 patients responded to the combination therapy and 4 patients had disease progression (Ribas et al, 2017). These results of the phase 1b study supported continuation of the phase 3 portion of the MASTERKEY-265 study which is a randomized trial comparing combination of talimogene laherparepvec and pembrolizumab to pembrolizumab monotherapy. Enrollment is complete and treatment is ongoing.

This study is intended to provide additional clinical data to support the combination of talimogene laherparepvec and pembrolizumab in patients with unresectable/metastatic IIIB-IVM1d melanoma who have progressed after receiving a checkpoint inhibitor.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To evaluate the efficacy of talimogene laherparepvec in combination with pembrolizumab as assessed by objective response rate (ORR) in subjects with unresectable/metastatic stage IIIB-IVM1d melanoma who have progressed on prior anti-PD-1 therapy	• Overall response (complete response [CR]+partial response [PR]) (by investigator assessment using modified Response Evaluation Criteria in Solid Tumor [RECIST v1.1])
Key Secondary	
• To evaluate the efficacy of talimogene laherparepvec in combination with pembrolizumab, as assessed by: ○ Complete response rate (CRR), best overall response (BOR), durable response rate (DRR),	• Complete response, BOR, durable response, DOR, and disease control, (investigator assessment using modified RECIST v1.1 and modified irRC-RECIST) and overall response using modified irRC-RECIST by investigator assessment

duration of response (DOR), and disease control rate (DCR) ○ ORR using modified irRC-RECIST ○ Progression free survival (PFS) ○ Overall survival (OS)	• PFS (by investigator assessment using modified RECIST v1.1 and modified irRC-RECIST) • OS
• To evaluate the safety of talimogene laherparepvec in combination with pembrolizumab as assessed by incidence of treatment-emergent and treatment-related adverse events, and abnormal laboratory tests in patients who have progressed on prior anti-PD-1 therapy	• Incidence of treatment-emergent and treatment-related adverse events (all adverse events, grade ≥ 3 adverse events, serious adverse events, fatal adverse events, adverse events defined as events of interest), and abnormal laboratory tests
• To evaluate time to subsequent anticancer therapy	• Time to subsequent anticancer therapy

Hypothesis

No formal hypothesis testing will be performed. All analyses will be descriptive in nature.

Overall Design

This is a phase 2, open-label, single-arm, multicenter clinical trial designed to evaluate the efficacy and safety of talimogene laherparepvec in combination with pembrolizumab following disease progression on prior anti-PD-1 therapy in unresectable/metastatic melanoma (stage IIIB-IVM1d) or prior anti-PD-1 therapy in the adjuvant setting.

Subject must have received prior anti-PD-1 therapy for at least 2 to 3 consecutive cycles within an 8-week period (based on administration schedule) and have disease progression as defined by RECIST v1.1 criteria. The initial evidence of disease progression must have been confirmed by a second assessment no less than 4 weeks from the first documented disease progression, in the absence of rapid clinical progression. The anti-PD-1 therapy must be the immediate prior line of therapy before enrollment and subjects with disease progression on more than 1 line of anti-PD-1 therapy are not eligible.

Subjects will be enrolled into 1 of 4 cohorts based on prior anti-PD-1 experience:

- **Cohort 1 – Locally Recurrent/Metastatic - Primary Resistance**

Subjects who received anti-PD1 therapy in the locally recurrent/metastatic setting and experienced a best overall response of disease progression or stable disease prior to confirmed disease progression. The initial date of disease progression must be within 12 weeks of the last dose of a PD-1 inhibitor.

- **Cohort 2 – Locally Recurrent/Metastatic - Acquired Resistance**

Subjects who received anti-PD-1 therapy in the locally recurrent/metastatic setting and experienced confirmed disease progression following a complete or partial response on anti-PD-1 therapy. The disease progression must occur within 12 weeks of the last dose of a PD-1 inhibitor.

- **Cohort 3 – Adjuvant Setting – Disease Free Interval < 6 months**

Subjects who received anti-PD-1 therapy in the adjuvant setting and experienced confirmed disease progression following a disease-free interval of < 6 months after starting the adjuvant anti-PD-1 therapy.

- **Cohort 4 – Adjuvant Setting – Disease Free Interval ≥ 6 months**

Subjects who received anti PD-1 therapy in the adjuvant setting and experienced confirmed disease progression following a disease-free interval of ≥ 6 months after starting the adjuvant PD-1 inhibitor.

Number of Subjects

Seventy-two subjects **were** enrolled with **27** subjects in **c**ohort 1 **and 15** subjects in **c**ohort**s** 2, 3**,** and 4.

Summary of Subject Eligibility Criteria

Key Inclusion Criteria:

This study will enroll subjects who are male or female age ≥ 18 years at the time of informed consent with histologically confirmed diagnosis of melanoma (unresectable or metastatic stage IIIB, IIIC, IIID, IVM1a, IVM1b, IVM1c, or IVM1d melanoma). Subjects with stage IVM1d and up to 3 cerebral metastases may be enrolled, provided that all lesions have been adequately treated with stereotactic radiation therapy, craniotomy, or gamma knife therapy, with no evidence of progression and not requiring steroids for at least 2 months prior to enrollment. Subjects must have measurable disease and be a candidate for intralesional therapy. Subjects must have Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1 and adequate hematologic, hepatic, renal, and coagulation function. Subject must also have received prior anti-PD-1 therapy for at least 2 to 3 consecutive cycles within an 8-week period and have disease progression as defined by RECIST v1.1 criteria. Note: subjects with prior treatment and disease progression on more than 1 line of anti-PD-1 therapy are excluded.

Key Exclusion Criteria:

Subjects must not have clinically active cerebral melanoma metastases and/or carcinomatous meningitis. Subjects must not have primary uveal or mucosal melanoma, history or evidence of melanoma associated with immunodeficiency states (eg, hereditary immune deficiency, organ transplant, or leukemia), or history of other malignancy within the past 3 years with the exceptions noted in Section 6.2.

Subjects must not have been previously treated with talimogene laherparepvec, any other oncolytic viruses, or tumor vaccine (unless administered in the adjuvant setting). Subjects must not have a history or evidence of symptomatic autoimmune glomerulonephritis, vasculitis, or other symptomatic autoimmune disease, or active autoimmune disease or syndrome that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs) except vitiligo or resolved childhood asthma/atopy. Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. Subjects must not have active herpetic skin lesions or prior complications of herpetic infection (eg, herpetic keratitis or encephalitis) and must not require intermittent or chronic treatment with an antiherpetic drug (eg, acyclovir), other than intermittent topical use.

For a full list of eligibility criteria, please refer to Section 6.1 to Section 6.2.

Treatments

Talimogene laherparepvec and pembrolizumab are administered at a once every 3 weeks (Q3W) frequency. When they are administered on the same day, talimogene laherparepvec should be administered first when possible.

Investigational Product(s)/Amgen Medicinal Product(s) (AMP): Talimogene laherparepvec

Talimogene laherparepvec will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures. The supply for the 10^6 PFU/mL concentration will be packaged separately from the supply for the 10^8 PFU/mL concentration.

On day 1 the first dose of talimogene laherparepvec will be up to 4.0 mL of 10^6 PFU/mL by intralesional injection into injectable cutaneous, subcutaneous, and nodal lesions with or without image ultrasound guidance. The second dose of up to 4.0 mL of 10^8 PFU/mL talimogene laherparepvec should be administered 21 (+3) days after the initial dose. Subsequent doses of up to 4.0 mL of 10^8 PFU/mL talimogene laherparepvec should be given every 3 weeks (± 3 days).

The maximum volume of talimogene laherparepvec administered at any dose is 4.0 mL for any individual lesion. The maximum dose in any treatment visit is 4.0 mL. Investigators are encouraged to use the maximum amount whenever lesions' properties allow.

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 1-1.

Table 1-1. 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

Non-Amgen Investigational Product(s): Pembrolizumab

Pembrolizumab will be manufactured by Merck. Pembrolizumab will be labeled, packaged, and distributed by Amgen (or designee) using Amgen (or designee) clinical study drug distribution procedures. Pembrolizumab is supplied as pembrolizumab 100 mg/4 mL vials (25 mg/mL) solution for IV infusion. Pembrolizumab at a dose of 200 mg will be administered IV every 3 weeks (+ 3 days for week 3, ± 3 days after week 3).

Procedures

Written informed consent must be obtained from all subjects before any study-specific screening procedures are performed.

The following procedures will be completed during the screening period at the time point designated in the Schedule of Activities (Table 2-1):

- Collection of medical, surgical, and medication history, review of prior anticancer therapy, a physical examination including body weight, electrocardiogram (ECG), vital signs, ECOG PS, local laboratory assessments including: chemistry, hematology, urinalysis, lactate dehydrogenase (LDH), coagulation, thyroid function tests and pregnancy test for females of childbearing potential (FCBP).
- Clinical and radiographic tumor assessment using modified RECIST v1.1 and modified irRC-RECIST and tumor biopsy.

At specified visits, outlined in the Schedule of Activities (Table 2-1), the following measurements will be collected: body weight, ECGs, vital signs, recording of concomitant medications, as well as review of adverse events and serious adverse events. Blood will be collected for local laboratory testing, including chemistry, hematology, and thyroid function tests. [redacted]. Urine will be collected for urinalysis. Additionally, in FCBP urine or serum pregnancy tests will be performed.

Clinical and radiographic tumor assessments and tumor response assessments using modified RECIST v1.1 and modified irRC-RECIST will be performed, a tumor biopsy will be taken, and a swab may be taken of suspected herpetic lesions.

For a full list of study procedures, including the timing of each procedure, please refer to Section 9.2 and the Schedule of Activities in Table 2-1.

Statistical Considerations

Sample Size Considerations:

This is a single-arm estimation study. It is assumed that if the ORR using modified RECIST v1.1 is at least 25%, for this study (N = 100) the lower bound of the 95% CI for objective response is > 15%.

The 95% CIs for different sample sizes with an assumed ORR of 25% are presented below:

Subjects Enrolled N	Assumed ORR N (%)	95% CI %	Width %
15	4 (26.7)	7.8, 55.1	47.3
30	8 (26.7)	12.3, 45.9	33.6
40	10 (25.**0**)	12.7, 41.2	28.5
70	18 (25.7)	16.0, 37.6	21.6
72	**18 (25.0)**	**15.5, 36.6**	**21.0**
100	25 (25.**0**)	16.9, 34.7	17.8

Actual number of subjects enrolled in the study: a total of 72 subjects were enrolled in the study (instead of N = 100 subjects planned at the beginning of the study). Twenty-seven subjects were enrolled into cohort 1 and 15 subjects were enrolled into cohorts 2, 3, and 4.

Planned Analyses:

A futility analysis is planned for cohorts 1 and 2. Details are provided in Section 10.4.1.1.

The primary analysis will occur when all treated subjects had the opportunity to be followed for at least 24 weeks for tumor assessment. The final analysis will occur when all subjects complete the study. Ad hoc analyses may be conducted before the planned analyses to support program level activities.

All analyses will be descriptive with no formal hypothesis testing. Analyses will be performed separately for each cohort. In addition, analyses with cohorts pooled together for cohorts that were not terminated early due to futility will also be performed.

Efficacy analysis will be performed on the Full Analysis Set (FAS) defined as all enrolled subjects who received at least 1 dose of talimogene laherparepvec and at least 1 dose of pembrolizumab in combination and the Per Protocol Analysis Set (PPAS). The PPAS is a subset of the FAS and includes subjects who do not have important protocol deviations that are considered to have an impact on efficacy outcomes. The proportion of responders for binary endpoints will be summarized with a corresponding exact binomial 95% CI. Duration of response (DOR) among responders, and other time to event endpoints (eg, PFS and OS) will be estimated using the Kaplan-Meier method.

Safety analyses will be performed on the Safety Analysis Set (SAS) defined as all enrolled subjects who received at least 1 dose of talimogene laherparepvec or pembrolizumab. Summaries of the incidence of treatment-emergent and

treatment-related adverse events (all adverse events, grade ≥ 3 adverse events, serious adverse events, fatal adverse events, adverse events defined as events of interest) will be provided. Incidence of all grade 3 and higher laboratory toxicities will be reported. Descriptive statistics will be provided for laboratory test results and biomarker endpoints as appropriate.

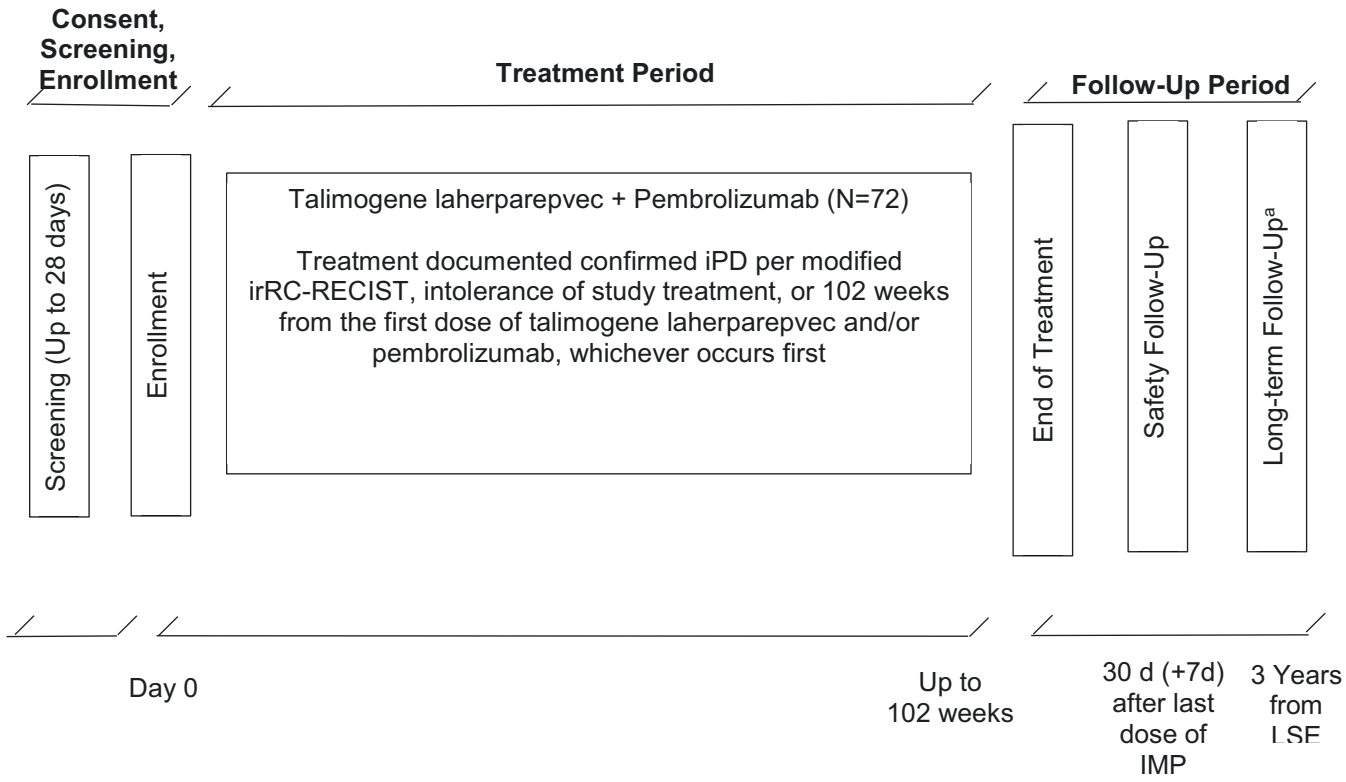
For a full description of statistical analysis methods, please refer to Section 10.

Sponsor Name: Amgen Inc.

2. Study Schema and Schedule of Activities

2.1 Study Schema

Figure 2-1. Study Schema



d = days; iPD = progressive disease (by modified irRC-RECIST); irRC-RECIST = immune-related Response Criteria simulating Response Evaluation Criteria in Solid Tumors; IMP = investigational medicinal product; LSE= last subject enrolled; LTFU = long term follow-up

[a] LTFU is every 12 weeks (± 28 days) following the safety follow-up visit until death, subject withdraws full consent, or up to 36 months after the last subject is enrolled.

2.2 Schedule of Activities

Table 2-1. Schedule of Activities

	Screening			Treatment Period (Weeks)[a]										Follow-up		
PROCEDURE	**≤ 28 days**	**≤ 14 days**	**≤ 72 hr**	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**>24[b]**	**Safety (30 [+7] days post last dose)[c]**	**Survival[d]**	**Notes**
GENERAL AND SAFETY ASSESSMENTS																
Informed consent	X															
Inclusion and exclusion criteria	X															
Demographics	X															
Medical, surgical, and medication history	X															
Substance use history	X															Substances: alcohol and tobacco
Prior anticancer therapy	X															
Physical examination including body weight	X			X										X		
12-lead ECG	X													X		
Vital signs	X			X	X	X	X	X	X	X	X	X	Q3W	X		Systolic/diastolic blood pressure, heart rate, respiration rate, and temperature. When scheduled on dosing days, vital signs are to be performed prior to study treatment administration.
ECOG PS	X			X	X	X	X	X	X	X	X	X	Q3W	X		
Adverse events				X ———										X	X	All adverse events that occur after the first dose of investigational product/study treatment protocol required therapies through the safety follow-up visit will be recorded in the CRF. In addition, talimogene laherparepvec related adverse events that occur after the safety follow-up visit until the end of the long term follow-up will be recorded in the CRF.

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Table 2-1. Schedule of Activities

PROCEDURE	Screening			Treatment Period (Weeks)[a]										Follow-up		Notes
	≤ 28 days	≤ 14 days	≤ 72 hr	0	3	6	9	12	15	18	21	24	>24[b]	Safety (30 [+7] days post last dose)[c]	Survival[d]	
Serious adverse events	X			—	—	—	—	—	—	—	—	—	—	—	X	All serious adverse events that occur after the subject has signed the main informed consent through 90 (+7) days after the cessation of all study treatment or 30 (+7) days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, will be reported to Amgen and recorded in the CRF. In addition, talimogene laherparepvec related serious adverse events that occur after the safety follow-up visit until the end of the long term follow-up will be reported to Amgen and recorded in the CRF **as described in Section 9.2.3.1.1.2. There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after end of study. However, these serious adverse events, including deaths due to progression of the melanoma, should be reported to Amgen (regardless of causality) if the investigator becomes aware of them, as described in Section 9.2.3.1.1.3 (per regional regulatory requirements).** Serious adverse events must be reported to Amgen within 24 hours of the investigator **awareness** of the event.
Pembrolizumab events of clinical interest				X	—	—	—	—	—	—	—	—	X			Selected non-serious and serious AEs known as pembrolizumab Events of Clinical Interest that occur after the first dose of pembrolizumab through 90 (+7) days after the last dose of pembrolizumab, or 30 (+7) days after initiation of a new anticancer therapy, whichever is earlier, must be reported to Amgen within 24 hours of the investigator's **awareness** of the event regardless of attribution to pembrolizumab.
Concomitant therapies review	X			—	—	—	—	—	—	—	—	—	X			

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Table 2-1. Schedule of Activities

PROCEDURE	Screening			Treatment Period (Weeks)[a]										Follow-up		Notes
	≤ 28 days	≤ 14 days	≤ 72 hr	0	3	6	9	12	15	18	21	24	> 24[b]	Safety (30 [+ 7] days post last dose)[c]	Survival[d]	
Subsequent anticancer therapies														X	X	Subsequent anticancer therapies will be collected from the end of investigational product administration through safety and survival follow-up until the subject ends study.
LABORATORY ASSESSMENTS																
Chemistry		X		X	X	X		X		X		X	Q6W	X		Results should be reviewed prior to scheduled study treatment administration.
Hematology		X		X	X	X		X		X		X	Q6W	X		Results should be reviewed prior to scheduled study treatment administration.
Urinalysis		X		X	X	X		X		X		X	Q6W	X		
LDH		X		X	X	X		X		X		X	Q6W	X		
T3 (or FT3), FT4, TSH		X		X	X	X		X		X		X	Q6W	X		Results should be reviewed prior to scheduled study treatment administration if there are symptoms of hypothyroidism or hyperthyroidism.
PT, INR, PTT/aPTT		X														
HSV-1				X	X	X										
Serum and/or urine pregnancy test (females of childbearing potential only)			X											X		Urine or serum pregnancy test to be performed on females of childbearing potential. A urine pregnancy test should be performed within 72 hours prior to enrollment and at the safety follow-up. If urine pregnancy test result is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Note: Additional (eg, monthly) on treatment pregnancy testing should be conducted as required per local laws and regulations, where applicable.

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Table 2-1. Schedule of Activities

PROCEDURE	Screening			Treatment Period (Weeks)[a]										Follow-up		Notes
	≤ 28 days	≤ 14 days	≤ 72 hr	0	3	6	9	12	15	18	21	24	>24[b]	Safety (30 [+7] days post last dose)[c]	Survival[d]	
CLINICAL OUTCOME ASSESSMENTS																
Lesion assessments including radiographic and clinical assessments	X							X				X	Q12W	X	Q12W	Radiographic tumor imaging (CT, PET/CT, or MRI) of the chest, abdomen, and pelvis, and CT or MRI of the brain are required at screening. Tumor assessments must also include all other sites of disease. For subjects who discontinue treatment for any reason other than confirmed **i**PD per modified irRC-RECIST, every effort should be made to complete radiographic assessments every 12 weeks (±1 week) or more frequently if clinically indicated during the long-term follow-up until documentation of confirmed iPD per modified irRC-RECIST (Section 12.10), clinical progression, start of new anticancer therapy, or end of study, whichever occurs first. Subjects who have reached a confirmed CR may increase their interval of radiographic assessments up to 6 months (26 weeks) after the first 2 years beyond confirmed CR and up to 12 months (52 weeks) after the first 5 years beyond confirmed CR as long as CR is maintained. Radiographic imaging is only required at the safety follow up visit if the subject ended treatment prior to confirmed PD and has not had radiographic tumor imaging performed within 4 weeks (+1 week) of the visit.
Modified RECIST v1.1	X							X				X	Q12W	X	Q12W	Following modified RECIST v1.1 tumor assessments will continue through **to** PD. See Section 12.10
Modified irRC-RECIST	X							X				X	Q12W	X	Q12W	Following modified irRC-RECIST, tumor assessments will continue until confirmed iPD. See Section 12.10

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Table 2-1. Schedule of Activities

PROCEDURE	Screening			Treatment Period (Weeks)[a]										Follow-up		Notes
	≤ 28 days	≤ 14 days	≤ 72 hr	0	3	6	9	12	15	18	21	24	>24[b]	Safety (30 [+7] days post last dose)[c]	Survival[d]	
CLINICAL OUTCOME ASSESSMENTS (CONTINUED)																
Survival assessment															X	Subjects will be followed for survival every 12 weeks (± 28 days) from the date of the safety follow-up visit (or from the planned visit date if the safety follow-up visit does not occur) until: death, subject withdraws full consent, or up to 36 months after the last subject is enrolled. Assessments will include anticancer therapy, radiation, surgery, disease progression**, and serious adverse event reporting as described above and in Sections** 9.2.3.1.1.2 **and** 9.2.3.1.1.3**.**
[redacted]																

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Table 2-1. Schedule of Activities

PROCEDURE	Screening			Treatment Period (Weeks)[a]										Follow-up		Notes
	≤ 28 days	≤ 14 days	≤ 72 hr	0	3	6	9	12	15	18	21	24	>24[b]	Safety (30 [+7] days post last dose)[c]	Survival[d]	
Swab of herpetic lesion for qPCR				X	———	———	———	———	———	———	———	———	X			Upon notification of a suspected herpetic lesion by the subject, the subject should be instructed to return to clinic within 3 days of the occurrence of reportable lesion suspected to be herpetic in origin such as cold sores or vesicles. The lesion should be evaluated by the investigator and swabbed if HSV infection is suspected. The sample will be collected, stored, and ultimately tested for the detection of talimogene laherparepvec DNA using qPCR.
OPTIONAL PHARMACOGENETIC ASSESSMENT																
Optional pharmacogenetic assessments	X			X	X	X						X[e]				Additional samples are not collected for this part of the study. Assessments are performed on residual or back-up samples from other assessments. Additional informed consent is required.
STUDY TREATMENT																
Talimogene laherparepvec				X	X	X	X	X	X	X	X	X	Q3W			The first dose of talimogene laherparepvec will be up to 4.0 mL of 10^6 PFU/mL by intralesional injection. Subsequent doses of up to 4.0 mL of 10^8 PFU/mL should be given Q3W until confirmed iCR, disappearance of all injectable lesions, documented confirmed iPD per modified irRC-RECIST, intolerance of study treatment, or 102 weeks from the first dose of talimogene laherparepvec, whichever occurs first.

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Table 2-1. Schedule of Activities

PROCEDURE	Screening			Treatment Period (Weeks)[a]										Follow-up		Notes
	≤ 28 days	≤ 14 days	≤ 72 hr	0	3	6	9	12	15	18	21	24	>24[b]	Safety (30 [+7] days post last dose)[c]	Survival[d]	
STUDY TREATMENT (CONTINUED)																
Pembrolizumab				X	X	X	X	X	X	X	X	X	Q3W			Pembrolizumab at a dose of 200 mg will be administered intravenously every 3 weeks (+ 3 days for week 3, ± 3 days after week 3) **thereafter** until documented confirmed iPD per modified irRC-RECIST, intolerance of study treatment, or 102 weeks from the first dose of pembrolizumab, whichever occurs first.
REPORTING EXPOSURE TO TALIMOGENE LAHERPAREPVEC																
Exposure of healthcare provider or close contact				X———									———X			

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aPTT = activated partial thromboplastin time; $BRAF^{v600}$ = serine/threonine protein kinase BRAF V600; CR = complete response; CRF = case report form; CT = computed tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group Performance Status; FT3 = free triiodothyronine; FT4 = free thyroxine; HSV = herpes simples virus; INR = international normal; iCR = complete response (by modified irRC-RECIST); iPD = progressive disease (by modified irRC-RECIST); irRC-RECIST = immune-related Response Criteria simulating Response Evaluation Criteria in Solid Tumors; iSD = stable disease (by modified irRC-RECIST); LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; PD = progressive disease; PD-L1 = programmed cell death-1 ligand 1; PET = positron emission tomography; PR = partial response; PT = prothrombin time; PTT = partial thromboplastin time; Q3W = once every 3 weeks; Q6W = once every 6 weeks; Q12W = once every 12 weeks; qPCR = real-time polymerase chain reaction; RECIST = Response Evaluation Criteria in Solid Tumor; T3 = triiodothyronine; TSH = thyroid-stimulating hormone

[a] During the treatment period, assessments and procedures will be performed within ± 3 days of the planned visit except where noted. **(Note: the -3 day window does not apply to week 0 and all assessments should be completed following enrollment, using the + 3 day window for the first dose as described in Section 7, if required).**

[b] Each subject will continue in the treatment period with study visits conducted Q3W up to week 102 or until there is a confirmed complete response or confirmed disease progression per modified irRC-RECIST, unacceptable toxicity, or no injectable disease (pembrolizumab administration can continue if talimogene laherparepvec is discontinued due to no injectable disease). Assessments will be performed at the frequencies noted within the respective rows in the table.

[c] .Safety follow-up will be performed approximately 30 (+ 7) days after the last dose of talimogene laherparepvec or pembrolizumab, whichever is later.

[d] Long term follow-up visits will be conducted every 12 weeks (± 28 days) following the safety follow-up visit until death, subject withdraws full consent, or up to 36 months after the last subject is enrolled. **Talimogene laherparepvec related serious adverse events that occur after the safety follow-up visit until the end of the long-term follow-up will be reported to Amgen and recorded in the CRF as described in Section 9.2.3.1.1.2. There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after end of study. However, these serious adverse events, including deaths due to progression of the melanoma, should be reported to Amgen (regardless of causality) if the investigator becomes aware of them (per regional regulatory requirements), as described in Section 9.2.3.1.1.3.**

[redacted]

3. Introduction

3.1 Study Rationale

3.1.1 Rationale for Combination Therapy of Talimogene Laherparepvec and Pembrolizumab in Stage IIIB-IVM1d Unresectable Melanoma Following Progression on a Prior PD-1 Therapy

Historical studies referenced in Section 3.1 to Section 3.3 refer to melanoma staging using the American Joint Committee on Cancer (AJCC) ed. 7 (seventh edition of the AJCC Cancer Staging Manual [Gershenwald et al, 2017]) or earlier editions, while the current study refers to melanoma staging using the AJCC ed. 8 (eighth edition of the AJCC Cancer Staging Manual [Gershenwald et al, 2017]).

Anti-programmed cell death-1 (PD-1) therapies, pembrolizumab and nivolumab, are currently considered the standard of care for advanced melanoma in the first line metastatic setting. For patients who fail anti-PD-1 therapy, treatment options are limited in advanced melanoma following disease progression during or after anti-PD-1 therapy, thus it is considered an unmet medical need. In patients with advanced metastatic melanoma who harbor a BRAF V600 mutation, both immunotherapy and targeted therapy are recommended as first line treatment in the metastatic setting (ESMO, 2019; NCCN, 2019). National Comprehensive Cancer Network (NCCN) guidelines recommend that targeted therapy is preferred when a rapid clinical response is desired, and treatment continue until maximum clinical benefit is reached. Additionally, for those treated with a BRAF target therapy who have achieved maximum clinical benefit (but not complete remission) a switch to immune checkpoint inhibitor therapy may be considered. Therefore, this protocol allows prior BRAF/MEK inhibitor therapy if clinically indicated but does not mandate prior progression on BRAF/MEK inhibitor. If these patients progress on or after anti-PD-1 therapy, they are also considered an unmet medical need.

Additionally, with the recent availability of checkpoint inhibitors in the adjuvant setting, it remains to be understood how patients will be treated upon progression to metastatic disease. The purpose of this study is to explore the safety and efficacy of the talimogene laherparepvec and pembrolizumab combination in patients with unresectable, injectable metastatic IIIB-IVM1d melanoma who have progressed following anti-PD-1 therapy.

Talimogene laherparepvec and PD-1 blockade likely play complementary roles in regulating adaptive immunity. Talimogene laherparepvec likely augments dendritic cell-mediated tumor antigen presentation through local expression of

granulocyte-macrophage colony-stimulating factor (GM-CSF) (Kaufman et al, 2010) and local antigen release by direct tumor lysis. Pembrolizumab prevents T-cell exhaustion in peripheral tissues. The combination of an agent that increases tumor-specific immune activation with 1 that blocks inhibitory T-cell checkpoints could produce greater antitumor activity than either agent alone.

The combination of talimogene laherparepvec and pembrolizumab in the first line metastatic setting is being investigated in the MASTERKEY-265 phase 1b/3 study in subjects with unresectable/metastatic IIIB-IVM1c melanoma. The phase 1b portion of the study enrolled 21 subjects who received talimogene laherparepvec and pembrolizumab in combination to establish the safety of the combination. There were no unanticipated safety signals observed with the combination of talimogene laherparepvec and pembrolizumab. At the time of the phase 1b 6-month primary analysis, the confirmed objective response rate (ORR) and complete response rate (CRR) were 57.1% and 23.8%, respectively, per immune-related Response Criteria (irRC). Median PFS was not reached, with 71% of subjects not having progressed at 6 months (Long et al, 2016). Baseline and on therapy biopsies of talimogene laherparepvec injected lesions, showed that the combination of talimogene laherparepvec and pembrolizumab changed the tumor microenvironment by increasing the CD8+ T cell infiltration. The response was independent of the baseline CD8+ T cell density. Of the 13 patients with CD8+ density < 1,000 cells/mm^2 at baseline, 9 patients responded to the combination therapy and 4 patients had disease progression (Ribas et al, 2017). These results of the phase 1b study supported continuation of the phase 3 portion of the MASTERKEY-265 study which is a randomized trial comparing talimogene laherparepvec and pembrolizumab combination to pembrolizumab monotherapy. Enrollment is complete and treatment is ongoing.

Several retrospective analyses of the safety and clinical activity of various immunotherapies following progression on or shortly after anti-PD-1 therapy were reviewed (Gogas et al 2018, Long et al, 2017). In a retrospective analysis of the Keynote-006 study, 97 subjects were identified who progressed during pembrolizumab treatment and received ipilimumab in the first line of subsequent therapy. Of these 97 subjects, the median duration of time following the last dose of pembrolizumab to the first dose of ipilimumab was 5 weeks and the ORR reported for ipilimumab was 14% (best overall response of complete response [CR] in 3%, PR in 11%, stable disease [SD]

in 33%, progressive disease [PD] in 33%, and unknown in 23% of subjects) (Long et al, 2017).

A retrospective analysis evaluated talimogene laherparepvec monotherapy following progression on prior checkpoint inhibitor therapies in patients with unresectable Stage IIIB-IVM1c metastatic melanoma. In Studies 20120324 and 20120325, 17 and 26 patients, respectively, progressed on prior checkpoint inhibitors, including pembrolizumab, nivolumab, ipilimumab, or nivolumab/ipilimumab prior to enrolling on these studies. The ORR following talimogene laherparepvec was 24% (4 of 17 subjects) and 21% (6 of 26 subjects) including 1 CR (20110324) and 9 PRs (total in both 20120324 and 20120325). Although the retrospective analysis is limited, the ORR and safety observed in this subgroup following talimogene laherparepvec administration is consistent with the ORR observed in the phase 3 OPTiM trial and warrants further studies to understand if talimogene laherparepvec demonstrates clinical activity in the post PD-1 setting (Gogas et al, 2018).

This study is intended to provide additional clinical data to support the combination of talimogene laherparepvec and pembrolizumab in unresectable/metastatic IIIB-IVM1d melanoma specifically in patients who have progressed on prior anti-PD-1 based therapy.

In this study, talimogene laherparepvec will be administered every 3 weeks following the talimogene laherparepvec dosing schedule in Section 7.1.1.1 and pembrolizumab will be administered at a fixed dose of 200 mg every 3 weeks as per Pembrolizumab Investigator's Brochure.

3.2 Background

3.2.1 Disease

In adults, cutaneous melanoma is the fifth most common cancer in men and the seventh most common cancer in women in the United States of America (USA), with an estimated 96,480 new cases and 7,230 deaths expected in 2019 (Siegel et al, 2019). In Europe, the annual incidence of melanoma is somewhat lower than that in the USA, with a crude rate of approximately 15 per 100,000 as compared with 25 per 100,000 in the USA, but is the seventh most common cancer among women (Ferlay et al, 2018; Siegel et al, 2019). In Europe as a whole, approximately 144,200 new cases were diagnosed in 2018 (Ferlay et al, 2018). The incidence of melanoma is increasing rapidly worldwide, with a 270% increase in the USA between 1973 and 2002. This increase is

the most rapid of any cancer with the exception of lung cancer in women (Jemal et al, 2006; Ries et al, 2000).

Cancer has developed multiple mechanisms to successfully avoid recognition by the immune-system and resultant antitumor effector functions, thus limiting the benefits of cancer immunotherapies (Whiteside, 2006). Therapeutic strategies have recently been developed to overcome a tumor's ability to protect itself from targeted immune response. Antibodies that block the inhibitory receptor cytotoxic T-lymphocyte associated antigen 4 (CTLA-4), such as ipilimumab, have been shown to release 1 of these negative immune regulatory pathways, leading to durable responses in a subgroup of patients with metastatic melanoma and an overall survival (OS) benefit in patients with metastatic melanoma (Hodi et al, 2010; Robert et al, 2011).

The PD-1 receptor is another inhibitory receptor expressed by T cells. Its primary ligand, programmed cell death-1 ligand 1 (PD-L1), is frequently expressed within the tumor microenvironment, including cancer cells and tumor-infiltrating macrophages. The PD-1 receptor has a second ligand, programmed cell death-1 ligand 2 (PD-L2), which is preferentially expressed by antigen-presenting cells (Pardoll, 2012). In tumor models, PD-1 negatively regulates the effector phase of T-cell responses after ligation of PD-L1 expressed by the tumor (Blank et al, 2004). It has been postulated that antibodies that block the interaction between PD-1 and PD-L1 in tumors may preferentially release the cytotoxic function of tumor-specific T cells with fewer systemic toxic effects than those that are seen with other immune checkpoint inhibitors (Okazaki and Honjo, 2007; Pardoll, 2012; Ribas; 2012). Inhibitory antibodies targeted to PD-1 and PD-L1 have demonstrated objective responses in multiple tumor types including melanoma (Brahmer et al, 2012; Hamid et al, 2013; Robert et al, 2015a; Robert et al, 2015b). The combination of PD-1 blockade with nivolumab and CTLA-4 blockade with ipilimumab has resulted in longer PFS than either agent alone but was associated with a high rate of grade 3 or 4 adverse events (Larkin et al, 2015).

3.2.2 Amgen Investigational Product Background: Talimogene Laherparepvec

Talimogene laherparepvec is an intralesionally delivered oncolytic immunotherapy comprised of a genetically engineered herpes simplex virus type 1 (HSV-1) that selectively replicates in tumor tissue (Talimogene Laherparepvec Investigator's Brochure). The genes encoding neurovirulence factor ICP34.5 and ICP47 are functionally deleted in the virus, while the gene for human GM-CSF is inserted.

The ICP34.5 functional deletion allows the virus to replicate selectively in tumors. The deletion of ICP47 prevents its function of blocking the transporter associated with antigen processing 1 and 2 and subsequent antigen presentation on major histocompatibility complexes I and II. ICP47 deletion also allows the increased expression of the US11 gene, which 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.

In the open-label, randomized, phase 3 study of talimogene laherparepvec monotherapy versus subcutaneously administered GM-CSF in stage IIIB-IVM1c unresectable melanoma, talimogene laherparepvec or GM-CSF was administered until CR, clinically significant PD, intolerable side effects, 12 months of therapy without an objective response, or withdrawal of consent (OPTiM study, Study 005/05). The primary endpoint of the study was DRR, defined as the rate among subjects with an objective response (CR or partial response [PR]) lasting continuously for 6 months and starting any time within 12 months of initiating therapy. Primary analysis of the OPTiM study showed a statistically significant difference between the rate of durable response among subjects treated with talimogene laherparepvec (16%; 95% CI: 12%, 21%) versus those treated with GM-CSF (2%; 95% CI: 0%, 5%) (p value < 0.0001). Responses were seen in injected, non-injected, and visceral lesions. A difference in the secondary endpoint of OS was also seen with a hazard ratio 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 1, 2, 3, and 4 years 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.

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

remaining 2 fatal adverse events (sepsis in the setting of salmonella infection; myocardial infarction) were not considered treatment-related per investigator (Andtbacka et al, 2013).

The combination of talimogene laherparepvec with ipilimumab, an immune checkpoint inhibitor, for the treatment of subjects with unresected stage IIIB-IV melanoma is currently being evaluated in the ongoing 20110264 phase 1b/2 study. The phase 1b portion of this study enrolled 19 treatment naïve patients of whom 18 were treated with the combination of both talimogene laherparepvec and ipilimumab (Puzanov et al, 2014). The most common adverse events were chills, fatigue, and pyrexia occurring in 11 subjects (58%) each. grade 3 or 4 adverse events of any kind occurred in 6 subjects (32%). The only grade 3 or 4 adverse event occurring in more than 1 subject was grade 3 nausea in 2 subjects. 2 subjects (11%) experienced possible immune-related grade 3 or 4 adverse events attributed either to ipilimumab or the combination of ipilimumab and talimogene laherparepvec. There were no unexpected adverse events attributable to the combination therapy that have not been seen previously with either ipilimumab or talimogene laherparepvec individually. 1 grade 5 adverse event of metastases to the central nervous system occurred during the treatment and safety follow-up period. Analysis performed at a median tumor follow-up time of 15.6 months revealed 9 objective responses (50%) with 4 confirmed CRs (33%) and DRR 44% by irRC (Puzanov et al, 2015). Median PFS was not yet reached with 50% of patients still without progression at 18 months. Median OS was not yet reached with 67% of patients still alive at 18 months. Median time to response was 4.1 months, and median duration of treatment was 13.3 weeks.

phase 2 of the 20110264 study is currently ongoing. Primary analysis of the phase 2 portion of the study was recently reported (Chesney et al, 2018). 198 patients were randomized: 98 in the talimogene laherparepvec + ipilimumab arm and 100 in the ipilimumab arm. Thirty-8 patients (39%) in the combination arm and 18 patients (18%) in the ipilimumab arm had an ORR (odds ratio, 2.9; 95% CI: 1.5 to 5.5; p = 0.002). Responses were not limited to injected lesions. Visceral lesion decreases were observed in 51 patients (52%) in the combination arm and 23 patients (23%) in the ipilimumab arm. Of 183 patients in the safety set (93 in the combination arm and 90 in the ipilimumab arm), the incidences of grade 3/4 treatment related adverse events were 45% in the combination arm and 35% in the ipilimumab arm. The most frequently occurring adverse events included fatigue (combination: 59%, ipilimumab: 42%

respectively), chills (53%, 3%), diarrhea (42%, 35%), pruritus (40%, 36%), rash (39%, 28%) and nausea (38%, 24%). 3 patients in the combination arm had fatal adverse events that were not treatment related.

Refer to the Talimogene Laherparepvec Investigator's Brochure for additional information related to safety and efficacy of talimogene laherparepvec (Talimogene Laherparepvec Investigator's Brochure).

3.2.3 Non-Amgen Investigational Product Background: Pembrolizumab

Pembrolizumab is a potent humanized immunoglobulin G4 monoclonal antibody (mAb) with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Investigator's Brochure.

Refer to the Pembrolizumab Investigator's Brochure/approved labeling for detailed background information on pembrolizumab.

3.2.3.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades (Disis, 2010). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma (Dudley et al., 2005; Hunder et al., 2008).

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28)

and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD L1 and/or PD-L2) (Greenwald et al., 2005; Okazaki et al., 2001).

The structure of murine PD-1 has been resolved (Zhang et al., 2004). PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade (Okazaki et al., 2001; Chemnitz et al., 2004; Shepard et al., 2004; Riley, 2009). The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins (Parry et al., 2005; Francisco et al, 2010). As a consequence, the PD 1/PD-L1 pathway is an attractive target for therapeutic intervention in melanoma.

3.2.3.1.1 Preclinical and Clinical Trials

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities (Hirano et al., 2005; Blank et al., 2004; Weber, 2010; Strome et al., 2003; Spranger, 2014; Curran et al., 2010; Pilon et al., 2010). Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia and colorectal carcinoma (Strome et al., 2003; Curran et al., 2010; Pilon et al., 2010; Nomi et al., 2007; Zhang et al., 2004). In such studies, tumor infiltration by CD8+ T cells and increased IFN-γ, granzyme B and perforin expression were observed, indicating that the mechanism underlying the antitumor activity of PD-1 checkpoint inhibition involved local infiltration and activation of effector T cell function in vivo Curran et al., 2010. Experiments have confirmed the in vivo efficacy of anti-mouse PD-1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models (see the Pembrolizumab Investigator's Brochure).

3.3 Benefit/Risk Assessment

The following benefit risk assessment supports the conduct of this clinical trial.

Reference should be made to the Talimogene Laherparepvec Investigator's Brochure, for further data on talimogene laherparepvec.

3.3.1 Key Benefits

Talimogene laherparepvec is a well-tolerated, durable treatment option for patients with unresectable locoregional melanoma, particularly in stage IIIB/C disease. The key evidence of efficacy is based on Study 005/05, a phase 3 (OPTiM), randomized, open-label study comparing talimogene laherparepvec and GM-CSF in 436 subjects with stage IIIB, stage IIIC, and stage IV melanoma that was not surgically resectable. The key benefits of talimogene laherparepvec based on the monotherapy Study 005/05 are as follows:

- Treatment with talimogene laherparepvec statistically significantly improved DRR compared with GM-CSF (16.3% vs 2.1%, $p < 0.0001$).
- Treatment with talimogene laherparepvec also resulted in a higher overall response rate per endpoint assessment committee (26.4% talimogene laherparepvec, 5.7% GM-CSF), particularly with regard to the proportion of subjects with a CR (10.8% talimogene laherparepvec, 0.7% GM-CSF).
- In the primary analysis of OS, at a median follow-up time of 44.4 months, the median OS for the intent-to-treat population was 4.4 months longer in the talimogene laherparepvec arm than in the GM-CSF arm (hazard ratio: 0.79; 95% CI: 0.62, 1.00; $p = 0.051$). In the final descriptive analysis of OS (conducted when all subjects had been followed for at least 3 years after randomization), 1 additional death occurred, with the results consistent with the primary analysis (hazard ratio: 0.79; descriptive $p = 0.049$).
- The estimated median time to treatment failure was 8.2 months in the talimogene laherparepvec arm and 2.9 months in the GM-CSF arm (hazard ratio: 0.42; 95% CI: 0.32, 0.54).
- The treatment effect of talimogene laherparepvec on DRR and OS was heterogeneous across subgroups based on key covariates. The magnitude of the estimated treatment effect on DRR and OS was statistically significantly greater (ie, nominal $p = 0.05$, not adjusted for multiplicity) in subjects with stage IIIB/C and IVM1a disease. Differences in efficacy based on disease substage.

3.3.2 Key Risks

The key risks associated with talimogene laherparepvec (ie, those that were considered most relevant to assessing the benefit-risk profile of talimogene laherparepvec) are described in Section 3.3.2.1.

3.3.2.1 Risks

3.3.2.1.1 Immune-mediated Adverse Reactions

It is plausible that immune activation in response to viral infection or secondary to tumor cell destruction/GM-CSF expression could exacerbate underlying (patient-specific) immune conditions. Immune-mediated adverse events considered possibly related to talimogene laherparepvec were reported in 2% of subjects treated with talimogene laherparepvec (5 subjects in the phase 3 melanoma study and 1 subject in the phase 3 melanoma extension study) and included events of vasculitis, glomerulonephritis, acute renal failure, pneumonitis, and worsening psoriasis. Most cases were grade 2 or 3 and causality was not clearly established as other contributory factors were identified in several of these cases (including pre-existing immune-mediated conditions, other concurrent medications, and intercurrent medical events). In a phase 2 open-label, multicenter, randomized portion of a phase 1b/2 study to further assess the safety and efficacy of talimogene laherparepvec in combination with ipilimumab in 190 subjects, immune-mediated adverse events and serious adverse events were similar in the ipilimumab (serious adverse events = 16%, adverse events = 40%) and ipilimumab + talimogene laherparepvec groups (serious adverse events = 16%, adverse events = 44%).

3.3.2.1.2 Cellulitis at the Injection Site

Intralesional administration of talimogene laherparepvec has been associated with cellulitis at the injection site. In some cases, a local inflammatory reaction with localized tumor necrosis developed, and in other cases, a bacterial infection developed. In the phase 3 melanoma study, the subject incidence of adverse events in the bacterial cellulitis category was 6.2% (n = 18) in the talimogene laherparepvec group and 1.6% (n = 2) in the GM-CSF group. Seven subjects (2.4%) in the talimogene laherparepvec group and 1 subject (0.8%) in the GM-CSF group experienced serious adverse events of cellulitis. Fever, elevated white blood cell count, bacteremia or sepsis, and hospitalization for IV antibiotics were reported in 5 of the 7 cases in the talimogene laherparepvec group. None of the serious cellulitis events resulted in permanent study treatment discontinuation.

3.3.2.1.3 Plasmacytoma at the Injection Site

A plasmacytoma near the injection site was reported in 1 subject treated with talimogene laherparepvec in the phase 3 melanoma study. This case was considered possibly related to treatment with talimogene laherparepvec. No other cases of plasmacytoma have been reported in clinical trials with talimogene laherparepvec to date.

3.3.2.1.4 Obstructive Airway Disorder

In the phase 3 melanoma study, 1 subject treated with talimogene laherparepvec reported the adverse event of obstructive airway disorder. The event was grade 4 and resolved with sequelae. Study medication was permanently discontinued.

3.3.2.1.5 Impaired Wound Healing at the Injection Site

One serious adverse event of impaired wound healing was reported in an elderly subject following treatment with talimogene laherparepvec to a recurrent lower extremity melanoma lesion that resulted in a below-the-knee amputation 7 months after the last treatment in the phase 3 melanoma study. In the phase 3 melanoma study, the incidence of adverse events in the impaired wound healing category was 5.5% (n = 16) in the talimogene laherparepvec group and 2.4% (n = 3) in the GM-CSF group.

3.3.2.1.6 Symptomatic Herpetic Infection

Administration of talimogene laherparepvec could potentially lead to symptomatic herpetic infection. In the phase 3 melanoma study, herpetic events were reported for 5.5% of talimogene laherparepvec-treated subjects (4.8% oral herpes); no serious herpes complications were reported. Whether any of these events was due to talimogene laherparepvec or wild-type herpes simplex virus (HSV) could not be confirmed as viral testing was not routinely performed. This risk may be increased in patients who are severely immunocompromised. Talimogene laherparepvec has not been studied in immunocompromised patients.

3.3.2.1.7 Accidental Exposure of Health Care Providers to Talimogene Laherparepvec

Accidental exposure of talimogene laherparepvec may lead to transmission and herpetic infection. Accidental needle stick and splash back have been reported in health care providers during preparation and administration of talimogene laherparepvec.

3.3.2.1.8 Transmission to Close Contacts or Health Care Providers

Talimogene laherparepvec is an attenuated replication competent HSV-1 virus. Thus, exposure to patient secretions/excretions containing live virus could lead to secondary transmission and infection. Transmission to close contacts and health care providers has not been reported in clinical trials to date. Key uncertainties in the safety data to date include characterization of the potential for herpetic infections in immunocompromised individuals, the transmission risk to close contacts, the long-term safety profile (including any potential for reactivation), and full characterization of the viral shedding profile. The safety concerns are summarized in Table 3-1.

Table 3-1. Summary of Safety Concerns

Important identified risks	• Disseminated herpetic infection in severely immunocompromised individuals (those with any severe congenital or acquired cellular and/or humoral immune deficiency) • Accidental exposure of HCP to talimogene laherparepvec • Immune-mediated adverse reactions
Important potential risks	• Disseminated herpetic infection in immunocompromised patients (such as those with HIV/AIDS, leukemia, lymphoma, common variable immunodeficiency, or those who require high-dose steroids or other immunosuppressive agents) • Transmission of talimogene laherparepvec from patient to close contacts or HCPs via direct contact with injected lesions or body fluids resulting in symptomatic infection (primary or reactivation) • Symptomatic talimogene laherparepvec infection in non-tumor tissue in treated patients • Symptomatic herpetic infection due to latency and reactivation of talimogene laherparepvec or wild-type HSV-1 in patients • Immunocompromised patients treated with talimogene laherparepvec and suffering from concomitant infection • Combination with other therapies like chemotherapy or immunosuppressive agents • Talimogene laherparepvec-mediated anti-GM-CSF antibody response
Missing information	• Pregnant and lactating women • Pediatric patients • Long-term safety data • Long-term efficacy data • Treatment of patients with metastatic lesions greater than 3 cm

AIDS = acquired immune deficiency syndrome; GM-CSF = granulocyte-macrophage colony-stimulating factor; HCP = healthcare provider; HIV = human immunodeficiency virus; HSV-1 = herpes simplex virus type 1

4. Objectives, Endpoints and Hypotheses

4.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of talimogene laherparepvec in combination with pembrolizumab as assessed by objective response rate (ORR) in subjects with unresectable/metastatic stage IIIB-IVM1d melanoma who have progressed on prior anti-PD-1 therapy	• Overall response (complete response [CR] + partial response [PR]) (by investigator assessment using modified RECIST v1.1)
Key Secondary	
• To evaluate the efficacy of talimogene laherparepvec in combination with pembrolizumab, as assessed by: o Complete response rate (CRR), best overall response (BOR), durable response rate (DRR), duration of response (DOR), and disease control rate (DCR) o ORR using modified irRC-RECIST o Progression free survival (PFS) o Overall Survival (OS)	• Complete response, BOR, durable response, DOR, and disease control, (investigator assessment using modified RECIST v1.1 and modified irRC-RECIST) and overall response using modified irRC-RECIST by investigator assessment • PFS (by investigator assessment using modified RECIST v1.1 and modified irRC-RECIST) • OS
• To evaluate the safety of talimogene laherparepvec in combination with pembrolizumab as assessed by incidence of treatment-emergent and treatment-related adverse events, and abnormal laboratory tests in patients who have progressed on prior anti-PD-1 therapy	• Incidence of treatment-emergent and treatment-related adverse events (all adverse events, grade ≥ 3 adverse events, serious adverse events, fatal adverse events, adverse events defined as events of interest), and abnormal laboratory tests
• To evaluate time to subsequent anticancer therapy	• Time to subsequent anticancer therapy

Exploratory
[redacted]

4.2 Hypotheses

No formal hypothesis testing will be performed. All analyses will be descriptive in nature.

5. Study Design

5.1 Overall Design

This is a phase 2, open-label, single-arm, multicenter clinical trial designed to evaluate the efficacy and safety of talimogene laherparepvec in combination with pembrolizumab following disease progression on prior anti-PD-1 therapy in unresectable/metastatic melanoma (stage IIIB-IVM1d) or prior anti-PD-1 therapy in the adjuvant setting.

Subject must have received prior anti-PD-1 therapy for at least 2 to 3 consecutive cycles within an 8-week period (based on administration schedule) and have disease progression as defined by RECIST v1.1 criteria. The initial evidence of disease progression must have been confirmed by a second assessment no less than 4 weeks from the first documented disease progression, in the absence of rapid clinical progression. The anti-PD-1 therapy must be the immediate prior line of therapy before enrollment and subjects with disease progression on more than 1 line of anti-PD-1 therapy are not eligible.

Subjects will be enrolled into 1 of 4 cohorts based on prior anti-PD-1 experience:

- **Cohort 1 – Locally Recurrent/Metastatic - Primary Resistance**

Subjects who received anti-PD1 therapy in the locally recurrent/metastatic setting and experienced a best overall response of disease progression or stable disease prior to

confirmed disease progression. The initial date of disease progression must be within 12 weeks of the last dose of a PD-1 inhibitor.

- **Cohort 2 – Locally Recurrent/Metastatic - Acquired Resistance**

Subjects who received anti-PD-1 therapy in the locally recurrent/metastatic setting and experienced confirmed disease progression following a complete or partial response on anti-PD-1 therapy. The disease progression must occur within 12 weeks of the last dose of a PD-1 inhibitor.

- **Cohort 3 – Adjuvant Setting – Disease Free Interval < 6 months**

Subjects who received anti-PD-1 therapy in the adjuvant setting and experienced confirmed disease progression following a disease-free interval of < 6 months after starting the adjuvant anti-PD-1 therapy.

- **Cohort 4 – Adjuvant Setting – Disease Free Interval ≥ 6 months**

Subjects who received anti PD-1 therapy in the adjuvant setting and experienced confirmed disease progression following a disease-free interval of ≥ 6 months after starting the adjuvant PD-1 inhibitor.

The overall study design is described by a study schema in Section 2.1. The endpoints are defined in Section 4.1.

5.2 Number of Subjects

A total of 72 subjects were enrolled in the study. Twenty-seven subjects were enrolled into cohort 1 and 15 subjects were enrolled into cohorts 2, 3, and 4.

Subjects in this clinical investigation shall be referred to as “subjects.” For the sample size justification, see Section 10.1.

5.2.1 Replacement of Subjects

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

5.2.2 Number of Sites

Approximately 60 investigative sites in Australia, Europe, and North America will be included in the study. Sites that do not enroll subjects within 3 months of site initiation may be closed. Additional regions, countries, and/or sites may be added.

5.3 End of Study

5.3.1 End of Study Definition

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the

primary endpoints, whether the study concluded as planned in the protocol or was terminated early.

The primary completion date is the date when the last subject has completed the assessments for week 24.

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

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

5.3.2 Study Duration for Subjects

The study will consist of a screening period of up to 28 days, a treatment period of up to 102 weeks, a 30 (+ 7) day safety follow-up, and a long-term follow-up of 3 years from the time of last subject enrolled. The subject accrual period **was** planned to be approximately 1 year. The actual duration for individual subjects will vary based on evidence of clinical progression, tolerability of talimogene laherparepvec in combination with pembrolizumab, and willingness to participate in the study. The study duration for an individual subject may be up to approximately 4 years.

5.4 Justification for Investigational Product Dose

5.4.1 Amgen Investigational Product: Talimogene Laherparepvec

The dose and dosing frequency of talimogene laherparepvec in this study were selected based on the totality of data from the talimogene laherparepvec development program, including the following key studies in the use of talimogene laherparepvec monotherapy in melanoma and combination therapy in melanoma and head and neck squamous cell carcinoma (HNSCC):

- Clinical data from the OPTiM (005/05) trial establishing efficacy and safety in the melanoma with an initial dose at 10^6 PFU/mL and subsequent doses at 10^8 PFU/mL
- Clinical data from trials in the combined talimogene laherparepvec and pembrolizumab treatment across melanoma (20110265) and HNSCC (20130232).

The intralesional volume administered and the prioritization of injected lesions is outlined in the talimogene laherparepvec Investigational Product Instruction Manual (IPIM) and follows the guidance established in the above studies.

5.4.2 Non-Amgen Investigational Product: Pembrolizumab

The planned dose of pembrolizumab for this study is 200 mg once every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies **in melanoma and non-small cell lung cancer (NSCLC) indications** demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg once every 2 weeks (Q2W) **representing an approximate 5- to 7.5-fold exposure range (refer to the Investigator's Brochure),**
- Clinical data showing meaningful improvement in benefit-risk including OS at 200 mg Q3W across multiple indications**,**
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK analysis) at 200 mg Q3W**, and**
- **Population PK analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W.**

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and NSCLC, covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a physiologically-based PK analysis was conducted to predict

tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

5.5 Patient Input on Study Design

Patient input on study design was not obtained for this study.

6. Study Population

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening). This log may be completed and updated via Interactive Response Technology (IRT).

Eligibility criteria will be evaluated during screening.

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Section 12.3).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions will not be provided.

6.1 Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

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

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

Disease Related Criteria

103 Histologically confirmed diagnosis of melanoma.

104 Disease stage: unresectable or metastatic melanoma, defined as either 1 of the following (per the eighth edition of the American Joint Committee on Cancer [AJCC] Cancer Staging Manual [Gershenwald et al, 2017]):

- Stage IIIB, IIIC, IIID, IVM1a, IVM1b, or IVM1c

OR

- Stage IVM1d with up to 3 cerebral metastases, provided that all lesions have been adequately treated with stereotactic radiation therapy, craniotomy, or gamma knife therapy, with no evidence of progression and not requiring steroids for at least 2 months prior to enrollment.

105 Candidate for intralesional therapy defined as either 1 of the following:

- ≥ 1 injectable cutaneous, subcutaneous, or nodal melanoma lesion ≥ 10 mm in longest diameter;

OR

- Multiple injectable melanoma lesions that in aggregate have a longest diameter ≥ 10 mm injectable disease.

106 Eastern Cooperative Oncology Group Performance Status (ECOG PS) = 0 or 1.

107 Measurable disease, defined as at least 1 visceral or nodal/soft tissue melanoma lesion that can be accurately and serially measured in at least 1 dimension and for which the longest diameter is ≥ 10 mm as measured by computed tomography (CT) scan or magnetic resonance imaging (MRI). Lymph nodes must measure ≥ 15 mm in their short axis to be considered measurable by CT scan or MRI or positron emission tomography (PET)-CT.

Prior/Concurrent Therapy Criteria

108 Subject must have recovered from all adverse events, including immune related adverse events, due to prior anticancer therapy (residual toxicity ≤ grade 1) prior to enrollment, with the exception of subjects with ≤ grade 2 neuropathy or ≤ grade 2 alopecia. Subjects with grade 2 endocrinopathies (ie, requiring replacement therapy only) may be enrolled upon review and approval by the medical monitor.

109 If subject received major surgery, must have recovered adequately from toxicity and/or complications from the intervention prior to enrollment.

110 Subject must have had prior treatment with a PD-1 inhibitor in the adjuvant or metastatic setting (monotherapy or in combination with anti-CTLA-4). Combinations other than anti-PD-1 plus anti-CTLA-4 must be reviewed with the medical monitor for approval.

111 Subject must have received prior anti-PD-1 therapy for at least 2 to 3 consecutive cycles within an 8-week period (based on administration schedule). PD-1 inhibitors other than pembrolizumab or nivolumab must be reviewed by the medical monitor

112 The anti-PD-1 therapy must be the immediate prior line of therapy before enrollment.

113 Subject must have disease progression as defined by RECIST v1.1 criteria. The initial evidence of disease progression must be confirmed by a second assessment no less than 4 weeks from the first documented disease progression (confirmatory scan may be conducted at screening), in the absence of rapid clinical progression.

Cohort 1 – Locally Recurrent/Metastatic - Primary Resistance

114 Subject received anti-PD1 therapy in the locally recurrent/metastatic setting and experienced a best overall response of disease progression or stable disease prior to confirmed disease progression. The initial date of disease progression must occur within 12 weeks of the last dose of a PD-1 inhibitor.

OR

Cohort 2 – Locally Recurrent/Metastatic - Acquired Resistance

115 Subject received anti-PD-1 therapy in the locally recurrent/metastatic setting and experienced confirmed disease progression following a complete or partial response on anti-PD-1 therapy per investigator assessment. The initial date of disease progression must occur within 12 weeks of the last dose of a PD-1 inhibitor.

OR

Cohort 3 – Adjuvant Setting - Disease Free Interval < 6 months

116 Subject received anti PD-1 therapy in the adjuvant setting and experienced confirmed disease progression following a disease-free interval of < 6 months after starting the adjuvant PD-1 inhibitor.

OR

Cohort 4 – Adjuvant Setting - Disease Free Interval ≥ 6 months

117 Subject received anti PD-1 therapy in the adjuvant setting and experienced confirmed disease progression following a disease-free interval of ≥ 6 months after starting the adjuvant PD-1 inhibitor.

Clinical Laboratory Criteria

118 Adequate organ function determined within 14 days prior to enrollment, defined as follows:

- Hematological
  - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
  - platelet count $\geq 100 \times 10^9$/L
  - hemoglobin $\geq$ 90 g/L (without need for hematopoietic growth factor or transfusion support)
- Renal
  - serum creatinine $\leq$ 1.5 x upper limit of normal (ULN), OR 24-hour urine creatinine clearance $\geq$ 60 mL/min for subject with creatinine levels > 1.5 x ULN. (Note: 24-hour urine creatinine clearance need not be determined if the baseline serum creatinine is within normal limits. Creatinine clearance should be calculated per institutional standard).
- Hepatic
  - serum bilirubin $\leq$ 1.5 x ULN OR direct bilirubin ≤ ULN for a subject with total bilirubin level > 1.5 x ULN

- aspartate aminotransferase (AST) ≤ 2.5 x ULN OR ≤ 5 x ULN for subject with liver metastases
- alanine aminotransferase (ALT) ≤ 2.5 x ULN OR ≤ 5 x ULN for subject with liver metastases

- Coagulation
  - international normalization ratio (INR) or prothrombin time (PT) ≤ 1.5 x ULN unless the subject is receiving anticoagulant therapy as long as PT and partial thromboplastin time (PTT)/activated PTT (aPTT) is within therapeutic range of intended use of anticoagulants

119 Lactate dehydrogenase (LDH) levels ≤ 1.5 x ULN within 14 days prior to enrollment

120 Female subjects of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to enrollment. If the urine pregnancy test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

6.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

Disease Related

201 Considered by the investigator to have rapid clinical progression due to melanoma.

231 Subjects with prior treatment and disease progression on more than 1 line of anti-PD-1 therapy

202 Stage IVM1d with greater than 3 cerebral melanoma metastases, or clinically active cerebral melanoma metastases requiring therapy, and/or carcinomatous meningitis regardless of clinical stability.

203 Primary uveal or mucosal melanoma.

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

205 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 enrollment 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 enrollment;
- adequately treated cervical carcinoma in situ without evidence of disease at the time of enrollment;

- adequately treated breast ductal carcinoma in situ without evidence of disease at the time of enrollment;
- prostatic intraepithelial neoplasia without evidence of prostate cancer at the time of enrollment;
- adequately treated superficial or in-situ carcinoma of the bladder without evidence of disease at the time of enrollment.

Other Medical Conditions

206 History or evidence of symptomatic autoimmune glomerulonephritis, vasculitis, or other symptomatic autoimmune disease, or active autoimmune disease or syndrome that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs) except vitiligo or resolved childhood asthma/atopy. Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

207 Evidence of clinically significant immunosuppression such as the following:

- diagnosis of immunodeficiency;
- concurrent opportunistic infection;
- receiving systemic immunosuppressive therapy (> 2 weeks) or within 7 days prior to the first dose of study treatment, including oral steroid doses > 10 mg/day of prednisone or equivalent Subjects that require intermittent use of bronchodilators or local steroid injection will not be excluded from the study.

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

209 Known human immunodeficiency virus (HIV) disease.

210 Known acute or chronic hepatitis B or hepatitis C infection.

211 Has undergone prior allogeneic hematopoietic stem cell transplantation within the last 5 years. Subjects who have had a transplant > 5 years ago are eligible as long as there are no symptoms of Graft versus Host Disease.

212 Has a known history of active Bacillus tuberculosis.

213 Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.

Prior/Concomitant Therapy

214 Prior therapy with talimogene laherparepvec or any other oncolytic viruses.

215 Prior therapy with tumor vaccine (unless administered in the adjuvant setting).

216 Received prior systemic anticancer therapy including investigational agents within 28 days prior to enrollment.

Note: Subjects must have recovered from all adverse events due to previous therapies to ≤ grade 1 or baseline, subjects with ≤ grade 2 neuropathy may be eligible. If subject received major surgery, he/she must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment.

217 Received prior radiotherapy within 14 days of enrollment. Subjects must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 7-day washout is permitted for palliative radiation (≤ 2 weeks of radiotherapy) to non-central nervous system disease.

218 Received live vaccine within 28 days prior to enrollment.

219 Requires intermittent or chronic treatment with an antiherpetic drug (eg, acyclovir), other than intermittent topical use.

Prior/Concurrent Clinical Study Experience

220 Currently receiving treatment in another investigational device or drug study, or < 28 days since ending treatment on another investigational device or drug study.

221 Expected to require other cancer therapy while on study with the exception of local radiation treatment to the site of bone and other metastasis for palliative pain management.

222 Other investigational procedures while participating in this study.

Diagnostic Assessments

Other Exclusions

223 Female subject is pregnant or breastfeeding or planning to become pregnant or breastfeed during study treatment and through 3 months after the last dose of talimogene laherparepvec or 4 months after the last dose of pembrolizumab (or 30 [+7] days following cessation of pembrolizumab if the subject initiates new anticancer therapy), whichever is later.

224 Female subject of childbearing potential who is unwilling to use at least 1 acceptable method of effective contraception during study treatment and through 3 months after the last dose of talimogene laherparepvec or 4 months after the last dose of pembrolizumab (or 30 [+7] days following cessation of pembrolizumab if the subject initiates new anticancer therapy), whichever is later. Refer to Section 12.5 for additional contraceptive information.

225 Male subjects with pregnant partner or a female partner of childbearing potential who are unwilling to practice sexual abstinence (refrain from heterosexual intercourse) or use acceptable method of effective contraception during study treatment and through 3 months after the last dose of talimogene laherparepvec or 4 months after the last dose of pembrolizumab, whichever is later. Refer to Section 12.5 for additional contraceptive information.

226 Sexually active subjects and their partners unwilling to use a male or female latex condom to avoid potential viral transmission during sexual contact while on-treatment and within 30 days after treatment with talimogene laherparepvec or pembrolizumab. For those with latex allergies, polyurethane condoms may be used.

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

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

229 Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures (eg, Clinical Outcome Assessments) to the best of the subject and investigator's knowledge.

230 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.

232 Male subjects unwilling to abstain from donating sperm during treatment and through 3 months after the last dose of talimogene laherparepvec or 4 months after the last dose of pembrolizumab, whichever is later.

6.3 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, as applicable (see Section 12.3).

The subject must personally sign and date the IRB/IEC and Amgen approved informed consent before commencement of study-specific procedures.

Each subject who enters into the screening period for the study (within 28 days prior to enrollment) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned (eg, IRT). This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

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

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

6.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information will be collected that includes demography, screen failure details, eligibility criteria, and any serious adverse events (medical history and concomitant medications will be collected for all subjects experiencing serious adverse events).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Refer to Section 9.1.1.

7. Treatments

Study treatment is defined as any investigational product(s), non-investigational product(s), placebo, or medical device(s) intended to be administered to a study subject according to the study protocol.

Note that in several countries, investigational product and non-investigational product are referred to as investigational medicinal product and non-investigational medicinal product, respectively. The IPIM, a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of each treatment shown in Section 7.1.

Talimogene laherparepvec and pembrolizumab treatment should begin as soon as possible after enrollment via IRT but no later than 3 days after enrollment. During treatment, assessments and procedures will be performed within ± 3 days of the planned visit unless otherwise indicated.

Talimogene laherparepvec and pembrolizumab are administered at a Q3W frequency. When they are administered on the same day, talimogene laherparepvec should be administered first when possible.

7.1 Treatment Procedures

7.1.1 Amgen Investigational Product: Talimogene Laherparepvec

Talimogene laherparepvec will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures. The supply for the 10^6 PFU/mL concentration will be packaged separately from the supply for the 10^8 PFU/mL concentration.

7.1.1.1 Talimogene Laherparepvec 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 5.0 (Section 12.4). Complete blood count with differential and chemistry panels including liver function laboratory tests (ALT, AST, and total bilirubin) and thyroid function tests (T3 or FT3 per local standard, FT4, and TSH) should be obtained according to the Schedule of Activities (Table 2-1) and the results should be checked

prior to the administration of scheduled dose of study drugs. Dosing will occur only if these test values are acceptable, per Section 7.4.1.1.

Note: Thyroid function tests must be collected, but if there are no symptoms of hypothyroidism or hyperthyroidism, study treatment can be initiated prior to the reporting of the laboratory results.

Talimogene laherparepvec will be administered by intralesional injection only into injectable cutaneous, subcutaneous, and nodal tumors, with or without image ultrasound guidance. Talimogene laherparepvec must not be administered into visceral organ metastases.

On day 1 the first dose of talimogene laherparepvec will be up to 4.0 mL of 10^6 PFU/mL by intralesional injection into injectable cutaneous, subcutaneous, and nodal lesions with or without image ultrasound guidance. The second dose of up to 4.0 mL of 10^8 PFU/mL talimogene laherparepvec should be administered 21 (+3) days after the initial dose. Subsequent doses of up to 4.0 mL of 10^8 PFU/mL talimogene laherparepvec should be given every 3 weeks (± 3 days).

The maximum volume of talimogene laherparepvec administered at any dose is 4.0 mL for any individual lesion. The maximum dose in any treatment visit is 4.0 mL. Investigators are encouraged to use the maximum amount whenever lesions' properties allow.

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 7-1.

Table 7-1. Talimogene Laherparepvec Injection Volume Guideline Based on Tumor Size

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

At baseline, if there are ≥ 2 lesions, 1 lesion (ie, the lesion considered lowest priority for injection) amenable for biopsy should be left uninjected at least until it is biopsied at week 6. Aside from leaving 1 lesion uninjected, all other reasonably injectable lesions

(cutaneous, subcutaneous and nodal disease that can be injected with or without ultrasound guidance) should be injected with the maximum dosing volume available on an individual dosing occasion (Table 7-1). On each treatment day, prioritization of injections is recommended as follows:

- any tumor that does not correspond to the uninjected lesion reserved for biopsy until week 6
- any new injectable tumor that has appeared since the last injection
- by tumor size, beginning with the largest tumor
- any previously uninjectable tumor(s) that is now injectable

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 7-1. Lesions should be injected until the maximum volume per day (4.0 mL) has been reached or there are no further injectable lesions, whichever comes first.

Subjects will be treated with talimogene laherparepvec until disappearance of all injectable lesions, documented confirmed iPD per modified irRC-RECIST, intolerance of study treatment, or 102 weeks from the first dose of talimogene laherparepvec, whichever occurs first. Due to the mechanism of action, subjects may experience growth in existing tumors or the appearance of new tumors prior to maximal clinical benefit of talimogene laherparepvec. Therefore, talimogene laherparepvec dosing should continue provided that the subject has no evidence of confirmed iPD per modified irRC-RECIST and is able to tolerate the treatment. The dose, start date, and lot number of talimogene laherparepvec are to be recorded on the electronic CRF as per the recommendation found in the electronic CRF specific instructions.

7.1.2 Non-Amgen Investigational Product: Pembrolizumab

Pembrolizumab will be manufactured by Merck. Pembrolizumab will be labeled, packaged, and distributed by Amgen (or designee) using Amgen (or designee) clinical study drug distribution procedures.

7.1.2.1 Pembrolizumab Dosage, Administration, and Schedule

Pembrolizumab is supplied as pembrolizumab 100 mg/4 mL vials (25 mg/mL) solution for IV infusion. Pembrolizumab at a dose of 200 mg will be administered IV every 3 weeks (+ 3 days for week 3, ± 3 days after week 3).

Pembrolizumab will be administered as a dose of 200 mg using a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes (-5 min/+10 min). Details on the preparation and administration are provided in the IPIM.

Pembrolizumab treatment will continue until subjects have documented confirmed iPD per modified irRC-RECIST, intolerance of study treatment, or 102 weeks from the first dose of pembrolizumab, whichever occurs first. **For subjects who have attained a confirmed CR, discontinuation of treatment may be considered if the subjects have been treated for at least 24 weeks with pembrolizumab and had at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared.** The dose, start date, and lot number are to be recorded on the electronic CRF as per the recommendation found in the electronic CRF specific instructions.

7.1.3 Medical Devices

Non-investigational medical devices (eg, syringes, sterile needles), 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.

7.1.4 Other Protocol-required Therapies

All other protocol-required therapies including, topical anesthetic or an injectable local anesthetic medications used for pretreatment of the talimogene laherparepvec injection site and oral or systemic steroids for management of pembrolizumab immune-related adverse events 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.

7.1.5 Other Treatment Procedures

Investigators may choose to resect lesions which become suitable for resection to render the subject free of macroscopic disease. Additionally, biopsies may be taken of cutaneous or subcutaneous lesions for tumor analysis during the study. However, resection of lesions may occur only following tumor assessment. If a subject undergoes resection of the lesion, the investigator or designee should notify the sponsor medical monitor as soon as possible. [redacted]

Local radiation treatment to the site of bone and other metastasis will be permitted for palliative pain management at any time during the study. If a subject undergoes local radiation, the investigator or designee should notify the sponsor's medical monitor as soon as possible.

If a subject demonstrates evidence of new or worsening central nervous system (CNS) metastases, all study treatments should be withheld and the investigator or designee should notify the sponsor's medical monitor as soon as possible. Subjects may be allowed to remain on study after discussion between the sponsor's medical monitor and the investigator to determine the appropriateness of treatment resumption provided CNS lesions can be treated with stereotactic radiotherapy, Gamma Knife, or craniotomy. After approval is obtained from the sponsor's medical monitor, subjects may be allowed to reinitiate talimogene laherparepvec and/or pembrolizumab treatment per Section 7.4.1, following stereotactic radiotherapy only when dosing of corticosteroid is below 1.5 mg dexamethasone, 10 mg prednisone or equivalent. If higher doses of corticosteroid are used, talimogene laherparepvec and/or pembrolizumab must be held until that dose level is reached during the period of steroid tapering.

7.1.6 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug(s) or device(s) after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material.

This includes any investigational products provisioned and/or repackaged/modified by Amgen.

7.1.7 Excluded Treatments, Medical Devices, and/or Procedures During Study Period

Subjects must not use any of the following therapies during the screening or treatment period, unless indicated otherwise:

- other investigational agents or procedures;
- concurrent experimental or approved antitumor therapies other than study drugs and radiation therapy required for palliation;
- immunosuppressive agents (with the exception of treatment for adverse events [see Section 7.4.1 and CNS metastases [see Section 7.1.5]);
- any live vaccine therapies used for the prevention of infectious disease within 28 days prior to enrollment and during the treatment period;

- antiherpetic drugs, other than if topically administered > 20 cm from a talimogene laherparepvec injection site;
- any surgery or radiotherapy for melanoma (other than the exceptions noted in Section 7.1.5).
- Subjects must not schedule any elective surgeries (other than the exceptions noted in Section 7.1.5) during the treatment period and for at least 30 days after the last administration of study drugs. If a subject undergoes any unexpected surgery during the course of the study, all study treatments 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 study drugs if both the investigator and 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 Section 6.2). The investigator or their designee must consult with the sponsor's medical monitor about subjects in the post-treatment follow up period who have not demonstrated confirmed disease progression or intolerance to pembrolizumab and/or talimogene laherparepvec prior to starting any experimental or approved antitumor therapies.

7.2 Method of Treatment Assignment

All subjects enrolled will receive the same treatment.

Subjects will be assigned to 1 of 4 cohorts as follows:

- **Cohort 1 – Locally Recurrent/Metastatic - Primary Resistance**

Subjects who received anti-PD1 therapy in the locally recurrent/metastatic setting and experienced a best overall response of disease progression or stable disease prior to confirmed disease progression. The initial date of disease progression must be within 12 weeks of the last dose of a PD-1 inhibitor.

- **Cohort 2 – Locally Recurrent/Metastatic - Acquired Resistance**

Subjects who received anti-PD-1 therapy in the locally recurrent metastatic setting and experienced confirmed disease progression following a complete or partial response on anti-PD-1 therapy. The disease progression must occur within 12 weeks of the last dose of a PD-1 inhibitor.

- **Cohort 3 – Adjuvant Setting – Disease Free Interval < 6 months**

Subjects who received anti-PD-1 therapy in the adjuvant setting and experienced confirmed disease progression following a disease-free interval of < 6 months after starting the adjuvant anti-PD-1 therapy.

- **Cohort 4 – Adjuvant Setting – Disease Free Interval ≥ 6 months**

Subjects who received anti PD-1 therapy in the adjuvant setting and experienced confirmed disease progression following a disease-free interval of ≥ 6 months after starting the adjuvant PD-1 inhibitor.

7.3 Blinding

This is an open-label study; blinding procedures are not applicable.

7.4 Dose Modification

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

7.4.1.1 Amgen Investigational Product: Talimogene Laherparepvec

The reason for dose change of talimogene laherparepvec is to be recorded on each subject's CRF.

If talimogene laherparepvec treatment was delayed by > 2 weeks, that dose will be deemed to have been missed and the subject will proceed to the next scheduled treatment visit. 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 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 > 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 pembrolizumab or talimogene laherparepvec related toxicities, talimogene laherparepvec dosing must be withheld until the corticosteroid dose has decreased to ≤ 10 mg prednisone daily (or equivalent).

All necessary supportive therapies except for those listed in Section 7.1.7 shall be available to subjects. Talimogene laherparepvec treatment should be continued based on the potential benefit/risk assessment of the subject.

If talimogene laherparepvec dosing is delayed by more than 6 weeks from the date of the planned 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 6 weeks from the date of the planned 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 doses may be given no less than 8 days apart **(**eg, day 1 and day 9), if needed, for the purpose of re-aligning dosing schedules for talimogene laherparepvec after a dose delay. The 8-day dosing should only be used for re-aligning the talimogene laherparepvec schedule. The allowable protocol dosing windows should be used for this purpose.

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. In this case, discontinuation from the treatment occurs immediately upon introduction of the new agent.
- Confirmed iPD occurs as defined per the modified irRC-RECIST (Section 12.10).
- 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 > 4 weeks from the date of the planned 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 > 4 weeks from the date of the planned 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).

- A female subject breast feeds while on study treatment.
- Concurrent medical illness that, in the judgment of the investigator, would make continued treatment with talimogene laherparepvec dangerous for the subject.

For additional information related special warnings and precautions for the use of talimogene laherparepvec please refer to the latest version of the Talimogene Laherparepvec Investigator's Brochure. At the investigator's discretion, pembrolizumab dosing may continue following discontinuation of talimogene laherparepvec.

7.4.1.2 Non-Amgen Investigational Product: Pembrolizumab

The reason for dose change of pembrolizumab is to be recorded on each subject's CRF.

7.4.1.3 Pembrolizumab Dose Modification and Toxicity Management for Immune-related Adverse Events Associated With Pembrolizumab

Adverse events associated with pembrolizumab exposure may represent an immune-related response. These immune-related adverse events may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than 1 body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most immune-related adverse events were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected immune-related adverse events, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of immune-related adverse events, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for immune-related adverse events associated with pembrolizumab are provided in Table 7-2. At the investigator's discretion, talimogene laherparepvec dosing may continue following discontinuation of pembrolizumab.

Table 7-2. Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab

General instructions:

1. The corticosteroid taper should begin when the immune-related adverse event is ≤ grade 1 and continue at least 4 weeks.
2. If pembrolizumab has been withheld, pembrolizumab may resume after the immune-related adverse event decreased to ≤ grade 1 after corticosteroid taper.
3. Pembrolizumab must be permanently discontinued if the immune-related adverse event does not resolve or the corticosteroid dose is not ≤ 10 mg within 12 weeks of the last pembrolizumab treatment.
4. Severe and life-threatening immune-related adverse events should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should be initiated if immune-related adverse events are not controlled by corticosteroids.

Immune-related Adverse Events	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken to Pembrolizumab	Corticosteroid and/or Other Therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 **to** 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Grade 3 or 4, or recurrent grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 **to** 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Recurrent grade 3 or grade 4	Permanently discontinue		

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Footnotes defined on last page of the table

Table 7-2. Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab

Immune-related Adverse Events	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken to Pembrolizumab	Corticosteroid and/or Other Therapies	Monitor and follow-up
AST / ALT elevation or Increased bilirubin	Grade 2[a]	Withhold	• Administer corticosteroids (initial dose of 0.5 **to** 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable**)**
	Grade 3[b] or 4[c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 **to** 2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM, or grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[d]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[d]		
Hypothyroidism	Grade 2**, 3, or** 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.

Footnotes defined on last page of the table

Table 7-2. Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab

Immune-related Adverse Events	Toxicity Grade or Conditions (CTCAE v5.0)	Action Taken to Pembrolizumab	Corticosteroid and/or Other Therapies	Monitor and follow-up
Nephritis grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 **to** 2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	**Grade 2**	**Withhold**	• **Based on severity of AE administer corticosteroids**	• **Ensure adequate evaluation to confirm etiology and/or exclude other causes**
	Grade 3 or 4	**Permanently discontinue**		
Myocarditis	Grade 2, 3 or 4	Permanently discontinue	• Based on severity of adverse event administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
Exfoliative Dermatologic Conditions	**Suspected SJS, TEN, or DRESS**	**Withhold**	• **Based on severity of AE administer corticosteroids**	• **Ensure adequate evaluation to confirm etiology or exclude other causes**
	Confirmed SJS, TEN, or DRESS	**Permanently discontinue**		
All other immune-related adverse events	**P**ersistent grade 2	Withhold	• Based on type and severity of adverse event administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event[e]		
	Grade 4 or recurrent grade 3	Permanently discontinue		

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = common terminology criteria for adverse events; **DRESS = Drug Rash with Eosinophilia and Systemic Symptom; SJS = Stevens-Johnson Syndrome; TEN = Toxic Epidermal Necrolysis;** T1DM = type 1 diabetes mellitus; ULN = upper limit of normal

Note: nonimmune-related AEs will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: > 3.0 to 5.0 x ULN if baseline normal; > 3.0 to 5.0 x baseline, if baseline abnormal; bilirubin: > 1.5 to 3.0 x ULN if baseline normal; > 1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: > 5.0 to 20.0 × ULN, if baseline normal; > 5.0 to 20.0 × baseline, if baseline abnormal; bilirubin: > 3.0 to 10.0 × ULN if baseline normal; > 3.0 to 10.0 × baseline if baseline abnormal

[c] AST/ALT: > 20.0 x ULN, if baseline normal; > 20.0 x baseline, if baseline abnormal; bilirubin: > 10.0 x ULN if baseline normal; > 10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ grade 2, pembrolizumab may be resumed

[e] Events that require discontinuation include but are not limited to: encephalitis, and **other clinically important immune-related adverse events (eg, vasculitis and sclerosing cholangitis).**

7.4.1.4 Dose Modification and Toxicity Management of Infusion-reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 7-3.

Table 7-3. Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	• Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hr.	• Stop Infusion. • Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg from 100 mL/hr to 50 mL/hr.). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. Participants who develop grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment	Participant may be premedicated 1.5 hr (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg orally (or equivalent dose of analgesic).

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Table 7-3. Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilator support indicated	• Stop Infusion. • Additional appropriate medical therapy may include but is not limited to: • Epinephrine** • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. • Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug treatment.	No subsequent dosing

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Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov

7.4.1.5 Other Allowed Dose Interruption for Pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related adverse events such as medical/surgical events or logistical reasons not related to study therapy. Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the subject's study record.

7.4.2 Hepatotoxicity Stopping and Rechallenge Rules

Refer to Section 12.7 for details regarding drug-induced liver injury guidelines, as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

7.5 Preparation/Handling/Storage/Accountability

Guidance and information on preparation, handling, storage, accountability, destruction, or return of the investigational products during the study are provided in the IPIM.

7.6 Treatment Compliance

Administration of talimogene laherparepvec and pembrolizumab will occur at the study site.

7.7 Treatment of Overdose

There is no clinical experience with an overdose of talimogene laherparepvec. In the event of a suspected overdose, the subject should be treated symptomatically and supportive measures instituted as required.

For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or ≥ 5 times the indicated dose.

No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

7.8 Prior and Concomitant Treatment

7.8.1 Prior Treatment

All therapy administered for treatment of melanoma prior to screening must be captured on the appropriate CRF, regardless of duration of time between prior therapy and screening.

For prior therapies that were being taken for melanoma, collect therapy name, indication, dose, unit, frequency, route, start date, and stop date. In addition, for prior PD-1 inhibitors taken for melanoma, also collect clinical response related information to support eligibility (ie, reason for stopping, first date of disease progression, date of confirmed disease progression, best overall response).

All other prior therapies that were being taken/used from 4 weeks prior to screening through the first dose of investigational product, will be collected. For all other prior therapies, collect therapy name, indication, dose, unit, frequency, route, start date, and stop date.

7.8.2 Concomitant Treatment

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 7.1.7.

Concomitant therapies are to be collected from signing of the informed consent form through 30 (+ 7) days after the last dose of investigational product. Subsequent treatment for melanoma will be recorded from the end of investigational product until the subject ends study.

For concomitant therapies being taken for melanoma, collect therapy name, indication, dose, unit, frequency, route, start date and stop date. For all other concomitant therapies, collect therapy name, indication, dose, unit, frequency, route, start date and stop date.

8. Discontinuation Criteria

Subjects have the right to withdraw from investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

The sponsor can decide to withdraw a subject(s) from investigational product, device, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Sections 8.1, 8.2.1, and 8.2.2.

8.1 Discontinuation of Study Treatment

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 possibilities for continuation of the Schedule of Activities (Table 2-1) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, and adverse events, as applicable and must document this decision in the subject's medical records. Subjects who have discontinued investigational product and/or other protocol-required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data. The investigator must document the change to the Schedule of Activities (Table 2-1) 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).

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 12.3.

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

- Decision by sponsor
- Lost to follow-up
- Death
- Ineligibility determined
- Protocol deviation
- Non-compliance
- Adverse event
- Subject request
- Disease progression
- Requirement for alternative therapy
- Pregnancy

8.2 Discontinuation From the Study

Full 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 and must document the subject's decision to withdraw in the subject's medical records.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must notify Amgen accordingly (see Section 12.6 for further details). Refer to the Schedule of Activities (Table 2-1) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8.2.1 Reasons for Removal From Washout, Run-in or Invasive Procedures

Not applicable.

8.2.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- Decision by sponsor
- Full withdrawal of consent from study
- Death
- Lost to follow-up

8.3 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or is able to continue in the study.
- In cases in which the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts are to be documented in the subject's medical record.

If the subject continues to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

- For subjects who are lost to follow-up, the investigator can search publicly 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.

9. Study Assessments and Procedures

Study procedures and their time points are summarized in the Schedule of Activities (Table 2-1).

As protocol waivers or exemptions are not allowed if an enrolled subject is subsequently determined to be ineligible for the study, this must be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject is to continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities (Table 2-1), is essential and required for study conduct.

9.1 General Study Periods

9.1.1 Screening and Enrollment

Informed consent must be obtained before completing any screening procedure or discontinuation of standard therapy for any disallowed therapy. After the subject has signed the informed consent form, the site will register the subject in the IRT and screen the subject in order to assess eligibility for participation. The screening window is up to 28 days.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, (see Section 6.4) as applicable.

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen fail. Screen fail subjects may only be re-screened once.

Rescreen subjects must first be registered as screen failures in IRT and subsequently registered as rescreens. Once the subject is registered as rescreened, a new 28-day screening window will begin. Subjects will retain the same subject identification number assigned at the original screening. If the rescreening period begins more than 30 days after the original signing of the informed consent form, all screening procedures, including informed consent, must be repeated within the screening windows specified in the Schedule of Activities (Table 2-1).

9.1.2 Treatment Period

Visits will occur per the Schedule of Activities (Table 2-1). On-study visits may be completed within ± 3 days **(excluding week 0, for which the -3 day window does not apply and all assessments should be completed following enrollment, using the + 3 day window for the first dose as described in Section 7, if required)**. The date of the first dose of protocol-required therapies is defined as day 1. All subsequent doses and study visits will be scheduled based on the day 1 date. Study treatment is to be administered after all other procedures are completed, unless otherwise stated during each visit that it is required.

9.1.3 Safety Follow-up

Upon permanent discontinuation from the study treatment for any reason, a safety follow-up visit will be performed approximately 30 (+ 7) days after the end of the last dosing interval of investigational product. If an end of treatment decision occurs > 30 (+ 7) days after the last treatment date, then the Safety follow-up should be performed as soon as possible (eg, within a week of the end of treatment decision).

9.1.4 Long-term Follow-up

All subjects who permanently discontinue study drug for any reason other than withdraw of full consent will be contacted by clinic visit or telephone to assess survival, initiation of additional melanoma therapy, and whether any talimogene laherparepvec related adverse events have occurred. Disease progression will also be collected for subjects who discontinue treatment for any reason other than confirmed disease progression Contact for all subjects will be attempted every 12 weeks (± 28 days) following the safety follow-up visit until death, subject withdraws full consent, or up to 36 months after the last subject is enrolled. **See Sections 9.2.3.1.1.2 and 9.2.3.1.1.3 for reporting requirements of serious adverse events during the long-term follow-up and after the end of the protocol-required reporting period.** The sponsor may request survival status to be assessed at additional time points during the course of the study. Subjects who wish not to be contacted every 12 weeks (± 28 days) but are willing to stay on study may be contacted prior to key analyses.

For subjects who discontinued treatment for any reason other than confirmed iPD, every effort should be made to complete radiographic assessments every 12 weeks (±1 week) or more frequently if clinically indicated during the long-term follow-up until documentation of confirmed iPD per modified irRC-RECIST (Section 12.10), clinical progression, start of new anticancer therapy, or end of study, whichever occurs first. Subjects who have reached a confirmed CR may increase their interval of radiographic assessments up to 6 months (26 weeks) after the first 2 years beyond confirmed CR and up to 12 months (52 weeks) after the first 5 years beyond confirmed CR as long as CR is maintained.

All subjects treated with talimogene laherparepvec and who permanently discontinue study may be eligible to continue follow-up for survival under an ongoing separate registry protocol that is in place for the long-term follow-up of subjects treated with talimogene laherparepvec in clinical trials. The registry protocol will not apply until the end of the study or 3 years after the last subject is enrolled, whichever comes first;

however, if the registry study ends prior to these milestones, then the registry study will not apply. In addition to survival, the registry protocol will also monitor for late and long-term adverse events thought to be potentially related to talimogene laherparepvec.

9.2 Description of General Study Assessments and Procedures

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

9.2.1 General Assessments

9.2.1.1 Informed Consent

All subjects or their legally authorized representative must sign and personally date the IRB/IEC approved informed consent before any study-specific procedures are performed.

9.2.1.2 Demographics

Demographic data collection including sex, age, race, and ethnicity will be collected in order to study their possible association with treatment effectiveness. Additionally, demographic data will be used to study the impact on biomarkers variability.

9.2.1.3 Medical History

The Investigator or designee will collect a complete medical and surgical history that started within 3 years prior to enrollment through the start of the date of investigational medicinal product administration. Medical history will include information on the subject's concurrent medical conditions. Record all findings on the medical history CRF. In addition to the medical history above, melanoma history must date back to the original diagnosis. The current toxicity grade will be collected for each condition that has not resolved.

9.2.1.4 Physical Examination

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

9.2.1.5 Physical Measurements

Weight in kilograms is to be measured without shoes.

9.2.1.6 Substance Abuse History

Obtain a detailed history of prior and/or concurrent use of alcohol and tobacco.

9.2.1.7 Performance Status

Subject performance status will be assessed using the ECOG PS (Section 12.9).

9.2.2 Efficacy Assessments

Disease assessments will be based on local laboratory data and local imaging obtained until confirmed iPD (Section 12.4) irrespective of cycle duration including dose delays and treatment discontinuation as indicated in the Schedule of Activities (Table 2-1). For subjects discontinued from treatment for any reason other than confirmed iPD, every effort should be made to complete efficacy assessments every 12 weeks (±1 week) or more frequently if clinically indicated during the long-term follow-up until documentation of confirmed iPD per modified irRC-RECIST (Section 12.4), start of new anticancer therapy, or end of study, whichever occurs first. Subjects who have reached a confirmed CR may increase their interval of radiographic assessments up to 6 months (26 weeks) after the first 2 years beyond confirmed CR and up to 12 months (52 weeks) after the first 5 years beyond confirmed CR as long as CR is maintained. Planned time points for all efficacy assessments are listed in the Schedule of Activities (Table 2-1).

9.2.2.1 Radiographic Tumor Imaging

Radiographic tumor imaging assessments must include CT scan, PET/CT, or MRI of the abdomen, pelvis, and chest and all other sites of disease. In addition, CT scan or MRI of the brain will be performed at screening and then only if signs or symptoms suggestive of CNS metastasis are present. Imaging will be performed independent of treatment cycle at the time points indicated in the Schedule of Activities (Table 2-1). Imaging should not be adjusted for cycle initiation delays and performed according to the calendar. The imaging modality and image acquisition methods selected (eg, CT or MRI) will remain constant for any individual subject. The radiographic tumor imaging assessments and measurements are performed locally and the response will be assessed by the investigator using modified RECIST v1.1 criteria and modified irRC-RECIST criteria (Section 12.10). However, treatment decisions should be made based on modified irRC-RECIST criteria, NOT based on modified RECIST v1.1 criteria. For subjects who discontinue treatment for any reason other than confirmed iPD per modified irRC-RECIST, every effort should be made to complete radiographic assessments every 12 weeks (±1 week) or more frequently if clinically indicated during the long-term follow-up until documentation of confirmed iPD per modified irRC-RECIST (Section 12.10), clinical progression, start of new anticancer therapy, or end of study, whichever occurs first. Subjects who have reached a confirmed CR may increase their interval of radiographic assessments up to 6 months (26 weeks) after the first 2 years beyond confirmed CR and up to 12 months (52 weeks) after the first 5 years beyond confirmed CR as long as CR is maintained. Radiographic imaging is only required at the

safety follow-up visit if the subject ended treatment prior to confirmed PD and has not had radiographic tumor imaging performed within 4 weeks (+ 1 week) of the visit.

Radiographic scans taken to confirm disease progression following prior anti-PD-1 therapy may be used for baseline tumor assessments, providing they were performed within 28 days of enrollment.

9.2.2.2 Modified RECIST v1.1

A modified version of RECIST v1.1 will be used to determine eligibility, for evaluation of the primary endpoint (objective response) and some secondary efficacy endpoints including complete response, BOR, durable response, DOR, disease control, and PFS based on the investigator's review of the radiographic data. Following modified RECIST v1.1 tumor assessments will continue through **to** the first PD.

9.2.2.3 Modified irRC-RECIST

A modified version of the irRC-RECIST defined by (Nishino et al, 2014) (Section 12.10), will be used to account for unique tumor response characteristics observed with immunotherapies and enable treatment decisions beyond progression (per modified RECIST v1.1). The modified irRC-RECIST criteria will be used by the investigator for evaluation of secondary efficacy endpoints including objective response, complete response, iBOR, durable response, iDOR, disease control, and iPFS based on the investigator's review of the radiographic data. Following modified irRC-RECIST, tumor assessments will continue until confirmed iPD.

9.2.3 Safety Assessments

Planned time points for all safety assessments are listed in the Schedule of Activities see (Table 2-1).

9.2.3.1 Adverse Events

9.2.3.1.1 Time Period and Frequency for Collecting and Reporting Safety Event Information

9.2.3.1.1.1 Adverse Events

The adverse event grading scale to be used for this study will be the CTCAE version 5.0 and is described in Section 12.4.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after first dose of talimogene laherparepvec or pembrolizumab through the safety follow-up visit (30 [+ 7] days after the cessation of study treatment) are reported using the Event**s** CRF.

In addition, talimogene laherparepvec related adverse events that occur after the safety follow-up visit until the end of the long-term follow-up will be recorded in the CRF.

9.2.3.1.1.2 Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through 90 (+ 7) days after the cessation of all study treatment or 30 (+ 7) days following cessation of treatment if the subject initiates new anticancer therapy, are reported using the Event CRF. In addition, talimogene laherparepvec related serious adverse events that occur after the safety follow-up visit until the end of the long-term follow-up will be reported to Amgen and recorded in the CRF.

All serious adverse events will be collected, recorded and reported to the sponsor or designee within 24 hours, as indicated in Section 12.4. The investigator will submit any updated serious adverse event data to the sponsor within 24 hours of it being available.

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.

9.2.3.1.1.3 Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period **(as defined in Section 9.2.3.1.1.2)** or after end of study. However, these serious adverse events**, including deaths due to progression of the melanoma, should** be reported to Amgen **(regardless of causality) if the investigator becomes aware of them (per regional regulatory requirements)**. Per local requirements in some countries, investigators are required to report serious adverse events that they become aware of after end of study. If serious adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's **awareness** 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 and handled accordingly based on relationship to investigational product.

The method of recording, evaluating, and assessing causality of adverse events and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Section 12.4.

9.2.3.1.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

9.2.3.1.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/serious adverse event report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All adverse events and serious adverse events will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Section 12.4.

All new information for previously reported serious adverse events must be sent to Amgen within 24 hours following **awareness** of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Event**s** CRF.

9.2.3.1.4 Regulatory Reporting Requirements for Serious Adverse Events

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

Prompt notification by the investigator to the sponsor of serious adverse events is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

Individual safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.3.1.5 Safety Monitoring Plan

Subject safety will be routinely monitored as defined in Amgen's safety surveillance and signal management processes.

9.2.3.1.6 Pregnancy and Lactation

Details of all pregnancies in female subjects and female partners of male subjects and/or lactation in female subjects will be collected after the start of study treatment and until 3 months after the last dose of talimogene laherparepvec or 4 months after the last dose of pembrolizumab, whichever is later.

If a pregnancy or lactation case is reported, the investigator is to inform Amgen within 24 hours of **awareness** of the pregnancy and/or lactation and is to follow the procedures outlined in Section 12.5. Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

Further details regarding pregnancy and lactation are provided in Section 12.5.

9.2.3.2 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure, heart rate, respiration rate, and 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 signs CRF. The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs CRF. Record all measurements on the vital signs CRF.

9.2.3.3 Electrocardiograms (ECGs)

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

9.2.3.4 Vital Status

Vital status must be obtained for all subjects within the limits of local law. This includes subjects who may have discontinued study visits with or without withdrawing consent and should include interrogation of public databases, if necessary. If deceased, the date and reported cause of death should be obtained. **See Sections 9.2.3.1.1.2 and 9.2.3.1.1.3 for reporting requirements of serious adverse events during the long-term follow-up and after the end of the protocol-required reporting period.**

9.2.3.5 Swab of Herpetic Lesions

Upon notification of a suspected herpetic lesion by the subject, the 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 real-time polymerase chain reaction (qPCR) analysis will be performed on the swab sample to evaluate whether the talimogene laherparepvec DNA is detectable in the sample.

9.2.3.6 Reporting of Unintentional 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, has signs or symptoms suspected to be herpetic in origin or is accidentally exposed to talimogene laherparepvec), while the subject is taking talimogene laherparepvec, report the exposure to Amgen as specified below. In addition to reporting an unintended exposure case during the study treatment, investigators should monitor for potential exposure cases that occur after the last dose of talimogene laherparepvec through 30 (+ 7) days after the last dose of talimogene laherparepvec.

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

9.2.3.7 Pembrolizumab Events of Clinical Interest

Selected non-serious and serious adverse events known as Pembrolizumab Events of Clinical Interest (ECI) that occur after the first dose of pembrolizumab through 90 (+ 7) days after the last dose of pembrolizumab, or 30 (+ 7) days after initiation of a new anticancer therapy, whichever is earlier must be reported to Amgen within 24 hours.

Pembrolizumab ECI for this trial include:

- an overdose of pembrolizumab, as defined in Section 9.2.3.8.
- an elevated AST or ALT lab value that is greater than or equal to 3 x ULN and an elevated total bilirubin lab value that is greater than or equal to 2 x ULN and, at the same time, an alkaline phosphatase lab value that is less than 2 x ULN, as determined by way of protocol specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be made available. It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the Sponsor Clinical Director. However, abnormalities of liver blood tests that do not meet the criteria noted above are not ECIs for this trial.

9.2.3.8 Definition and Reporting of an Overdose of Pembrolizumab

For the purpose of this trial, an overdose of pembrolizumab will be defined as > 1000 mg (5 times the dose of pembrolizumab). No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) or serious adverse event(s) is associated with ("result from") the overdose of pembrolizumab, the adverse event(s) or serious adverse event is to be reported to Amgen as described in Sections 9.2.3.1.1.2 and 9.2.3.1.1.3, respectively. In addition, the adverse event(s) or serious adverse event(s) associated with ("result from") the overdose of pembrolizumab should be reported as Event of Clinical Interest as described in Section 9.2.3.7.

9.2.4 Clinical Laboratory Assessments

Refer to Section 12.2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (Table 2-1) for the timing and frequency.

The investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in the Event CRF. The investigator must determine 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.

All protocol-required laboratory assessments, as defined in Section 12.2, must be conducted in accordance with the laboratory manual and the Schedule of Activities (Table 2-1).

9.2.4.1 Pregnancy Testing

A highly sensitive urine pregnancy test should be completed at screening (within 72 hours prior to enrollment) for females of childbearing potential. If urine pregnancy test result is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

Note: Females who have undergone a bilateral tubal ligation/occlusion should have pregnancy testing per protocol requirements. (If a female subject, or the partner of a male subject, becomes pregnant it must be reported on the Pregnancy Notification Worksheet, see Figure 12-2). Refer to Section 12.5 for contraceptive requirements.

A pregnancy test should be performed at the safety follow-up visit approximately 30 (+ 7) days after discontinuing protocol-required therapies.

Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as required per local laws and regulations.

[redacted]

[redacted]

9.2.6 Pharmacogenetic Assessments

If the subject consents to the optional pharmacogenetic portion of this study, DNA analyses 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 melanoma and/or to identify subjects who may have positive or negative response to talimogene laherparepvec. Additional samples are not collected for this part of the study. For subjects who consent to these analyses, DNA may be extracted.

The final disposition of samples will be described in Section 12.6.

9.2.7 Antibody Testing Procedures

HSV-1 serostatus will be assessed at baseline and during the study at the time points noted in Table 2-1.

9.2.8 Health Economics OR Medical Resource Utilization and Health Economics

Not applicable.

9.2.9 Other Assessments

Not applicable.

10. Statistical Considerations

10.1 Sample Size Determination

This is a single-arm estimation study. It is assumed that if the ORR using modified RECIST v1.1 is at least 25%, for this study (N = 100) the lower bound of the 95% confidence interval for an objective response is > 15%.

The 95% CIs for different sample sizes with an assumed ORR of 25% are presented below:

Subjects Enrolled N	Assumed ORR N (%)	95% CI %	Width %
15	4 (26.7)	7.8, 55.1	47.3
30	8 (26.7)	12.3, 45.9	33.6
40	10 (25.**0**)	12.7, 41.2	28.5
70	18 (25.7)	16.0, 37.6	21.6
72	**18 (25.0)**	**15.5, 36.6**	**21.0**
100	25 (25.**0**)	16.9, 34.7	17.8

Actual number of subjects enrolled in the study: a total of 72 subjects were enrolled in the study (instead of N = 100 subjects planned at the beginning of the study). Twenty-seven subjects were enrolled into cohort 1 and 15 subjects were enrolled into cohorts 2, 3, and 4.

10.2 Analysis Sets, Subgroups, and Covariates

10.2.1 Analysis Sets

The Full Analysis Set (FAS) is defined as all enrolled subjects who have received at least 1 dose of talimogene laherparepvec and 1 dose of pembrolizumab in combination.

The Per Protocol Analysis Set (PPAS) is a subset of the FAS which includes subjects who do not have important protocol deviations that are considered to have an impact on efficacy outcomes.

Subjects with any of the following eligibility criteria for important protocol deviations will be removed from the PPAS:

- Subject does not have histologically confirmed diagnosis of melanoma
- Subject does not have unresectable or metastatic melanoma, defined as either
  - Stage IIIB, IIIC, IIID, IVM1a, IVM1b, or IVM1c;

    OR
  - Stage IVM1d with up to 3 cerebral metastases, provided that all lesions have been adequately treated with stereotactic radiation therapy, craniotomy, or gamma knife therapy, with no evidence of progression and not requiring steroids for at least 2 months prior to enrollment.
- Subject is not a candidate for intralesional therapy, and a candidate is defined as either 1 of the following:
  - At least 1 injectable cutaneous, subcutaneous, or nodal melanoma lesion ≥ 10 mm in longest diameter;

    OR
  - Multiple injectable melanoma lesions which in aggregate have a longest diameter of ≥ 10 mm

Additionally, the subjects with any of the following important protocol deviations related to prior PD-1 inhibitor use will be removed from the PPAS:

- Subject has not received prior treatment with a PD-1 inhibitor in the adjuvant or metastatic setting (monotherapy or in combination with anti-CTLA-4). Combinations other than anti-PD-1 plus anti-CTLA-4 must have been reviewed with the medical monitor for approval.
- Subject has not received prior anti-PD-1 therapy for at least 2 to 3 consecutive cycles within an 8-week period (based on administration schedule).
- Subject for whom the anti-PD-1 therapy is not the immediate prior line of therapy before enrollment.

The FAS and PPAS will be used in the analysis of the efficacy endpoints.

The Safety Analysis Set (SAS), defined as all enrolled subjects who received at least 1 dose of talimogene laherparepvec or pembrolizumab, will be used in the analysis of the safety endpoints.

10.2.2 Covariates

No covariate analyses will be performed.

10.2.3 Subgroups

Efficacy analyses on ORR and DCR will be repeated within the following subgroups, overall with cohorts pooled and separately for each cohort:

- PD-L1 status (positive, negative) at baseline
- Disease stage (stage IVM1a or lower, stage IVM1b/c/d) at baseline
- Disease stage (stage IVM1b or lower, stage IVM1c/d) at baseline
- *BRAF*^{V600} mutation at baseline (yes, no)
- Region (Europe, Non-Europe)
- Age (< 65, ≥ 65; < 75, ≥ 75 years)
- LDH (≤ ULN, > ULN)
- Sex (female, male)
- ECOG PS (0, 1)
- HSV-1 serostatus at baseline (positive, negative, missing/unknown)
- In-transit disease at baseline
- Prior PD-1 therapy (nivolumab, ipilimumab/nivolumab, pembrolizumab)

10.2.4 Handling of Missing and Incomplete Data

Every effort will be made to obtain complete data in the clinical study. Partial or missing dates of adverse events, concomitant medications and death date will be imputed. Details of the imputation algorithm will be provided in the Statistical Analysis Plan.

10.3 Adaptive Design

Futility analyses are planned for each of cohorts 1 and 2, separately. The futility criteria are detailed in Section 10.4.1.1.

10.4 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock. Below is a summary of the timing and methods for the planned statistical analyses. To preserve study integrity, the final analysis will be conducted and reported following the end of study, as defined in Section 5.3.1.

10.4.1 Planned Analyses

10.4.1.1 Interim Analysis and Early Stopping Guidelines

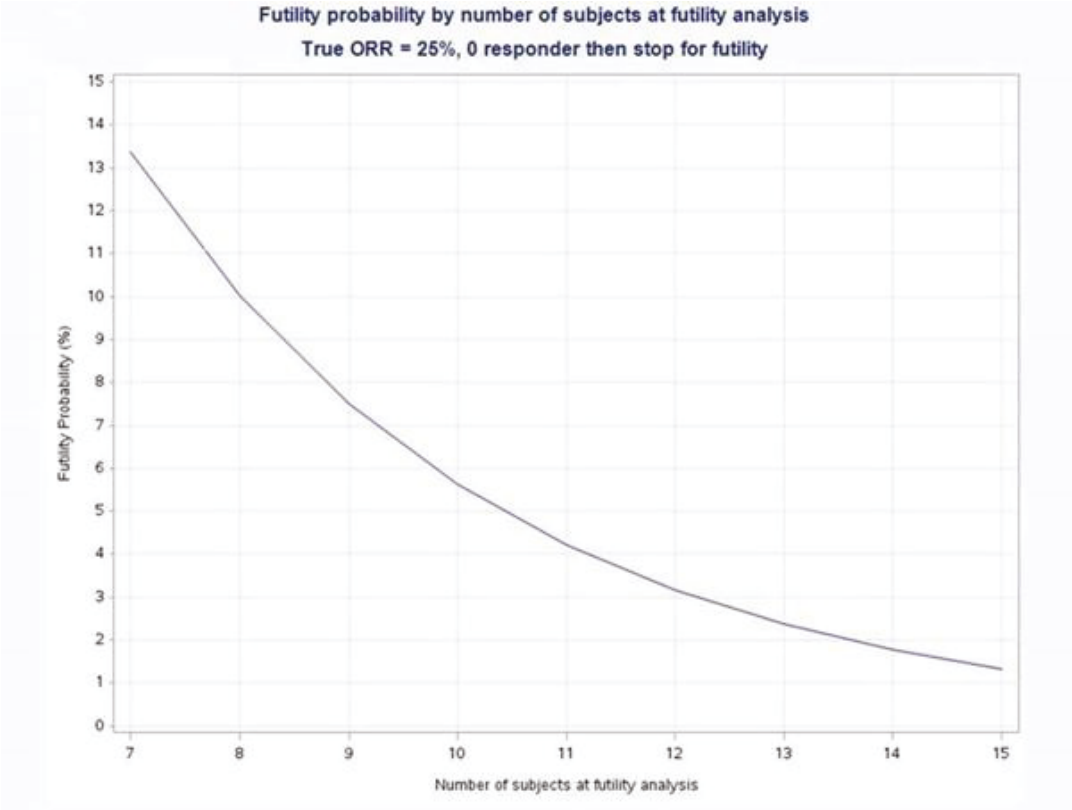
Futility analyses are not planned for cohorts 3 and 4. In cohorts 1 and 2, if there is at least 1 unconfirmed responder (PR/CR) in the first 10 subjects of a cohort, enrollment will continue in that cohort without a futility analysis. Otherwise, a futility analysis of unconfirmed response is planned for cohorts 1 and 2 (performed separately and only once for each cohort) when 15 subjects within a cohort are evaluable for response.

Screening in the respective cohort will be paused during the futility analysis. The below table presents the futility criteria:

Number of Evaluable Subjects* at Futility Analysis	Minimum Number of Subjects with an unconfirmed CR/PR to Continue	Probability of Futility (%) True ORR = 25%
15	1	< 5%

* number of subjects treated and who have had the opportunity to be followed for at least 12 weeks for tumor assessment.

When the true response is 25%, the probability of futility is < 5% with at least 1 responder among 15 evaluable subjects.



A data review team (DRT) will review safety and efficacy data approximately every 3 months until the data snapshot for the primary analysis to ensure no avoidable increased risk for harm to subjects. In addition, the DRT will oversee the futility analysis for each of cohorts 1 and 2. The DRT may request ad hoc meetings at any time. The DRT also has a responsibility to review and evaluate study conduct to determine whether the study integrity may affect the ability of the DRT to fulfil its primary responsibility. Therefore, the DRT will review and evaluate eligibility/recruitment/retention of participants, management of participants, and

adherence to protocol-specified criteria. The DRT will make recommendations concerning the continuation or alteration of the study on the basis of its review of the data.

The DRT will be comprised of an Amgen clinical research medical director, Amgen safety officer, and Amgen biostatistician who are external to the talimogene laherparepvec product team.

Membership, procedures, and meeting timing will be described in the study DRT charter.

10.4.1.2 Primary Analysis

The primary analysis will occur when all subjects treated with at least 1 dose of talimogene laherparepvec or pembrolizumab have had the opportunity to be followed for at least 24 weeks for tumor assessment.

Before the primary analysis, ad hoc analyses may be conducted to support program level activities.

10.4.1.3 Final Analysis

The final analysis will occur when all subjects have completed the study.

10.4.2 Methods of Analyses

10.4.2.1 General Considerations

Unless otherwise specified, all safety analyses will be performed on the SAS and all efficacy analyses on the FAS. All analyses will be descriptive with no formal hypothesis testing. Analyses will be performed separately for each cohort. In addition, analyses with cohorts pooled together (all cohorts pooled, cohorts 1 and 2 pooled, and cohorts 3 and 4 pooled) will be performed. Cohorts stopped for futility will not be pooled with other cohorts. Cohort data collected on the CRF will be used in the analysis. Cohort data will be checked and reviewed during the study to ensure that subjects are recorded in the correct cohort for analyses prior to database lock.

Continuous variables will be summarized by the non-missing sample size (n), mean, standard deviation, median, first and third quartiles, minimum, and maximum. Categorical variables will be summarized by the n and percentage in each category. Proportions and the corresponding 95% exact CIs will be provided (Clopper and Pearson, 1934). Time to event endpoints will be summarized with Kaplan-Meier (KM) (Kaplan and Meier, 1958) curves, KM estimates at selected time points, KM quartiles (when estimable), the number of subjects with events and the

number of subjects censored. Accompanying 2-sided 95% CI for KM quartiles (Brookmeyer and Crowley, 1982) and KM estimates will be provided.

10.4.2.2 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	ORR per modified RECIST v1.1, ORR is defined as the incidence of a BOR of CR or PR ORR: Binomial proportions and exact 95% CIs.
Secondary	CRR is defined as the incidence of a BOR of CR. DRR is defined as the percent of subjects with a CR or PR with a DOR ≥ 6 months. DCR is defined as the incidence of a BOR of CR, PR or SD. DOR is defined as the time of an initial response (CR or PR) to PD or death, whichever is earlier. Subjects who have not ended their response at the time of analysis will be censored at their last evaluable tumor assessment before the start of the first subsequent anticancer therapy. OS is defined as the time from enrollment to death. Subjects without an event will be censored at their last known to be alive date. PFS is defined as the time from enrollment to PD or death, whichever is earlier. Subjects without an event will be censored at their last evaluable tumor assessment if available, otherwise will be censored on day 1. Time to subsequent anticancer therapy is defined as the time from enrollment to the start of subsequent anticancer therapy. Subjects who have not started subsequent anticancer therapy will be censored on their last visit date. iORR per modified irRC-RECIST, and CRR, BOR, DRR, and DCR, per modified RECIST v1.1 and modified irRC-RECIST will follow the analysis described for the primary endpoint: Binomial proportions and exact 95% CIs DOR per modified RECIST v1.1 and modified irRC-RECIST: KM method among responders (CR and PR). OS per modified RECIST v1.1 and modified irRC-RECIST: KM method. PFS per modified RECIST v1.1 and modified irRC-RECIST: KM method. Time to subsequent anticancer therapy: KM method.
Exploratory	Will be described in the statistical analysis plan finalized before database lock

10.4.2.3 Safety Analyses

10.4.2.3.1 Adverse Events

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product or other protocol-required therapies, and significant treatment emergent adverse events will also be provided.

10.4.2.3.2 Laboratory Test Results

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

10.4.2.3.3 Vital Signs

Summary statistics over time will be provided.

10.4.2.3.4 Electrocardiogram

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

10.4.2.3.5 Exposure to Investigational Medicinal Product

Summary statistics for exposure to talimogene laherparepvec, including total doses administered, total volume administered, duration from the first to the last administration, and the average volume received by subject per visit will be provided and will be separated by first (concentration of 10^6 PFU/ml) and subsequent doses (concentration of 10^8 PFU/ml). Subject incidence rate and reasons for investigational product delay, or dose change/withheld, will be tabulated.

Descriptive statistics of total dose (mg), relative dose intensity, duration of usage (from first to last administration), average dose received by subject per visit, number and percentage of subjects and the reasons for dose modifications, investigational medicinal product delay, and withdrawal will be produced to describe the exposure to pembrolizumab.

10.4.2.3.6 Exposure to Concomitant Medication

Number and proportion of subjects receiving therapies of interest will be summarized by preferred term as coded by the World Health Organization Drug dictionary.

The subject incidence and time to first use of subsequent anticancer therapies will be summarized.

10.4.2.4 Other Analyses

[redacted]

11. References

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12. Appendices

12.1 Appendix 1. List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition/Explanation
AJCC	American Joint Committee on Cancer
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BOR	best overall response
$BRAF^{v600}$	serine/threonine protein kinase B-Raf V600
CD28	cluster of differentiation 28
CFR	U.S. Code of Federal Regulations
CI	confidence interval
CRF	case report form
CR	complete response
CRR	complete response rate
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte associated antigen 4
DCR	disease control rate
DILI	drug induced liver injury
DOR	duration of response
DRR	durable response rate
DRT	data review team
ECG	electrocardiogram
ECI	events of clinical interest
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EDC	electronic data capture
Enrollment	a subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria
End of Study (primary completion)	defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoints, whether the study concluded as planned in the protocol or was terminated early
End of Study (end of trial)	defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable
ESMO	European Society for Medical Oncology

Abbreviation or Term	Definition/Explanation
FAS	Full Analysis Set
FCBP	females of childbearing potential
FSH	follicle stimulating hormone
FT3	free triiodothyronine
FT4	free thyroxine
GCP	Good Clinical Practice
GM-CSF	granulocyte-macrophage colony-stimulating factor
HIV	human immunodeficiency virus
HNSCC	head and neck squamous cell carcinoma
HRT	hormone replacement therapy
HSV	herpes simplex virus
ICF	informed consent form
ICH	International Conference on Harmonisation
iCR	complete response (by modified irRC-RECIST)
iCRR	complete response rate (by modified irRC-RECIST)
iDCR	disease control rate (by modified irRC-RECIST)
iDRR	durable response rate (by modified irRC-RECIST)
iDOR	duration of response (by modified irRC-RECIST)
IEC	Independent Ethics Committee
IMP	investigational medicinal product
INR	international normalization ratio
iORR	objective response rate (by modified irRC-RECIST)
iPD	progressive disease (by modified irRC-RECIST)
IPIM	Investigational Product Instruction Manual
iOFS	progression free survival (by modified irRC-RECIST)
IRB	Institutional Review Board
irRC	immune-related Response Criteria
irRC-RECIST	immune-related Response Criteria simulating Response Evaluation Criteria in Solid Tumors
IUD	intrauterine device
IUS	intrauterine hormonal-releasing system
IRT	interactive response technology that is linked to a central computer in real time as an interface to collect and process information
KM	Kaplan-Meier
LDH	lactate dehydrogenase
mAb	monoclonal antibody
MRI	magnetic resonance imaging

Abbreviation or Term	Definition/Explanation
NCCN	National Comprehensive Cancer Network
NCT	National Clinical Trials
ORR	objective response rate
OS	overall survival
PD-1	programmed cell death-1
PD-L1	programmed cell death-1 ligand 1
PD-L1	programmed cell death-1 ligand 2
PET	positron emission tomography
PFS	progression free survival
PK	pharmacokinetic
PPAS	Per Protocol Analysis Set
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
Q2W	once every 2 weeks
Q3W	once every 3 weeks
qPCR	real-time polymerase chain reaction
RECIST	Response Evaluation Criteria in Solid Tumor
SAS	Safety Analysis Set
SD	stable disease
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
Study day 1	defined as the first day that protocol-specified investigational product(s)/protocol-required therapies is/are administered to the subject
T3	triiodothyronine
TBL	total bilirubin
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
[redacted]	

12.2 Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 12-1 will be performed by the local laboratory unless otherwise stated.

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Sections 6.1 to 6.2 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 12-1. Analyte Listing

Laboratory: Chemistry	Laboratory: Coagulation	Thyroid Function	Laboratory: Hematology	Other Labs
Sodium Potassium Chloride Calcium Magnesium Phosphorus Uric acid Total protein Albumin BUN/Urea Creatinine Bilirubin (direct and total) Alkaline-phosphatase AST ALT Glucose	PT or INR PTT or aPTT	TSH T3 or FT3 FT4	RBC Hemoglobin Hematocrit Platelets WBC ANC Differential • Neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes	Pregnancy (urine or serum) LDH Urinalysis • Blood • Glucose • Protein • Specific gravity • Microscopic exam (only reflexively for abnormal urinalysis results) 24-hour urine creatinine clearance PD-L1 expression[a] BRAF mutation[b] qPCR for talimogene laherparepvec DNA[b] HSV-1 antibody[a] [redacted]

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; aPTT = activated partial thromboplastin time; BUN = blood urea nitrogen; FT3 = free triiodothyronine; FT4 = free thyroxine; HSV = herpes simplex virus; INR = international normalized ratio; LDH = lactate dehydrogenase; PD-L1 = programmed cell death-1 ligand 1; PT = prothrombin time; PTT = partial thromboplastin time; qPCR = real-time polymerase chain reaction; T3 = triiodothyronine; TSH = thyroid stimulating hormone; WBC = white blood cell count

[a] Performed at central laboratory.

[b] Performed at central laboratory when a local result is not available.

12.3 Appendix 3. Study Governance Considerations

Data Review Team

The data review team (DRT) will be comprised of an Amgen clinical research medical director, Amgen safety officer, and Amgen biostatistician who are external to the talimogene laherparepvec product team. The DRT will review safety and efficacy data approximately every 3 months until the data snapshot for the primary analysis to ensure no avoidable increased risk or harm to subjects. In addition, the DRT will oversee the futility analysis for each of cohorts 1 and 2. The DRT may request ad hoc meetings at any time. The DRT also has a responsibility to review and evaluate study conduct to determine whether the study integrity may affect the ability of the DRT to fulfil its primary responsibility. Therefore, the DRT will review and evaluate eligibility/recruitment/retention of participants, management of participants, and adherence to protocol-specified criteria. The DRT will make recommendations concerning the continuation or alteration of the study on the basis of its review of the data.

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable ICH laws and regulations

The protocol, protocol amendments, informed consent form, Investigator's Brochure, and other relevant documents (eg, subject recruitment advertisements) must be submitted to an institutional review board/independent ethics committee (IRB/IEC) by the investigator and reviewed and approved by the IRB/IEC. 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.

Amgen may amend the protocol at any time. 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 must send a copy of the approval letter from the IRB/IEC and amended protocol Investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- 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
- Notifying the IRB/IEC of serious adverse events occurring at the site, deviations from the protocol or other adverse event reports received from Amgen, in accordance with local procedures
- Overall conduct of the study at the site and adherence to requirements of Title 21 of the U.S. Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, and all other applicable local regulations

Recruitment Procedures

Site staff will identify potential subjects from their existing patient population or may seek referral patients through existing professional networks or other community sources such as patient advocacy groups. All patient-facing materials must be reviewed/approved by the sponsor (Amgen Inc.) and the IRB/IEC, where required.

Informed Consent Process

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 sample informed consent form are to be communicated formally in writing from the Amgen Trial Manager to the investigator. The written informed consent form is to be prepared in the language(s) of the potential patient population.

The investigator or his/her delegated representative will explain to the subject, or his/her legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study before any protocol-specific screening procedures or any investigational product(s) is/are administered, and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or there legally authorized representative will then be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study site.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the informed consent form.

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 unless it is a local requirement. The investigator shall then inform the primary care physician. 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 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. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records; refer to Section 8.

Subjects must be re-consented to the most current version of the informed consent form(s) during their participation in the study.

The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the informed consent form(s) must be provided to the subject or the subject's legally authorized representative.

Data Protection/Subject Confidentiality

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

Subject will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

On the Case Report Form (CRF) demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

For serious adverse events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and age (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 governmental regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the 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.

Publication Policy

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

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals International Committee of Medical Journal Editors Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states: Authorship credit is to be based on: (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors need to meet conditions 1, 2, 3, and 4.

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

Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multicenter 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

Data Quality Assurance

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data, centrally or adjudicated data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Clinical monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable

from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements per the sponsor's monitoring plan.

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.

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.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Research and Development 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.

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

Case report forms (CRF) 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.

Source Documents

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 provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

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. Source documents may also include data captured in the interactive response technology (IRT) system (if used, such as subject ID and randomization number) and CRF entries if the CRF is the site of the original recording (ie, there is no other written or electronic record of data, such as paper questionnaires for a clinical outcome assessment).

Data reported on the CRF or entered in the electronic CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

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.

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

Study and Site Closure

Amgen or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

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

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

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.

12.4 Appendix 4. Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment. • Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, combination product, medical device or procedure. • Note: Treatment-emergent adverse events will be defined in the statistical analysis plan (SAP).

Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an adverse event/serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae. • 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. • “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.

Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:
Results in death (fatal)
Immediately life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires in-patient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event is to be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.
Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:
Is a congenital anomaly/birth defect
Other medically important serious event Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording Adverse Events and Serious Adverse Events

Adverse Event and Serious Adverse Event Recording
• When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant adverse event/serious adverse event information in the Event case report form (CRF). Additionally, the investigator is required to report a fatal adverse event on the Event CRF. • The investigator must assign the following adverse event attributes: o Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms); o Dates of onset and resolution (if resolved); o **Did the event start prior to first dose of investigational product, other protocol-required therapies;** o **Assessment of seriousness;** o Severity (or toxicity defined below); o Assessment of relatedness to talimogene laherparepvec, pembrolizumab and/or study conduct; o Action taken**; and** o **Outcome of 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 Event**s** CRF. • It is not acceptable for the investigator to send photocopies of the subject's medical records to sponsor in lieu of completion of the Event**s** CRF page.

Adverse Event and Serious Adverse Event Recording
• If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to Amgen. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity
The investigator will make an assessment of severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on the Common Terminology Criteria for Adverse Events, version 5.0 which is available at the following location: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Assessment of Causality
• The investigator is obligated to assess the relationship between talimogene laherparepvec, pembrolizumab and/or study-mandated procedure and each occurrence of each adverse event/serious adverse event. • Relatedness means that there are facts or reasons to support a relationship between investigational product and the event. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. • The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment. • For each adverse event/serious adverse event, the investigator must document in the medical notes that he/she has reviewed the adverse event/serious adverse event and has provided an assessment of causality. • There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data.

Assessment of Causality
• The investigator may change his/her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment. • The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Event and Serious Adverse Event
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Amgen to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen. • If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide Amgen with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed Event**s** CRF. • The investigator will submit any updated serious adverse event data to Amgen within 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Electronic Data Collection Tool
• The primary mechanism for reporting serious adverse event will be the electronic data capture (EDC) system. • If the EDC system is unavailable for more than 24 hours, then the site will report the information to Amgen using **a paper-based** Serious Adverse **Event** Contingency Report Form **(also referred to as the** electronic Serious Adverse **Event [eSAE]** Contingency Report Form**)** (see Figure 12-1) within 24 hours of the investigator's **awareness** of the event. • The site will enter the serious adverse event data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new serious adverse event from a study subject or receives updated data on a previously reported serious adverse event after the EDC has been taken off-line, then the site can report this information on a paper Serious Adverse Event Report Form (see Figure 12-1).

- **Once the study has ended, serious adverse event(s) should be reported to Amgen (regardless of causality) if the investigator becomes aware of a serious adverse event. The investigator should use the paper-based Serious Adverse Event Contingency Report Form to report the event.**

Figure 12-1. Sample Electronic Serious Adverse Event Contingency Report Form (Paper-based Form)

AMGEN Study# 20180115 Talimogene Laherparepvec (T-VEC)	**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? T-VEC No✓	T-VEC Yes✓	Pembrolizumab No✓	Pembrolizumab Yes✓	Outcome of Event -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
				☐ Yes ☐ No							
				☐ Yes ☐ No							
				☐ Yes ☐ No							

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

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

Date Admitted Day Month Year	Date Discharged Day Month Year

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

IP/Amgen Device:		Date of Initial Dose Day Month Year	Prior to, or at time of Event: Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
Talimogene Laherparepvec (T-VEC)	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
Pembrolizumab	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____

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AMGEN Study# 20180115 Talimogene Laherparepvec (T-VEC)	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

								☐ Unavailable / 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✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med 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# 20180115 Talimogene Laherparepvec (T-VEC)	**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

12.5 Appendix 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information

Study-specific contraception requirements for male and female subjects of childbearing potential are outlined in Section 6.2.

Male and female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to the fetus if they become pregnant or father a child during treatment and for 3 months after the last dose of talimogene laherparepvec or 4 months after the last dose of pembrolizumab, whichever is later after the last dose of protocol-required therapies.

Definition of Females of Childbearing Potential

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

Females in the following categories are not considered female of childbearing potential:

- Premenopausal female with 1 of the following:
  - Documented hysterectomy;
  - Documented bilateral salpingectomy; or
  - Documented bilateral oophorectomy.

  Note: Site personnel documentation from the following sources is acceptable: 1) review of subject's medical records; 2) subject's medical examination; or 3) subject's medical history interview.
- Premenarchal female
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment

Contraception Methods for Female Subjects

Acceptable Methods of Effective Contraception

- Combined (estrogen and progestogen containing) or progestogen-only hormonal methods given via oral, intravaginal, transdermal, injectable, or implantable route)
- Intrauterine device (IUD)
- Intrauterine hormonal-releasing system (IUS)
- Bilateral tubal ligation/occlusion
- Vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)
- Male or female condom with or without spermicide
- Cap, diaphragm or sponge with spermicide
- Double barrier method: the male uses a condom and the female may choose either a cap, diaphragm, or sponge with spermicide (a female condom is not an option due to the risk of tearing when both partners use a condom)

Contraception Methods for Male Subjects

- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with protocol-required therapies; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)
- Use a condom during treatment and for an additional 3 months after the last dose of talimogene laherparepvec or 4 months after the last dose of pembrolizumab, whichever is later.

For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

The female partner should consider using an acceptable method of effective contraception such as: hormonal, IUD, IUS, female barrier method (diaphragm, cap, sponge [a female condom is not an option because there is a risk of tearing when both partners use a condom]).

Note: If the male's sole female partner is of non-childbearing potential or has had a bilateral tubal ligation/occlusion, he is not required to use additional forms of contraception during the study.

Unacceptable Methods of Birth Control for Male and Female Subjects

Birth control methods that are considered unacceptable in clinical trials include:

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicides only
- Lactational amenorrhea method

Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 3 months after the last dose of talimogene laherparepvec or 4 months after the last dose of pembrolizumab, whichever is later.
- Information will be recorded on the Pregnancy Notification Worksheet (see Figure 12-2). The worksheet must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws).
- After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 3 months after the last dose of talimogene laherparepvec or 4 months after the last dose of pembrolizumab, whichever is later of the study drug. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.
- If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a serious adverse event.

- Any serious adverse event occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described in Section 12.4. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female subject who becomes pregnant while participating will discontinue study treatment (see Section 8.1 for details).

Male Subjects With Partners Who Become Pregnant or Were Pregnant at the Time of Enrollment

- In the event a male subject fathers a child during treatment, and for an additional 3 months after the last dose of talimogene laherparepvec or 4 months after the last dose of pembrolizumab, whichever is later after discontinuing protocol-required therapies, the information will be recorded on the Pregnancy Notification Worksheet. The worksheet (see Figure 12-2) must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of the pregnancy. (Note: Sites are not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws).
- The investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.
- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 3 months after the last dose of talimogene laherparepvec or 4 months after the last dose of pembrolizumab, whichever is later.
- Information will be recorded on the Lactation Notification Worksheet (see below) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's **awareness** of event.

- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion Section 6.2.
- With the female subjects signed authorization for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 3 months after the last dose of talimogene laherparepvec or 4 months after the last dose of pembrolizumab, whichever is later after discontinuing protocol-required therapies.

Figure 12-2. Pregnancy and Lactation Notification Forms

Amgen Proprietary - Confidential

Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20180115

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 age (at onset):____(in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
Talimogene Laherparepvec (T-VEC)				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 last menstrual period (LMP) mm_____/ dd_____/ yyyy_____ ☐Unknown ☐N/A

Estimated date of delivery mm_____/ dd_____/ yyyy_____

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: _____

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Amgen Proprietary - Confidential

AMGEN® Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20180115

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 age (at onset):____(in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
Talimogene Laherparepvec (T-VEC)				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: _____

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12.6 Appendix 6. Sample Storage and Destruction

[redacted]

12.7 Appendix 7. Hepatotoxicity Stopping Rules: Suggested Actions and Follow-up Assessments and Study Treatment Rechallenge Guidelines

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBL]) and/or international normalized ratio (INR) and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of Amgen investigational product or other protocol-required therapies, as specified in the *Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009*.

Criteria for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

The following stopping and/or withholding rules apply to subjects for whom another cause of their changes in liver biomarkers (TBL, INR and transaminases) has not been identified.

Important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:

- Hepatobiliary tract disease
- Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
- Right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia
- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
- Heritable disorders causing impaired glucuronidation (eg, Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
- Alpha-1 antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic fatty liver disease including steatohepatitis
- Non-hepatic causes (eg, rhabdomylosis, hemolysis)

If investigational product(s) is/are withheld, the subject is to be followed for possible drug induced liver injury (DILI) according to recommendations in the last section of this appendix.

Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline (see next section in this appendix).

Table 12-2. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

Analyte	Temporary Withholding	Permanent Discontinuation
TBL	> 3x ULN at any time	> 2x ULN
		OR
INR	--	> 1.5x (for subjects not on anticoagulation therapy)
	OR	AND
AST/ALT	> 8x ULN at any time > 5x ULN but < 8x ULN for ≥ 2 weeks > 5x ULN but < 8x ULN and unable to adhere to enhanced monitoring schedule > 3x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, and jaundice)	In the presence of no important alternative causes for elevated AST/ALT and/or TBL values > 3x ULN (when baseline was < ULN)
	OR	
ALP	> 8x ULN at any time	--

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal

Criteria for Rechallenge of Amgen Investigational Product and Other Protocol-required Therapies After Potential Hepatotoxicity

The decision to rechallenge the subject is to be discussed and agreed upon unanimously by the subject, investigator, and Amgen.

If signs or symptoms recur with rechallenge, then Amgen investigational product and other protocol-required therapies, as appropriate are to be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 12-2) are never to be rechallenged.

Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation, according to the criteria specified in the above, require the following:

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate Case Report Form (CRF) (eg, Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to Amgen

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 12.4.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Table 12-2 or who experience AST or ALT elevations > 3 x upper limit of normal (ULN) or 2-fold increases above baseline values for subjects with elevated values before drug are to undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels.

Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (total and direct), and INR within 24 hours
- In cases of TBL > 2x ULN or INR > 1.5, retesting of liver tests, BIL (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.

Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL. The following are to be considered depending on the clinical situation:

- Complete blood count with differential to assess for eosinophilia
- Serum total immunoglobulin (Ig)G, anti-nuclear antibody anti-smooth muscle antibody, and liver kidney microsomal antibody-1 to assess for autoimmune hepatitis
- Serum acetaminophen (paracetamol) levels

- A more detailed history of:
  - Prior and/or concurrent diseases or illness
  - Exposure to environmental and/or industrial chemical agents
  - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
  - Prior and/or concurrent use of alcohol, recreational drugs and special diets
  - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
- Viral serologies
- Creatine phosphokinase, haptoglobin, lactate dehydrogenase and peripheral blood smear
- Appropriate liver imaging if clinically indicated
- Appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Hepatology consult (liver biopsy may be considered in consultation with a hepatologist)

Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or considered stable by the investigator. The "close observation period" is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

The potential DILI event and additional information such as medical history, concomitant medications and laboratory results must be captured in the corresponding CRFs.

12.8 Appendix 8. Protocol-specific Anticipated Serious Adverse Events

Anticipated serious adverse events are events that are anticipated to occur in the study population at some frequency independent of investigational product exposure and do not need to be reported individually as an FDA IND safety report by the sponsor. Identification and reporting of anticipated serious adverse events is the responsibility of the sponsor; the investigator is responsible for reporting adverse events and serious adverse events as described in Section 12.4.

Anticipated Serious Adverse Events for Study 20180115

Preferred Term[1]
Acral lentiginous melanoma
Acral lentiginous melanoma stage III
Acral lentiginous melanoma stage IV
Acral lentiginous melanoma stage unspecified
Central nervous system melanoma
Choroid melanoma
Ciliary body melanoma
Conjunctival melanoma
Desmoplastic melanoma
Dysplastic naevus
Epidermal naevus
Eye naevus
Gastrointestinal melanoma
Genitourinary melanoma
Intraocular melanoma
Iris melanoma
Lentigo melanoma
Malignant blue naevus
Malignant melanoma
Malignant melanoma of eyelid

Malignant melanoma stage III
Malignant melanoma stage IV
Melanoma recurrent
Melanocyte naevus
Metastatic malignant melanoma
Metastatic ocular melanoma
Naevoid melanoma
Naevus haemorrahge
Nodular melanoma
Primary pulmonary melanoma
Retinal melanoma
Skin neoplasm excision
Superficial spreading melanoma stage III
Superficial spreading melanoma stage IV
Superficial spreading melanoma stage unspecified
Urethral melanoma
Uveal melanoma

[1] MedDRA Version 21.1

12.9 Appendix 9. Eastern Cooperative Oncology Group (ECOG) Performance Status

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

12.10 Appendix 10. Tumor Response Assessments

Two tumor response evaluations will be performed by the investigator:

- Modified RECIST v1.1
- Modified irRC-RECIST

The investigator will add the lesion location, measurements, assessment and assessment method (ie, radiographic or clinical/visual) onto eCRFs corresponding to modified RECIST 1.1 and modified irRC-RECIST. Clinical decisions for treatment should only be made based on tumor assessment using modified irRC-RECIST.

Definitions and Guidelines

Measurable lesions are defined at baseline as lesions that can be accurately measured in at least 1 dimension (ie, longest diameter for non-nodal lesions and short axis for lymph nodes will be measured and followed) with a minimum size of:

- ≥ 10 mm by CT scan (CT scan slice thickness no greater than 5 mm) or MRI
- A lymph node must be ≥ 15 mm in the short axis when assessed by CT scan or MRI.

The distribution of the target lesions should be representative of the subject's overall disease burden (eg, largest lesions per organ). Target lesions must not be chosen from a previously irradiated field, or any other area subject to loco-regional therapy, unless there has been documented tumor progression in that field prior to enrollment. Brain lesions must not be selected as target lesions since enrolled subjects are not to have active cerebral metastases.

Non-measurable lesions include lesions not appearing as measurable lesions on radiographic imaging, small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 mm but < 15 mm short axis) and other truly non-measurable lesions. These will be considered non-measurable and characterized as non-target lesions. This will include any measurable lesions beyond the maximum number that were not chosen as target lesions. Other examples of non-measurable lesions include some bone lesions, leptomeningeal disease, inflammatory breast disease, lymphangitic involvement of the skin or (lymphangitis cutis/pulmonis), and groups of lesions that are small and numerous.

Bone lesions documented on bone scans, PET scans, or plain films can be used to confirm the presence or absence of bone lesions. Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, evaluated by CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of

measurability; only the soft tissue component of the bone lesion should be measured. Blastic bone lesions should not be selected as non-measurable at baseline since many blastic bone lesions might be benign. However, if new blastic lesions appear and are clearly progressing, they may be considered as new non-measurable lesions.

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable or non-measurable) since they are, by definition, simple cysts. Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions. If a cancerous cystic lesion has both cystic and solid components, the entire lesion should be measured across both components without excluding the cystic component.

Table 12-3 details guidelines for lesion measurement and status which are to be used at follow-up time points.

Table 12-3. Lesion Measurement/Status Guidelines for follow-up time points

Circumstance	Target/New Measurable Lesion Diameter	Non-target/New Non-measurable Lesion Status
Target lesion becomes too small to measure (ie, if lesion becomes so faint on CT/MRI that the radiologist may not feel comfortable assigning an exact measure)	5 mm will be assigned	N/A
Target lesion < 5mm and can be measured	Actual measurement	N/A
Non-nodal lesion disappears	0 mm	Absent
Nodal lesion normalizes (ie, short axis < 10mm)	Actual short axis measurement	Absent
Completely resected lesion*	0 mm	Absent
Partially resected lesion*	Actual measurement	Present
Positive or Unknown Biopsy Result for Melanoma	Actual measurement	Present
Negative Biopsy Result for Melanoma	0 mm	Absent

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Footnotes defined on next page of the table

Table 12-3. Lesion Measurement/Status Guidelines for follow-up time points

Circumstance	Target/New Measurable Lesion Diameter	Non-target/New Non-measurable Lesion Status
Merging lesions (for the current and all future assessments)	For 2 or more target/new measurable lesions: smaller lesion = 0 mm; larger lesion, longest diameter of the merged lesion. For 2 or more non-target/new non-measurable lesions: smaller lesion = absent; larger lesion = present. For target/new measurable lesion and a non-target/new non-measurable lesion: non-target/new non-measurable lesion = absent; target lesion/new measurable lesion, include both merged lesions. Any lesion with measurement 0 mm that resulted from merging with another lesion(s) should be documented as lesions that were combined with and not truly disappearing lesions.	
Separating lesion (for the current and all future assessments)	The largest measurable part of the split lesion should be considered to be the previously recorded target/new measurable lesion. The dimensions of the split parts would still be target/new measurable lesions. When a nontarget/new non-measurable lesion splits into 2 or more lesions, the split parts remain nontarget lesions. Any new lesions that result from separating should be documented as lesions that were generated by separating and not truly new lesions.	

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* If the resected lesion contained no melanoma under pathology evaluation, subsequent tumor assessments post-procedure may be used for tumor burden calculations and/or determination of response. If the resected lesion contained melanoma or pathology results were unknown, the recorded tumor assessments post-procedure may be used for tumor burden calculations, but determination of response will be considered unable to evaluable (UE) for both modified versions of RECIST 1.1 and irRC-RECIST, except in the case of PD. If the new tumor burden post-procedure is lower than the nadir before the procedure, the new nadir will be set to the post-procedure tumor burden. Otherwise, the previous pre-procedure nadir will be retained as the nadir and subsequent assessments for PD will be determined from the nadir.

Modified RECIST v1.1

RECIST v1.1 will be used with the following modifications to the guidelines as defined by Eisenhauer et al, 2009:

- Increased total target lesions to a maximum of 10 (up to a maximum of 5 per organ).
- Target lesions must be measurable by CT or MRI only; lesions not measurable by CT or MRI (ie, assessed via other imaging modalities or clinical measurements) are considered as non-target.

Table 12-4. Evaluation of Target Lesions

Target Response	Definition
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have a reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the nadir (this includes the baseline sum if that is the nadir). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm.
Stable Disease	Neither sufficient shrinkage to qualify for PR or CR nor sufficient increase to qualify for PD, taking as reference the nadir.
Unable to Evaluate (UE)	Any 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 target lesions were identified at baseline.
Not Done (ND)	No radiographic assessment completed at required time point.

Table 12-5. Evaluation of Non-target Lesions

Non-target Response	Definition
Complete Response (CR)	Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10mm short axis).
Non-CR/Non-PD	Persistence of 1 or more non-target lesion(s).
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions.
Unable to Evaluate (UE)	Any 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 non-target lesions were identified at baseline.
Not Done (ND)	No radiographic or clinical assessment completed at required timepoint.

Table 12-6. Time Point Modified RECIST v1.1 Overall Response Matrix

Target lesions (by CT/MRI)	Non-target lesions (by radiographic imaging or clinical assessment)	New lesions (by radiographic imaging or clinical assessment)	Overall Response
CR	CR	No	CR
NA	CR	No	CR
CR	Non-CR/non-PD or UE/ND	No	PR
PR	Non-PD or UE/ND	No	PR
SD	Non-PD or UE/ND	No	SD
NA	Non-CR/non-PD	No	Non-CR/non-PD
PD	Any	Yes (unequivocal**) or No	PD
Any	Unequivocal PD*	Yes (unequivocal**) or No	PD
Any	Any	Yes (unequivocal**)	PD
UE/ND	Non-PD	No	UE
NA	UE/ND	No	UE
NA	NA	No	UE

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

* Unequivocal PD is defined as overall level of substantial worsening in non-target disease such that even in the presence of SD/PR in target disease, the overall tumor burden has increased sufficiently.

** Unequivocal new lesions may be considered not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor. An example of an equivocal new lesion may be a small size where continued treatment and follow-up evaluation may clarify new disease (Eisenhauer et al, 2009).

Modified irRC-RECIST

irRC-RECIST defined by Nishino et al, 2014 will be used with the following modifications.

Otherwise, these guidelines follow irRC-RECIST defined by Nishino et al, 2014.

- Increased total target lesions to a maximum of 10 (up to a maximum of 5 target lesions per organ).
- Increased total new measurable lesions to a maximum of 10 (up to a maximum of 5 new measurable lesions per organ) at each follow-up time point.
- Target lesions and new measurable lesions must be measurable by CT or MRI only; lesions not measurable by CT or MRI are considered as non-target/new non-measurable.

Table 12-7. Modified irRC-RECIST Definition of Measurable Tumor Response

Measurable Tumor Response (Baseline Target and New, Measurable Lesions)	**Measurable Tumor Response Definition**
Complete Response (iCR)	Disappearance of all lesions (whether measurable or not and whether baseline or new) and confirmation by a repeat, consecutive assessment no less than 4 weeks (28 days) from the date first documented. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm.
Partial Response (iPR)	Decrease in tumor burden[a] ≥ 30% relative to baseline confirmed by a consecutive assessment at least 4 weeks (28 days) after first documentation.
Progressive Disease (iPD)	Increase in tumor burden[a] ≥ 20% and at least 5 mm absolute increase relative to nadir (minimum recorded tumor burden) confirmed by a repeat, consecutive assessment no less than 4 weeks (28 days) from the date of first documented iPD in the absence of clinical instability. • Unconfirmed iPD (Initial-iPD) - when measurable (target and new measurable lesions) tumor burden increase ≥ 20% and at least 5 mm absolute increase relative to nadir observed at 1 time point or non-consecutive time points. • Confirmed iPD - when measurable (target and new measurable lesions) tumor burden increase ≥ 20% and at least 5 mm absolute increase relative to nadir observed on 2 consecutive time points at least 4 weeks (28 days) apart in the absence of clinical instability. Date of progression is to be the date of initially reported-iPD prior to confirmed iPD.
Stable Disease (iSD)	Neither sufficient shrinkage to qualify for iCR or iPR nor sufficient increase to qualify for iPD.
Unable to Evaluate (iUE)	Any lesion present at baseline or a new measurable lesion 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. Exception: when iPD is documented based on a partial assessment.
Not Applicable (NA)	No target lesions were identified at baseline.
Not Done (ND)	Radiographic images were not performed at this time point to evaluate the response of measurable lesions.

[a] Tumor Burden = sum of diameter of target lesions + sum of new, measurable lesions. Diameters used:
• For nodal disease, shortest axis
• For non-nodal disease, longest diameters

Table 12-8. Time Point Modified irRC-RECIST Overall Response Matrix

Measurable Response	Non-measurable Response		Overall Response
Target and New, Measurable lesions (tumor burden)[a] (by CT/MRI)	Non-target lesions (by radiographic imaging or clinical assessment)	New, Non-measurable lesions (by radiographic imaging or clinical assessment)	
Decrease 100% [e]	Absent/NA[d]	Absent	iCR[b,]
Decrease 100%	Present/ND/UE	Any	iPR[b]
Decrease 100%	Unequivocal progression	Any	iPR[b]
Decrease ≥ 30%	Absent/Present/NA[d] /ND/UE	Any	iPR[b]
Decrease ≥ 30%	Unequivocal progression	Any	iPR[b]
Decrease < 30% to Increase < 20%	Absent/Present/NA[d] /ND/UE	Any	iSD
Decrease < 30% to Increase < 20%	Unequivocal progression	Any	iSD
Increase ≥ 20% [f]	Any	Any	iPD[b,f]
UE	Any	Any	iUE
ND	Any	Any	iUE
NA [c]	Any	Any	iUE

[a] Decreased disease relative to baseline, including new measurable lesions only (≥ 10 mm for non-lymph node lesions, ≥ 15mm in short axis for lymph nodes).
[b] iCR, iPR, or iPD should be confirmed by a second, consecutive assessment at least 4 weeks (28 days) apart. Rapid clinical deterioration is an exception for confirming initial PD.
[c] No target lesions identified at baseline. When a patient has only non-measurable disease (ie, no target lesions identified at baseline) the response will be unevaluable.
[d] No non-target lesions identified at baseline.
[e] Disappearance of all non-lymph node lesions and all lymph nodes < 10 mm in short axis would also be iCR even if lymph node measurements prevent 100% tumor burden reduction.
[f] In addition to relative increase of > 20%, the tumor burden must also demonstrate an absolute increase of > 5 mm from nadir for iPD. If the tumor burden does not demonstrate > 5 mm increase from nadir but tumor burden is increased > 20% from the nadir, response should be recorded as iSD.
Note: Unequivocal iPD of non-target lesions and/or the appearance of new, non-measurable lesions do not constitute overall iPD.

For subjects who have initial-PD, it is at the discretion of the investigator to continue a subject on study treatment until repeat imaging is obtained a minimum of 4 weeks later. Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of PD at the time are to be classified as “clinically unstable” based on the investigator’s clinical judgement of the subject’s overall clinical condition, including performance status, clinical symptoms, and laboratory data. Clinical instability considers the following criteria based on the investigator’s clinical judgement:

Signs and symptoms indicating PD:

- Decline in ECOG performance status
- Rapid clinical progression of disease
- Progressive tumor at critical anatomical sites (eg, cord compression, clinically active brain metastases, compression of vital organ structures) requiring urgent alternative medical intervention

Amendment 3

Protocol Title: Phase 2 Study of Talimogene Laherparepvec in Combination With Pembrolizumab in Subjects With Unresectable/Metastatic Stage IIIB-IVM1d Melanoma Who Have Progressed on Prior Anti-PD-1 Based Therapy

Amgen Protocol Number 20180115

EudraCT Number 2019-001906-61

NCT Number NCT04068181

Amendment Date: 09 June 2021

Rationale:

This protocol is being amended to include the following updates:

- The number of subjects 72 subjects were enrolled with 27 subjects in cohort 1 and 15 subjects in cohorts 2, 3, and 4.
- Updated language throughout the protocol to allow treatment with pembrolizumab to continue if a complete response was observed.
- Safety reporting language updated for adherence to current Amgen standard operating procedures (SOPs).
- Immune-related adverse events updated to include neurological toxicities and exfoliative dermatologic conditions to align with the pembrolizumab Investigator Brochure.
- Serious Adverse Events (SAEs) After the Protocol-required Reporting Period, specifically subjects ending study due to death, have not been reported as SAEs for other studies on the program. As a result, additional clarification was added to Section 9.2.3.1.1.3 - “Serious Adverse Events After the Protocol-required Reporting Period” and throughout the protocol for consistency to mitigate this. Furthermore, these changes align with Amgen’s current protocol template and guidance.
- Clarified that the visit windows are ± 3 days during the treatment period, as operationally, it is more reasonable for sites to have the minus window. It was further noted that the week 0 visit was an exception, where the -3 days does not apply. All assessments for Week 0 should be completed following enrollment (via Interactive Response Technology [IRT]), using the + 3-day window for the first dose.
- Additionally, the visit window for radiographic assessments for subjects who discontinued treatment for any reason other than confirmed progressive disease (by modified immune-related Response Criteria simulating Response Evaluation Criteria in Solid Tumors [irRC-RECIST]) (iPD) was updated from 12 weeks (+ 1 week) to (± 1 week).
- Minor clarifications added to align with the Statistical Analysis Plan:

  - Clarified in Section 9.2.2.2-Modified Response Evaluation Criteria in Solid Tumor (RECIST) v1.1, that "Following modified RECIST v1.1 tumor assessments will continue through to the first progressive disease (PD)"
  - Physical Measurements removed from safety analysis
- Administrative clarifications throughout.

Amendment 2

Protocol Title: Phase 2 Study of Talimogene Laherparepvec in Combination With Pembrolizumab in Subjects With Unresectable/Metastatic Stage IIIB-IVM1d Melanoma Who Have Progressed on Prior Anti PD-1 Based Therapy

Amgen Protocol Number (talimogene laherparepvec) 20180115

EudraCT number 2019-001906-61

NCT number: NCT04068181

Amendment Date: 10 March 2020

Rationale:

This protocol is being amended to:

- Add new exclusion criterion to exclude subjects who experience disease progression on more than 1 line of prior anti-programmed cell death-1 (PD-1) therapy.
- Align contraception requirements with Amgen Global Protocol template, including updates to and addition of new exclusion criterion for male subjects
- Align with the program level frequency of follow-up for patients who achieve a complete response.
- Add a Per Protocol Analysis Set (PPAS), which is a subset of the Full Analysis Set (FAS) in the efficacy analysis
- Update Table 7-2 – Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab to align with the Keytruda® European Union (EU) Summary of Product Characteristics (SmPC).
- Clarify Tumor Response Assessments:
  - Correct administrative/grammatical errors
- Administrative, typographical, and formatting changes were made throughout the protocol.

Amendment 1

Protocol Title: Phase 2 Study of Talimogene Laherparepvec in Combination With Pembrolizumab in Subjects With Unresectable/Metastatic Stage IIIB-IVM1d Melanoma Who Have Progressed on Prior Anti-PD-1 Based Therapy

Amgen Protocol Number (T-VEC) 20180115

EudraCT Number: 2019-001906-61

NCT Number: TBD

Amendment Date: 24 July 2019

Rationale:

This protocol is being amended to:

- Update the IVM1c melanoma stage to IVM1d (including central nervous system [CNS] lesions) globally in the protocol (including the title, primary objective, and eligibility criteria) per AJCC 8th edition (eighth edition of the American Joint Committee on Cancer [AJCC] Cancer Staging Manual [Gershenwald et al, 2017])
- Clarify that subjects must have received prior anti-programmed cell death-1 (PD-1) therapy for at least 2 to 3 consecutive cycles within an 8-week period
- Enrollment of subjects with stage IVM1d and up to 3 cerebral metastases to be added as key inclusion criteria and removed as key exclusion criteria
- Clarify the version of the AJCC staging used for the historical studies versus the current study
- Update inclusion criteria 104 with two bullet points (including definition of inactive brain metastases that are eligible)
- Inclusion criterion 108 with Exclusion criterion 206 with respect to replacement therapy
- Added urine pregnancy test in Inclusion criterion 120
- Update exclusion criteria 202 to exclude active brain metastases
- Add subsequent anticancer therapies as a procedure to the Schedule of Assessments, and update assessment for urinalysis from once every 12 weeks (Q12W) to once every 6 weeks (Q6W)
- Clarify concomitant therapy for subsequent treatment for melanoma to be recorded after end of investigational product until the subject ends study
- Remove “decision by investigator” as a reason for discontinuation of study treatment or removal from study

- Clarify and add a subgroup to the planned efficacy analysis; disease stage (stage IVM1a or lower, stage IVM1b/c/d) at baseline and disease stage (stage IVM1b or lower, stage IVM1c/d) at baseline
- List 24-hour urine creatinine clearance analyte separately from urinalysis in the analyte listing table
- Add clarification for unequivocal new lesions in RECIST 1.1 that can contribute to progressive disease (PD) rather than any new lesion