Title: A Phase 1b/3 Multicenter, Randomized Trial of Talimogene Laherparepvec in Combination With Pembrolizumab for the Treatment of Subjects With Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck

Amgen Protocol Number (Talimogene Laherparepvec) 20130232

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Amendment 1 07 June 2016

Superseding Amendment 28 June 2016

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Amendment 3 25 October 2017

Amendment 4 **11 May 2018**

Investigator's Agreement

I have read the attached protocol entitled A Phase 1b/3 Multicenter, Randomized Trial of Talimogene Laherparepvec in combination with Pembrolizumab for the Treatment of Subjects With Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck, dated **11 May 2018**, and agree to abide by all provisions set forth therein.

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

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

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

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

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

_____
Signature

_____ _____
Name of Investigator Date (DD Month YYYY)

Protocol Synopsis

Title: A Phase 1b/3 Multicenter, Randomized Trial of Talimogene Laherparepvec in combination with Pembrolizumab for theTreatment of Subjects With Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck

Study Phase: Phase 1b/3

Indication: Squamous Cell Carcinoma of the Head and Neck (SCCHN)

Primary Objective:

Phase 1b: To evaluate the safety, as assessed by incidence of dose limiting toxicity (DLT), of talimogene laherparepvec in combination with pembrolizumab in subjects with recurrent or metastatic SCCHN

Phase 3: To evaluate the efficacy, as assessed by overall survival (OS), of treatment with talimogene laherparepvec with pembrolizumab versus placebo with pembrolizumab in subjects with recurrent or metastatic SCCHN

Secondary Objective(s):

Phase 1b

- To evaluate the efficacy of talimogene laherparepvec in combination with pembrolizumab as assessed by:
  - Objective response rate (iORR), complete response rate (iCRR), and best overall response (iBOR); duration of response (iDOR), disease control rate (iDCR), and progression-free survival (iPFS) (response evaluation by investigator using immune-related Response Evaluation Criteria in Solid Tumors [irRECIST])
  - OS
- To evaluate the safety of talimogene laherparepvec in combination with pembrolizumab as assessed by incidence of adverse events and laboratory abnormalities.

Phase 3

- To evaluate the efficacy of talimogene laherparepvec with pembrolizumab versus placebo with pembrolizumab, as assessed by:
  - Objective response rate (ORR) and progression-free survival (PFS) (response evaluation by investigator using RECIST v1.1)
  - iORR and iPFS (response evaluation by investigator using irRECIST)
  - iCRR, iBOR; iDOR, and iDCR (response evaluation by investigator using irRECIST)
  - CRR, BOR, DOR, and DCR (response evaluation by investigator using RECIST v1.1)
  - 1-year, 2-year, and 3-year survival
  - Subject incidence of treatment-emergent and treatment-related adverse events (all adverse events, grade ≥ 3 adverse events, serious adverse events, fatal adverse events, adverse events and serious adverse events leading to discontinuation of treatment, and adverse events defined as events of interest)
- To evaluate patient reported outcomes (PRO) as assessed by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) Global Health Status/Quality of life (GHS/QoL) subscale.

Hypotheses:

Phase 1b

Talimogene laherparepvec in combination with pembrolizumab will be safe and well tolerated in subjects with recurrent or metastatic SCCHN.

Phase 3

The clinical hypothesis is that talimogene laherparepvec with pembrolizumab compared to placebo with pembrolizumab will improve OS. In addition to the hypothesis test for the primary endpoint, ORR, PFS, iORR, and iPFS in subjects given talimogene laherparepvec plus pembrolizumab versus placebo plus pembrolizumab will be compared.

Primary Endpoint:

Phase 1b

- Subject incidence of DLT

Phase 3

- OS

Secondary Endpoint(s):

Phase 1b

- iORR (complete response [iCR]+ partial response [iPR]), iCRR, iBOR, iDOR, iDCR, and iPFS (response evaluation by investigator using irRECIST)
- OS
- Subject incidence of treatment-emergent and treatment-related adverse events (all adverse events, grade ≥ 3 adverse events, serious adverse events, fatal adverse events, adverse events and serious adverse events leading to discontinuation of treatment, and adverse events defined as events of interest) and laboratory abnormalities.

Phase 3

- ORR and PFS (response evaluation by investigator using RECIST v1.1)
- iORR and iPFS (response evaluation by investigator using irRECIST)
- iCRR, iBOR; iDOR, and iDCR (response evaluation by investigator using irRECIST)
- CRR, BOR, DOR, and DCR (response evaluation by investigator using RECIST v1.1)
- 1-year, 2-year, and 3-year survival
- Subject incidence of treatment-emergent and treatment-related adverse events (all adverse events, grade ≥ 3 adverse events, serious adverse events, fatal adverse events, adverse events and serious adverse events leading to discontinuation of treatment, and adverse events defined as events of interest).
- Summary scores at each assessment and changes from baseline of PROs as assessed by QLQ-C30 GHS/QoL subscale.

Study Design: This is a phase 1b/3, multicenter clinical trial. The study will be conducted in 2 parts (phase 1b and phase 3). In phase 1b talimogene laherparepvec will be administered in combination with pembrolizumab to approximately 40 subjects with recurrent or metastatic SCCHN. DLT will be evaluated based on the first 18 DLT-evaluable subjects. An expansion cohort of an additional 22 treated subjects will be enrolled to further evaluate the safety and to estimate the efficacy of the combination of talimogene laherparepvec with pembrolizumab to support a decision to initiate the phase 3 study. The phase 3 is a multicenter, placebo-controlled, double-blind, randomized study to evaluate the efficacy, as assessed by OS, of treatment with talimogene laherparepvec with pembrolizumab versus placebo with pembrolizumab in subjects with recurrent or metastatic SCCHN. Subjects will be randomized 1:1 to receive the following:

- Arm 1: talimogene laherparepvec plus pembrolizumab (n = 225)
- Arm 2: placebo plus pembrolizumab (n = 225)

Randomization will be stratified by human papillomavirus (HPV) status at baseline (HPV-negative versus HPV-positive) and Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1).

All subjects who receive investigational product will complete a safety follow-up visit approximately 30 (+ 7) days after the last dose of study treatment. After the safety follow-up visit, all subjects will enter the long-term follow-up. Subjects will be followed for survival, subsequent anticancer therapies and talimogene laherparepvec/placebo related adverse events every 12 weeks from safety follow-up visit (± 28 days) for approximately 36 months after the last subject is **enrolled**.

Sample Size: Approximately 490 subjects will be enrolled in the study; 40 in the phase 1b study and 450 in phase 3 Global Full Analysis Set (FAS[G]).

Summary of Subject Eligibility Criteria: Subjects must be 18 years of age or older at the time of informed consent. Subjects must have histologically confirmed diagnosis of metastatic or recurrent SCCHN of the oral cavity, oropharynx, hypopharynx, or larynx, and disease must be unsuitable for curative surgical resection and must not be amenable to curative radiotherapy. The disease must have progressed after treatment with a platinum-containing regimen defined as either disease progression or recurrence between 3 to 6 months of prior curatively intended multimodal therapy including platinum therapy for locoregionally advanced SCCHN or disease progression or recurrence after prior platinum therapy in the recurrent or metastatic setting. Subjects with history of progression of disease within 3 months of completion of curatively intended treated for locoregionally advanced settings are excluded (note: this exclusion criteria is only applicable for subjects who have not had treatment in the metastatic/recurrent setting). The subject must be a candidate for intralesional therapy. Subject must have radiographically measurable disease per RECIST v1.1 and have ECOG performance status of 0 or 1 and adequate organ function. Female subjects of childbearing potential must have a negative pregnancy test. For a full list of eligibility criteria, please refer to Section 4.1 and 4.2.

Investigational Product

Amgen Investigational Product Dosage and Administration: Talimogene laherparepvec (or placebo in phase 3) will be administered into injectable cutaneous, subcutaneous, and nodal lesions with or without image ultrasound guidance. Talimogene laherparepvec/placebo must not be administered into the mucosal surface of tumor lesions or visceral metastases. See Section 6.2.1.1 for additional information regarding dosage and administration information.

Phase 1b:

The first dose of talimogene laherparepvec will be up to 8.0 mL of 10^6 PFU/mL. The second injection, up to 8.0 mL of 10^8 PFU/mL, will be administered 3 weeks (+3 days) after the initial injection (ie, no sooner than day 22 but should not be delayed more than 3 days after the 3 week time point). All subsequent injections, up to 8.0 mL of 10^8 PFU/mL, will be administered every 3 weeks (±3 days). The maximum volume of talimogene laherparepvec administered at any dose is 4.0 mL for any individual tumor lesion. The maximum volume in any treatment visit is 8.0 mL. When talimogene laherparepvec and pembrolizumab are administered on the same day, it is recommended that talimogene laherparepvec be administered first. Refer to Section 6.2.1.

Phase 3:

The initial dose of double-blind treatment is up to 8.0 mL of 10^6 PFU/mL talimogene laherparepvec/placebo (talimogene laherparepvec formulation excipients as described in the Talimogene Laherparepvec Investigator's Brochure). The second dose up to 8.0 mL of 10^8 PFU/mL talimogene laherparepvec/placebo should be administered 21 (+ 3) days after the initial dose. Subsequent doses up to 8.0 mL of 10^8 PFU/mL talimogene laherparepvec/placebo should be given every 3 weeks (± 3 days). The maximum volume of talimogene laherparepvec/placebo administered at any dose is 4.0 mL for any individual tumor lesion. The maximum volume at any treatment visit is 8.0 mL. When talimogene laherparepvec/placebo and pembrolizumab are administered on the same day, it is recommended that talimogene laherparepvec/placebo be administered first.

Non-Amgen Investigational Product Dosage and Administration: Pembrolizumab will be manufactured by Merck. Pembrolizumab is supplied in 100 mg/4mL vials (25 mg/mL) solution for intravenous infusion.

Phase 1b/3:

Pembrolizumab at a dose of 200 mg will be administered intravenously every 3 weeks (± 3 days). See Section 6.2.2.2 for additional information regarding dosage and administration of pembrolizumab.

Procedures: Written informed consent must be obtained from all subjects before any study specific screening procedures are performed. The following procedures will occur per the Schedule of Assessments (Table 5, Table 6, and Table 7): medical, surgical and medication history, physical examination and vital signs, body weight, height, ECOG performance status, 12-lead electrocardiogram (ECG), recording of concomitant medications, survival assessment, review of adverse events, disease related events and serious adverse events as well as reporting of potential or known unintended exposure to talimogene laherparepvec/placebo by a household member, caregiver, or healthcare provider. Blood will be collected for local laboratory testing including: chemistry, hematology, prothrombin time (PT) (seconds) or international normalization ratio (INR) (ratio) and partial thromboplastin time (PTT) (seconds) or activated PTT (aPTT) (seconds), thyroid function, hepatitis B surface antigen, hepatitis B core antibody and hepatitis C virus antibody. Urine will be collected for urinalysis. In females of childbearing potential urine or serum pregnancy test will be performed locally. Additional blood or urine for pregnancy testing (for women of child bearing potential) may be performed at the investigator's discretion or as defined in a country-specific protocol supplement at the end of the Appendix Section of the protocol as required by local laws and regulations. Central laboratory tests include: blood for biomarker analysis, herpes simplex virus type-1 (HSV-1) serostatus, anti-pembrolizumab antibodies and pembrolizumab pharmacokinetics (PK). Tumor tissue from either the primary tumor or a metastatic lesion (block or unstained tumor slides) and the associated pathology reports must be submitted within 28 days after enrollment for phase 1b and within 28 days before randomization for phase 3. See Section 7.5.2 for more details. A swab of all suspected herpetic lesions will be collected for qPCR testing. Radiographic (computed tomography [CT], positron emission tomography [PET]/contrast enhanced CT or magnetic resonance imaging [MRI]) scans and tumor assessment will also be performed. Biodistribution and shedding of talimogene laherparepvec will be performed in the phase 1b portion of the study only. Study treatment will be administered per Section 6.2.

For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedule of Assessments (Table 5, Table 6, and Table 7).

Statistical Considerations:

Sample size consideration:

For phase 1b, a maximum of 18 DLT-evaluable subjects will be enrolled to assess the DLT profile of the combination therapy based on a sequential stopping rule. If > 18 subjects receive the combination they will contribute to the overall safety analysis, but only the first 18 DLT-evaluable will be considered in the decision to declare the combination safe. Subjects may be replaced if they are not evaluable for DLT to obtain 18 DLT-evaluable subjects. An expansion cohort of up to an additional 22 treated subjects will be enrolled so there will be approximately 40 treated subjects in total to estimate the efficacy of the combination of talimogene laherparepvec with pembrolizumab.

For phase 3, the primary endpoint is OS. A hazard ratio ([HR] talimogene laherparepvec with pembrolizumab vs placebo with pembrolizumab) of 0.7 for OS is hypothesized in the FAS(G). The overall 2-sided Type 1 error rate is 0.05. The event goal for OS to achieve 90% power for a 2-sided 0.05 significance level test is 336. Assuming approximately 75% of subjects have an OS event at the time of OS primary analysis, the sample size is estimated to be 450 (225 per arm). The OS event goal is adjusted for the interim efficacy analysis but not for the interim futility assessment; however, the power loss due to futility is < 1% if considered binding.

Planned method of analyses:

For the Phase 1b part of the study, the DLT analysis set will be used to summarize the subject incidence of DLT for the study and, unless specified otherwise, the safety analysis set (SAS) will be used for all other analyses of safety endpoints including incidence of treatment-emergent and

treatment-related adverse events. Summaries of the incidence of DLTs will be provided. Descriptive statistics will be provided for efficacy, safety, talimogene laherparepvec DNA, and biomarker endpoints as appropriate.

Efficacy endpoints will be summarized using the Efficacy Analysis Set (EAS) and FAS. The subject incidence for binary response endpoints will be summarized with an associated 95% confidence interval (CI). Duration of response (DOR) among responders, and other time-to-event endpoints will be estimated using the Kaplan-Meier method.

For the phase 3 part of the study, efficacy analyses will be conducted on the FAS(G). Treatment effects on efficacy endpoints will be evaluated and compared between the 2 treatment arms according to the treatment as randomized.

For analysis of the primary endpoint of OS, a stratified log-rank test will be used as the primary method for testing the null hypothesis of no treatment difference. The randomization factors, along with programmed death-ligand 1 (PD-L1) status at baseline (PD-L1 positive vs PD-L1 not positive) will be used as stratification factors. A hazard ratio will be estimated using the Cox proportional hazards (PH) model stratified by the randomization factors per interactive voice response (IVR) system and PD-L1 status at baseline with Efron's method (Efron, 1977) used to handle ties. Kaplan-Meier time to event curves will be presented based on randomized treatment arm.

Statistical testing of OS, iORR, PFS, and iPFS will follow the multiple hypothesis testing procedure described in Section 10.5.1.

Two planned interim safety data reviews will occur after approximately 40 and 100 subjects have been enrolled in phase 3 and have had an opportunity to be followed up for at least 6 weeks after receiving study treatment. An additional, planned interim safety data review will occur when at least 10 subjects have received at least one treatment with a total volume > 4 mL of 10^8 PFU/mL of talimogene laherparepvec plus pembrolizumab and have had the opportunity to be followed up to 6 weeks after receiving the > 4 mL of 10^8 PFU/mL dose of talimogene laherparepvec and approximately every 6 months after the Data Monitoring Committee (DMC) meeting for the OS interim analysis. An interim safety data review will also occur that includes the first 8 subjects enrolled with 3 or more randomized into treatment arm from Japan in the phase 3 part of the study and have had the opportunity to be followed for at least 6 weeks after receiving study treatment. Additional analyses may be conducted for Japan enrolled subjects as needed for regulatory or safety.

An interim efficacy analysis for futility on OS will be conducted by the DMC when approximately 280 events have occurred.. The DMC will provide oversight of the analysis and indicate if the futility criterion at the OS interim analysis has been met. It is not planned for enrollment/randomization to be suspended during these ongoing phase 3 safety analyses.

For the phase 1b part of the study, the primary analysis will be repeated 1 year after the last subject enrolled.

ORR and iORR will be summarized by treatment arm as randomized with associated 95% CIs, and with treatment comparisons based on the Cochran-Mantel-Haenszel test stratified by the randomization stratification factors and PD-L1 status at baseline. Analysis of PFS and iPFS will follow the analysis described for the the primary endpoint of OS.

In addition, CRR, iCRR, DCR and iDCR will be summarized by treatment arm as randomized with associated 95% CIs. DOR and iDOR among responders will be summarized as a continuous variable.

Safety data, including laboratory test results, vital signs, treatment-emergent adverse events, serious adverse event and disease related events, will be summarized by treatment received. Subject incidence of anti-pembrolizumab antibodies and serum concentration of pembrolizumab will be summarized.

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

Sponsor: Amgen Inc.
Data Element Standards
Version(s)/Date(s): 5: 20 March 2015

Phase 1b Study Design and Treatment Schema

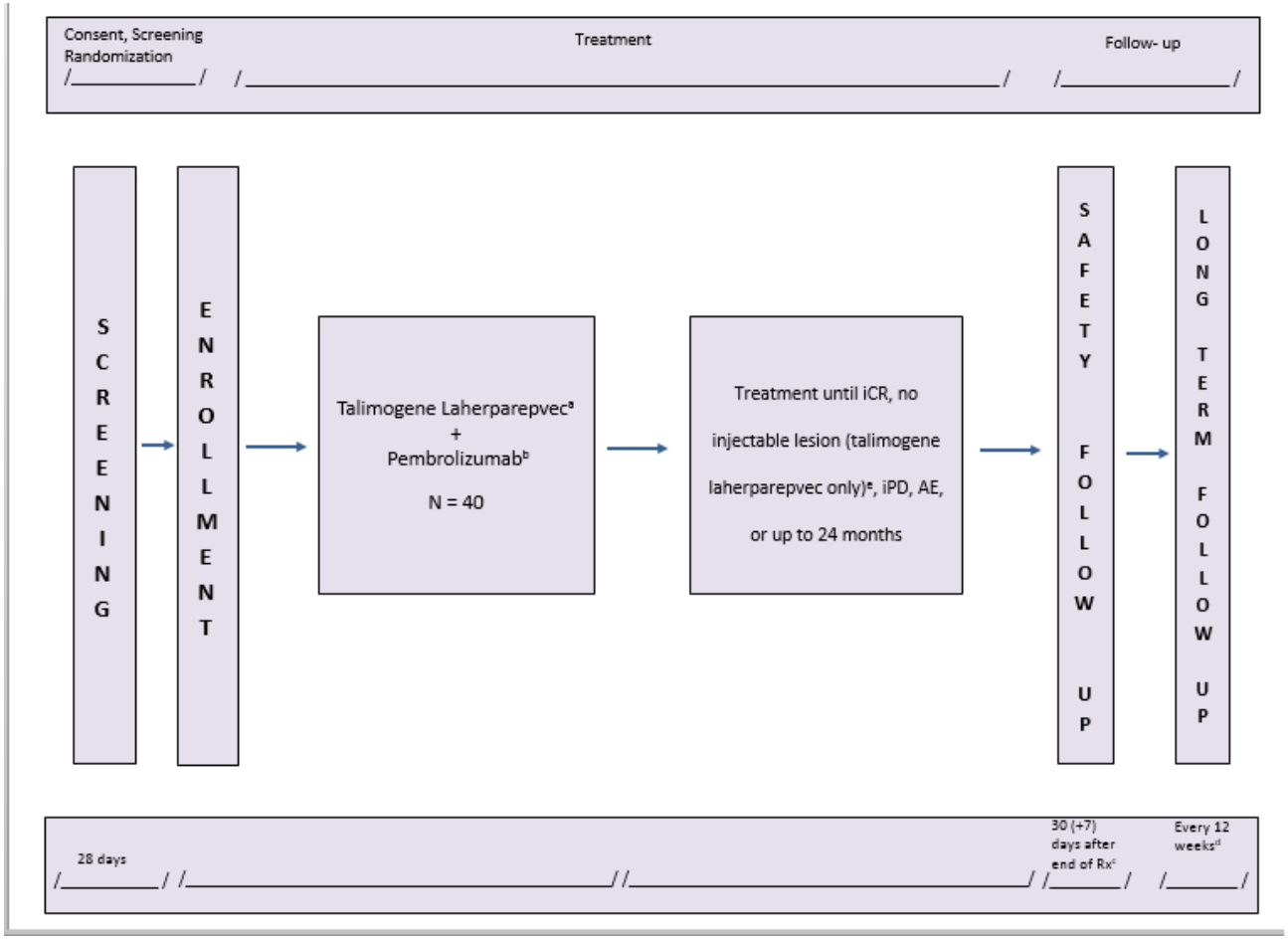

Figure legend defined on next page.of the figure

iCR = complete response (per irRECIST); iPD= progressive disease (per irRECIST); Rx = treatment

[a] Talimogene laherparepvec will be administered in combination with pembrolizumab starting on week 0, day 1. Talimogene laherparepvec: 10^6 PFU/mL followed 3 weeks (+ 3 days) later by 10^8 PFU/mL every 3 weeks (± 3 days).

[b] Pembrolizumab: 200 mg will be administered intravenously every 3 weeks (± 3 days). The second dose of pembrolizumab will be administered 3 weeks (+ 3 days) after the initial dose.

[c] Subjects will be followed up for serious adverse events until 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)

[d] Long-term follow-up every 12 weeks (± 28 days) from safety follow-up visit until approximately 36 months after last subject enrolled. Talimogene laherparepvec related adverse events that occur after the safety follow-up visit through the end of the long-term follow-up will be reported.

[e] Pembrolizumab may continue to be administered.

Phase 3 Study Design and Treatment Schema

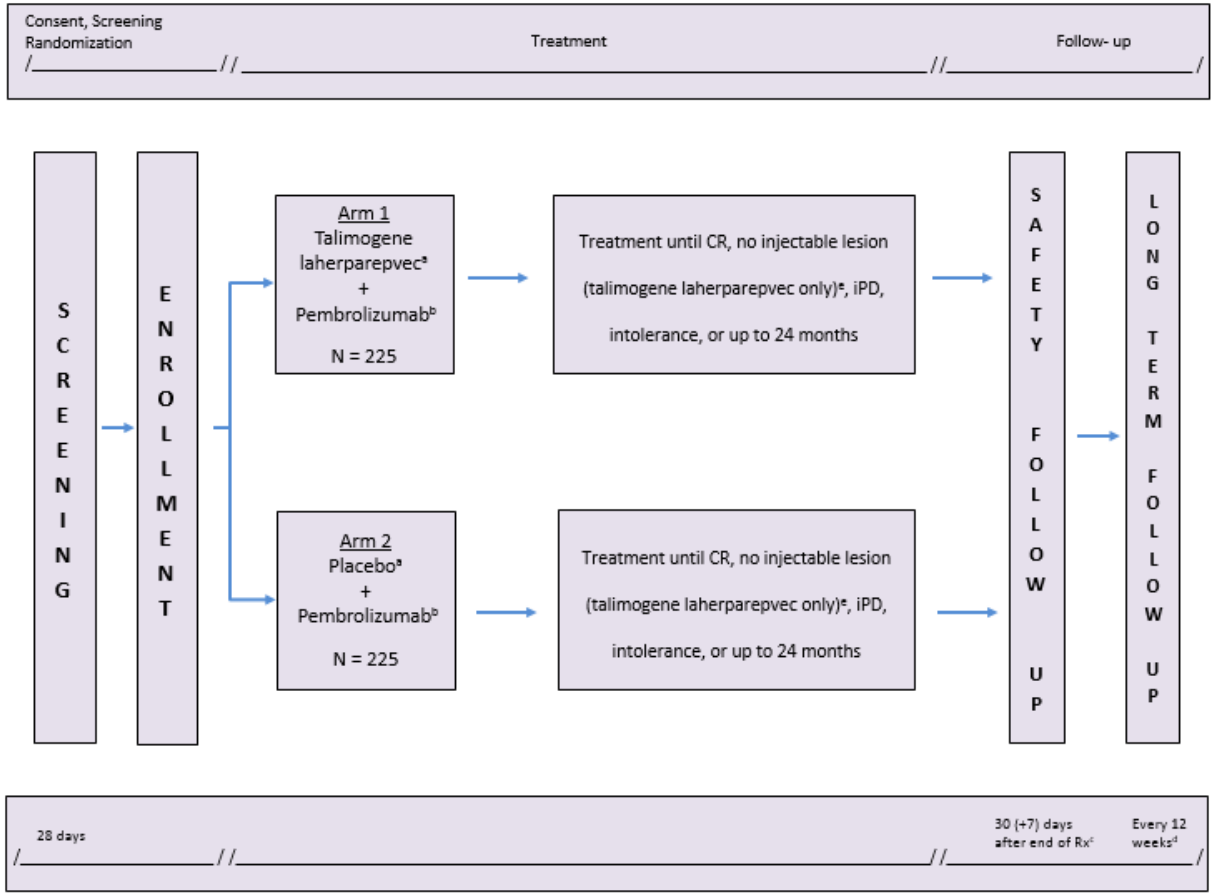

Figure legend defined on next page.of the figure

iCR= complete response (per irRECIST); iPD= progressive disease (per irRECIST); Rx = treatment

[a] Talimogene laherparepvec/placebo will be administered in combination with pembrolizumab starting on week 0, day 1. Talimogene laherparepvec: 10^6 PFU/mL followed 3 weeks (+ 3 days) later by 10^8 PFU/mL every 3 weeks (± 3 days).

[b] Pembrolizumab: 200 mg will be administered intravenously every 3 weeks (± 3 days). The second dose of pembrolizumab will be administered 3 weeks (+ 3 days) after the initial dose.

[c] Subjects will be followed up for serious adverse events until 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).

[d] Long-term follow-up every 12 weeks (± 28 days) from safety follow-up visit until approximately 36 months after last subject enrolled. Talimogene laherparepvec/placebo related adverse events that occur after the safety follow-up visit through the end of the long-term follow-up will be reported.

[e] pembrolizumab may continue to be administered.

Study Glossary

Abbreviation or Term	Definition/Explanation
ADA	anti-drug antibodies
AE	adverse event
AJCC	American Joint Commission on Cancer
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BICR	Blinded Independent Central Review
BOR	best overall response (per RECIST v1.1)
cHL	classical Hodgkin lymphoma
CI	confidence interval
CNS	central nervous system
CR	complete response (per RECIST v1.1)
CRF	case report form
CRR	complete response rate (per RECIST v1.1)
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate (per RECIST v1.1)
DILI	drug-induced liver injury
DLRT	Dose Level Review Team
DLT	dose limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response (per RECIST v1.1)
DRE	disease-related event
EAS	Efficacy Analysis Set
ECG	electrocardiogram
ECI	Events of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
End of Study for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject (ie, the date the subject withdraws full consent from the study, completes the safety follow-up visit or long-term follow-up [whichever is later] or death).

Abbreviation or Term	Definition/Explanation
End of Study (primary completion)	**Primary Completion:** defined as when the last subject is assessed or receives an intervention for the purposes of final collection of data for the **primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early.** **<u>Primary Completion Phase 1b only:</u> The time when the last phase 1b subject is assessed or receives an intervention for the purposes of final collection of data for the primary efficacy endpoint of phase 1b. The primary completion is anticipated to occur when the last phase 1b subject completes the week 9 tumor response assessment.**
End of Study (end of trial)	defined as 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**. This is anticipated to occur 36 months after the last subject **is enrolled**.
End of Treatment	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-5L	EuroQoL-5D-5 Level
EU	European Union
FAS	Full Analysis Set
FAS(G)	Global Full Analysis Set
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
FT3	free triiodothyronine
FT4	free thyroxine
GCP	Good Clinical Practice
GI	gastrointestinal
GM-CSF	granulocyte macrophage colony-stimulating factor
Heart rate	number of cardiac cycles per unit of time
HIV	human immunodeficiency virus
HNC	Head and neck carcinomas
HPV	Human papillomavirus
HR	hazard ratio
HSV-1	herpes simplex virus, herpes simplex virus type-1
IA	interim analysis
iBOR	best overall response (per irRECIST)
ICH	International Conference on Harmonisation
iCR	complete response (per irRECIST)

Abbreviation or Term	Definition/Explanation
ICP	infected cell protein
iCRR	complete response rate (per irRECIST)
iDCR	disease control rate (per irRECIST)
iDOR	duration of response (per irRECIST)
IHC	immunohistochemistry
ILD	interstitial lung disease
INR	international normalization ratio
iORR	objective response rate (per irRECIST)
iPD	progressive disease (per irRECIST)
iPFS	progression-free survival (per irRECIST)
IPIM	Investigational Product Instruction Manual
iPR	partial response (per irRECIST)
IRB/IEC	institutional review board/independent ethics committee
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors (RECIST)
iSD	stable disease (per irRECIST)
iUE	unable to evaluate (per irRECIST)
IV	intravenous
Interactive Voice Response (IVR)	telecommunication technology that is linked to a central computer in real time as an interface to collect and process information.
LDH	lactate dehydrogenase
LSE(G)	global last subject enrolled
MRI	magnetic resonance imaging
MSI-H	microsatellite instability-high
NCI	National Cancer Institute
NSAIDS	nonsteroidal anti-inflammatory drugs
NSCLC	non-small cell lung cancer
OR	odds ratio
ORR	objective response rate (per RECIST v1.1)
OS	overall survival
PA	primary analysis
PD	progressive disease (per RECIST v1.1)
PD-1	programmed cell death-1
PD-L1	programmed death ligand 1
PET	positron emission tomography
PFS	progression-free survival (per RECIST v1.1)
PFU	plaque-forming unit

Abbreviation or Term	Definition/Explanation
PK	pharmacokinetics
PR	partial response
PR Interval	PR interval is measured from the beginning of the P wave to the beginning of the QRS complex in the heart's electrical cycle as measured by ECG
PRO	patient reported outcome
PT	prothrombin time
PTT/aPTT	partial thromboplastin time/activated partial thromboplastin time
QLQ-C30	Quality of Life Questionnaire Core 30
QLQ-H&N35	Quality of Life Questionnaire Head & Neck 35
QOL	Quality of Life
qPCR	real-time polymerase chain reaction
QRS interval	QRS interval the interval between the Q wave and the S wave in the heart's electrical cycle as measured by ECG; represents the time it takes for the depolarization of the ventricles
QT interval	QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle as measured by ECG.
QTc interval	QT interval corrected for heart rate using accepted methodology
RECIST	Response Evaluation Criteria in Solid Tumor
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SAS(G)	Global Safety Analysis Set
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease (per RECIST v1.1)
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.
SSAP	Supplemental Statistical Analysis Plan
Study day 1	defined as the first day that protocol-specified investigational products are administered to the subject
T3	triiodothyronine
TCIP-H	T-cell enriched high phenotypes
TNM	Tumor, node, metastases
TSH	thyroid stimulating hormone

Abbreviation or Term	Definition/Explanation
UE	unable to evaluate (per RECIST v1.1)
ULN	upper limit of normal
US	ultrasound
VAS	visual analog scale

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1. OBJECTIVES

1.1 Primary

Phase 1b

- To evaluate the safety, as assessed by incidence of dose limiting toxicity (DLT), of talimogene laherparepvec in combination with pembrolizumab in subjects with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN)

Phase 3

- To evaluate the efficacy, as assessed by overall survival (OS), of treatment with talimogene laherparepvec with pembrolizumab versus placebo with pembrolizumab in subjects with recurrent or metastatic SCCHN

1.2 Secondary

Phase 1b

- To evaluate the efficacy of talimogene laherparepvec in combination with pembrolizumab as assessed by:
    - Objective response rate (iORR), complete response rate (iCRR), and best overall response (iBOR); duration of response (iDOR), disease control rate (iDCR), and progression-free survival (iPFS) (response evaluation by investigator using immune-related Response Evaluation Criteria in Solid Tumors [irRECIST])
    - OS
- To evaluate the safety of talimogene laherparepvec in combination with pembrolizumab as assessed by incidence of adverse events and laboratory abnormalities.

Phase 3

- To evaluate the efficacy of talimogene laherparepvec with pembrolizumab versus placebo with pembrolizumab, as assessed by:
    - Objective response rate (ORR) and progression-free survival (PFS) (response evaluation by investigator using RECIST v1.1)
    - iORR and iPFS (response evaluation by investigator using irRECIST)
    - iCRR, iBOR; iDOR, and iDCR (response evaluation by investigator using irRECIST)
    - CRR, BOR, DOR, and DCR (response evaluation by investigator using RECIST v1.1)
    - 1-year, 2-year, and 3-year survival
    - Subject incidence of treatment-emergent and treatment-related adverse events (all adverse events, grade ≥ 3 adverse events, serious adverse events, fatal adverse events, adverse events and serious adverse events leading to discontinuation of treatment, and adverse events defined as events of interest)
- To evaluate patient reported outcomes (PRO) as assessed by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life

Questionnaire Core 30 (QLQ-C30) Global Health Status/Quality of Life (GHS/QoL) subscale.

1.3 Exploratory

Phase 1b

- To evaluate ORR, CRR, BOR, DCR, and DOR (response evaluation by investigator using modified RECIST v1.1)
- To evaluate responses in injected and uninjected tumors by investigator assessment
- To estimate the incidence of detection of talimogene laherparepvec DNA in lesions suspected to be herpetic in origin
- To estimate the incidence of clearance of talimogene laherparepvec DNA from blood and urine
- To estimate the rate of detection and subject incidence of talimogene laherparepvec DNA and virus from blood, urine, exterior of occlusive dressing, surface of injected lesions and oral mucosa

CCI

Phase 3

- To evaluate responses in injected and uninjected tumors by investigator assessment
- To estimate the incidence of detection of talimogene laherparepvec DNA in lesions suspected to be herpetic in origin

CCI

- To evaluate the incidence of anti-pembrolizumab antibodies when pembrolizumab is administered in combination with talimogene laherparepvec/placebo
- To evaluate the PK of pembrolizumab when administered in combination with talimogene laherparepvec/placebo

CCI

CCI

- To evaluate PROs as assessed by the EORTC QLQ-C30 subscales and the EORTC Quality of Life Questionnaire Head & Neck 35 (QLQ-H&N35) subscales.
- To estimate health state utility values using the EQ-5D-5 level (EQ-**5D**-**5**L)

2. BACKGROUND AND RATIONALE

2.1 Disease

Head and neck carcinomas (HNC) are the fifth most common cancer in the world and annual incidence appears to be increasing. In 2014, it was estimated that about 55,070 new cases of oral cavity, pharyngeal, and laryngeal cancers would occur, which would account for about 3% of new cancer cases in the United States. An estimated 12,000 deaths from HNC would occur during the same time period (Siegel et al, 2014). SCCHN or a variant is the histologic type seen in more than 90% of these tumors. The four most common primary sites of SCCHN in the United States and Europe are the oral cavity, oropharynx, hypopharynx, and larynx. HNC are strongly associated with tobacco use and with excessive alcohol abuse in 80% of oral cancers. Other risk factors include HPV for oropharyngeal cancer, Epstein-Barr virus (nasopharyngeal), exposure to asbestos, and Barrett's esophagus in the case of hypopharyngeal cancer.

Stage at diagnoses predicts survival rates and guides management in patients with SCCHN. The 2010 American Joint Commission on Cancer (AJCC) staging classification system is currently used as the basis for treatment decisions. Approximately 30% to 40% of patients present with early stage disease (stage I or II) and have 5-year survival rates approaching 80% with single-modality surgery or radiotherapy (Gold et al, 2009). Locally advanced disease (stage III/IV-A/IV-B) comprises approximately 60% of patients at diagnosis and has 5 year survival rates of approximately 50% to 60% with combined modality standard of care treatment. Notably, a recent publication attempting to refine stage and prognostic groups for HPV related non metastatic (M0) oropharyngeal cancer found that with a refined prognostic model, patients with locally advanced disease had significantly improved survival prediction compared to seventh edition AJCC TNM staging (Huang et al, 2015). Approximately 10% of patients present with metastatic disease and have 5 year survival rates approaching 30% (Siegel et al, 2014). Approximately 50% of patients with locally

advanced SCCHN develop locoregional or distant relapses which are usually detected within the first 2 years of treatment (Argiris et al, 2008). For this population, the prognosis is extremely poor with DCR estimating 45%, and median OS estimates of 6 to 9 months (Vermorken et al, 2007). For distant metastases, the usual pattern of spread is to lung, liver, and bone, although this pattern may be different in HPV-positive disease which can spread to a range of other sites including intra-abdominal lymph nodes, pleural cavity, bowel and brain.

Chemotherapy is an integral part of the treatment of locally recurrent and metastatic SCCHN. Palliation is the main goal of treatment for patients with metastatic disease and locally recurrent disease not curable by radiation and/or surgery. The current standard of care for locally recurrent and/or metastatic SCCHN is concurrent platinum-based chemotherapy in patients with good performance status without severe comorbidities. The median OS is 7 to 10 months (Cohen et al, 2004; Peron et al, 2014). In a phase 3 randomized trial of patients with recurrent or metastatic SCCHN , cetuximab plus 5-fluorouracil/cisplatin or 5-fluorouracil/carboplatin improved median OS compared to the standard of care chemotherapy doublet (10.1 months compared to 7.4 months [Vermorken et al, 2008]). A similar trial design was employed for the SPECTRUM study, which evaluated panitumumab. Patients in both groups received up to six 3-weekly cycles of intravenous cisplatin (100 mg/m^2) and 5-fluorouracil (1 g/m^2 per day for 4 days), while those in the experimental group also received intravenous panitumumab. A total of 657 patients were randomized and the median overall survivals were 11.1 versus 9.0 months (hazard ratio [HR] 0.873; P=0.1403) in the panitumumab and control group, respectively (Vermorken et al, 2013).

After failure of first-line platinum based chemotherapy, cetuximab monotherapy in a phase 2 study demonstrated ORR 10% with a median OS of 5.8 months representing an increase of 2.5 months compared with platinum-refractory historical controls (Vermorken et al, 2007). Objective response to second-line cytotoxic chemotherapy are uncommon with little impact on prolonging OS (Leon et al, 2005). Locally advanced, metastatic and recurrent SCCHN remains an area of high unmet medical need. Therefore, clinical evaluation of novel therapeutic approaches such as modulation of the immune system is needed.

2.1.1 The Role of HPV

Genetic material from high risk-oncogenic strains (HPV types 16 and 18) is found in approximately 60% of oropharyngeal cancers arising from the palatine and lingual tonsils

(Ang et al, 2010). Patients with locoregionally advanced HPV-positive oropharyngeal SCCHN treated with chemo radiation have better survival than do HPV-negative patients (Ang et al, 2010; Chaturvedi et al, 2011; Licitra et al, 2006). The transforming potential of HPV infection is driven by viral proteins E6 and E7, which inactivate the tumor suppressor proteins p53 and pRb, which results in loss of cell cycle regulation, cellular proliferation, and chromosomal instability (Fakhry and Gillison, 2006). Squamous cell carcinoma of the head and neck patients with tumors that are HPV-positive have an improved survival compared with SCCHN patients who are HPV-negative. A retrospective multivariate analysis of a randomized, phase 3 trial, Radiation Therapy Oncology Group 0129 originally designed to compare accelerated-fractionation to standard fractionation radiotherapy when delivered with concurrent cisplatin has been reported (Ang et al, 2010). This analysis revealed significantly improved 3-year survival among SCCHN patients who were HPV-positive compared with SCCHN patients who were HPV negative (84% vs. 57% respectively). Patients with HPV-positive tumors had a 58% reduction in risk of death compared with patients with HPV-negative tumors (HR 0.42, 95% confidence interval [CI 0.27, 0.66]). In a multicenter Eastern Cooperative Oncology Group (ECOG) study in which patients with newly diagnosed stage III or IV SCCHN were treated with induction chemotherapy followed by chemoradiation, 60% of oropharynx primary tumors were found to be HPV-positive (Fakhry et al, 2008). The two-year PFS rate (86% vs.53%; p=0.02) and OS rate (95% vs. 62%; p=0.005) were also significantly better for patients with HPV-associated cancer compared to HPV-negative cancer. Another retrospective analysis of the SEER (Surveillance, Epidemiology, and End Results) data for patients with oropharyngeal cancer revealed a 4-fold higher median OS in patients who were HPV-positive compared with patients who were HPV-negative (131 months vs 20 months) (Chaturvedi et al, 2011). In contrast, the outcome for HPV-negative SCCHN patients has not improved despite intensification of standard chemotherapeutic agents and combinations. Novel therapeutic approaches are needed in this population.

2.1.2 Etiologies of SCCHN

SCCHN is caused by the accumulation of multiple gene alterations modulated by genetic predisposition and chronic inflammation, enhanced by environmental influences such as tobacco and alcohol abuse (non-HPV related) or by infection with HPV (The Cancer Genome Atlas Network, 2015). These etiologies involve a multistep process and result in alterations in both oncogenes and tumor suppressor genes.

2.1.3 Programmed Cell Death-1 (PD-1) in SCCHN

Recently a new class of monoclonal antibodies has been engineered to block or activate co-signaling pathways resulting in enhanced anti-tumor immunity. One of the most promising pathways for manipulation involves program death ligand 1 (PD-L1). PD-L1 expression is up regulated in solid tumors where it allows the tumor to evade attack by the immune system (Dong et al, 2002; Hirano et al, 2005). Inhibition of the interaction between PD-1 receptors (expressed on activated T cells) and PD-L1 has been shown to enhance T-cell responses (Fife et al, 2009).

Down-regulation of T-cells in SCCHN has been implicated in pathogenesis and progression of tumors (Albers et al, 2010; Tong et al, 2012;). High levels of PD-1 expression have been demonstrated in human SCCHN tissue samples across multiple primary sites (Strome et al, 2003) on 46% to 87% of tumors (Cho et al, 2011; Lyford-Pike et al, 2013; Strome et al, 2003; Ukpo et al, 2013). While most studies have analyzed surgical samples from initial diagnosis, one evaluation of oropharyngeal squamous cell samples included 28 recurrent tumors and 10 distant metastases of which 43% and 70% expressed PD-L1 respectively (Ukpo et al, 2013). PD-L1 expression was considered binarily positive in tumor cells if >5% staining (versus negative if 0 to 5% staining). These data suggest PD-L1 is expressed on SCCHN in the primary, recurrent, and metastatic settings and manipulation of the PD-L1: PD-1 pathway may be an important therapeutic target.

Given the importance of HPV in the etiology of oropharyngeal SCCHN, several studies have examined the correlation between HPV status and PD-L1 status.
Three independent studies have revealed higher expression of PD-L1 in HPV-positive compared to negative patients: 70 vs 29% (Lyford-Pike et al, 2013), 49.2% vs 34.1% (Ukpo et al, 2013), and 62.5% vs 40% (Badoual et al, 2013). Additionally, a 12-gene chemokine signature identifying a subset of CD-8 enriched (T-cell enriched phenotype-high) tumors was developed in SCCHN tumors. T-cell enriched high phenotypes (TCIP-H) were found in 51% of HPV-positive-tumors and in 21% of HPV-negative tumors indicating that the TCIP-H population may be a particularly important target in SCCHN (Saloura et al, 2014).

2.2 Amgen Investigational Product Background: Talimogene Laherparepvec

Talimogene laherparepvec is a virally-based oncolytic immunotherapy consisting of an immune-enhanced herpes simplex virus type-1 (HSV-1) that selectively replicates in

tumors. In this genetically modified strain, the HSV-1 viral genes encoding infected-cell protein (ICP) 34.5 (a neurovirulence factor) and ICP47 (which blocks viral antigen presentation to major histocompatibility complex class I and II molecules) have been functionally deleted. The coding sequence for human granulocyte macrophage colony-stimulating factor (GM-CSF) have been inserted in place of ICP34.5 and is intended to enhance the immune response to tumor antigens released after virus replication and lytic tumor cell death. Thus, talimogene laherparepvec has two mechanisms of action: (a) direct oncolysis of infected tumor cells and (b) immune activation through tumor-associated antigen release and local virus-mediated GM-CSF expression. Talimogene laherparepvec is administered by direct injection into tumors.

Intralesional injection of talimogene laherparepvec, also known as IMLYGIC®, has been approved by the United States Food and Drug Administration (FDA) for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in adult patients with melanoma recurrent after initial surgery. However, it has not been shown to increase OS or have an effect on metastases to internal organs including the liver and lungs. Additionally, in the European Union, talimogene laherparepvec (Imlygic™) has been approved for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (stage IIIB, IIC, and IVM1a) with no bone, brain, lung, or other visceral disease.

As of 30 June 2015, 15 clinical studies (including 2 extension studies) have been or are being conducted in several advanced tumor types with over 400 subjects treated with talimogene laherparepvec. For additional information, refer to the talimogene laherparepvec Investigator's Brochure.

Refer to the specific section of the Investigator's Brochure for additional information related to the physical, chemical, and pharmaceutical properties and formulation(s).

Talimogene Laherparepvec in SCCHN

A phase 1/2 study has been completed with talimogene laherparepvec in combination with radiotherapy and cisplatin in subjects with untreated stage III/IV SCCHN. Seventeen subjects with stage III/IVA/IVB SCCHN were enrolled and received chemoradiotherapy (70 Gray [Gy]/35 fractions with concomitant cisplatin 100 mg/m^2 on days 1, 22 and 43) and dose-escalating (10^6, 10^6, 10^6, 10^6 plaque-forming units (PFU)/mL for cohort 1; 10^6, 10^7, 10^7, 10^7 PFU/mL for cohort 2, 10^6, 10^8, 10^8, 10^8 PFU/mL, for cohort 3) talimogene laherparepvec injected into malignant cervical

lymph nodes on days 1, 22, 43, and 64. No injections were administered to mucosal surfaces of tumor lesions. Injections were administered using topical local anesthetics with lidocaine/prilocaine. Subjects underwent neck dissection 6 to 10 weeks later (Harrington et al, 2010). The recommended phase 2 dose of 10^6, 10^8, 10^8, 10^8 PFU/mL was established. Analysis of viral clearance of talimogene laherparepvec through biodistribution in blood and urine and shedding of live virus at various time points post injection was performed.

All 17 subjects were treated without delays to chemoradiotherapy or DLT. All subjects experienced at least 1 adverse event during the course of the study. The most common treatment-emergent adverse events observed across 4 cohorts were decreased weight (16 subjects; 94%), constipation (15 subjects; 88%), mucosal inflammation and radiation skin injury (each 14 subjects; 82%), anemia and nausea (each 13 subjects; 76% each), and dysphagia (12 subjects; 71%). The incidence of events was generally balanced across cohorts. Most adverse events (86%) were Common Terminology Criteria for Adverse Events (CTCAE) grade 1 or 2, and most (91.0%) were not considered related to talimogene laherparepvec by the investigator. Thirteen (2.7%) adverse events considered related to talimogene laherparepvec were grade 1 and 12 (2.3%) events were grade 2. There were no grade 3, grade 4, or grade 5 treatment-emergent adverse events considered related to talimogene laherparepvec. The most common grade 3 adverse events were mucosal inflammation (6 subjects; 35%); radiation skin injury (5 subjects; 29%); weight decreased and dysphagia (each 4 subjects; 24%); dehydration and leukopenia (each 3 subjects; 18%); febrile neutropenia, neutropenia, thrombocytopenia and nausea (each 2 subjects; 12%). Only three grade 4 adverse events were reported (lymphopenia, dysphagia, and respiratory failure). None of these events were considered related to treatment.

Sixteen of 17 subjects (94%) experienced treatment-emergent serious adverse events during the study. The most commonly reported serious adverse events were mucosal inflammation (5 subjects; 29%), febrile neutropenia (3 subjects, 18%), and pyrexia, renal failure, nausea, dysphagia and dehydration (each 2 subjects; 12%). All serious adverse events were considered unrelated to talimogene laherparepvec by the investigator and all but 6 events (grade 3 skin graft infection, grade 3 ulcerative colitis, grade 2 mucositis and dysphagia, grade 3 urinary tract infection, and grade 3 dysphagia) resolved by end of study. The ongoing events did not result in treatment discontinuation.

Two subjects experienced events of febrile neutropenia and neutropenia, respectively that were considered DLTs; however neither event was considered related to talimogene laherparepvec. The events of neutropenia were considered related to cisplatin administration, and in both cases, the cisplatin dose was reduced and the events resolved. No deaths or withdrawals due to adverse events occurred during the study.

Three of 17 subjects (18%) had talimogene laherparepvec DNA detected by swab analysis of the injection site following talimogene laherparepvec administration. This was detected in one subject at visit 0 (24 and 96 hours post injection, in another subject at visit 6 (48 hours post injection) and at the end of study (24 hours post injection), and for a third subject in cohort 4 at visit 3 (24 hours post injection). Swabs obtained from the dressings covering the injection site(s) were negative for the presence of virus for all subjects at all timepoints.

Biopsy samples (3 from needle biopsy, 12 from neck dissection specimens, and 1 from both needle biopsy and neck dissection specimens) were obtained for analysis of talimogene laherparepvec copy number from injected and uninjected nodes in 16 of the 17 subjects (94%). Viral DNA was detected in 42% of injected nodes and in 1 neighboring uninjected node (14%) suggesting virus replication and demonstrating spread of talimogene laherparepvec to an adjacent node. In 31% of subjects, talimogene laherparepvec viral levels were >50,000 copies per microgram of DNA, a level suggestive of productive viral replication in tumors.

The detection of virus in injected tumors at delayed time points after dosing appeared to be more likely at the highest dose administered. Overall, 3 of 17 subjects (18%) had positive plaque assays of the tumor swab at any time point and no subjects had a positive plaque assay of the exterior dressing swab. Urine and blood were not tested for viral shedding and biodistribution in this study.

Fourteen subjects (82.3%) showed tumor response by RECIST v1.1, and pathologic complete remission was confirmed in 93% of subjects at neck dissection. No subject developed locoregional recurrence, and disease-specific survival was 82.4% at a median follow-up of 29 months (Harrington et al, 2010).

2.3 Non-Amgen Investigational Product Background: Pembrolizumab

Pembrolizumab (Keytruda™ [US]), a humanized monoclonal antibody against the PD-1 protein, has been developed by Merck & Co for the treatment of cancer. Pembrolizumab is approved for treatment of melanoma in several countries; in the US and EU it is

approved for the treatment of advanced (unresectable or metastatic) melanoma in adults. Pembrolizumab has also been approved for treatment of non-small cell lung cancer (NSCLC) in several countries; in the US it is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy. Patients with NSCLC and EGFR or ALK genomic tumor aberrations should also have disease progression on FDA-approved therapy for those aberrations prior to receiving pembrolizumab.

Most recently, pembrolizumab has gained approval for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

Pembrolizumab has also gained accelerated conditional approval in the United States and several countries in the EU in the second line setting for recurrent/metastatic SCCHN with disease progression on or after platinum containing chemotherapy without any biomarker testing requirement based on the updated data of the phase 1b KEYNOTE-012 study (NCT01848834).

Mostly recently, pembrolizumab has further gained accelerated approval based on tumor response rate and durability of response in following tumor types: (1) adult and pediatric patients with refractory classical Hodgkin lymphoma (cHL), or who have relapsed after 3 or more prior lines of therapy; (2) urothelial carcinoma in locally advanced or metastatic setting for pts who are not eligible for cisplatin containing chemotherapy; (3) adult or pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. Continued approval for above indications may be contingent upon verification description of clinical benefit in the confirmatory trials.

Note: The safety and effectiveness of pembrolizumab in pediatric patients with MSI-H central nervous system cancers have not been established.

Pembrolizumab also has demonstrated initial clinical efficacy in single arm monotherapy trials including subjects with gastric cancer, triple negative breast cancer, and Hodgkin's Lymphoma as determined by response rate. Ongoing clinical trials are being conducted

in other tumor types including hematologic malignancies. For study details, please refer to the pembrolizumab Investigator's Brochure.

The first dose-escalation phase 1 study involving subjects with solid tumors showed that pembrolizumab was safe at the dose levels tested (1 mg/kg of body weight, 3 mg/kg, and 10 mg/kg, administered every 2 weeks) without reaching a maximum tolerated dose (Hamid et al, 2013). In addition, clinical responses were observed at all the dose levels (Patnaik et al, 2012).

For additional information, refer to the pembrolizumab Investigator's Brochure.

Pembrolizumab in SCCHN

On 08 August 2016, pembrolizumab gained accelerated conditional approval in the United States and several countries in the EU in the second line setting for recurrent/metastatic SCCHN based on the results of a pooled analysis of 2 recurrent/metastatic squamous cell carcinoma head and neck cohorts from KEYNOTE 012 (NCT01848834). In one cohort, subjects with positive PD-L1 expression (defined as a proportion score of > 1% PD-L1 immunohistochemistry expression in tumor cells or stroma) received pembrolizumab 10 mg/kg every 2 weeks. In a second cohort, subjects with both positive and negative PD-L1 expression received pembrolizumab 200 mg every 3 weeks. The evaluable population (n = 173) was heterogeneous in terms of numbers of prior lines of therapy; however, most patients had received prior platinum therapy. The ORR in the entire population was 23.7% (24.1% in the HPV-negative subset and 23.6% in the HPV-positive subset). The median PFS was 2.2 months (95% CI: 2.0 to 3.6) and the median overall survival was reported to be 9.6 months (95% CI: 6.6 to not reached). Treatment was well tolerated with grade 3/4 drug-related adverse events occurring in 12.5% of patients (Chow et al, 2015).

A phase 2 clinical trial of single agent pembrolizumab in platinum and cetuximab failure subjects is currently being conducted (NCT02255097). The primary endpoint will be ORR by RECIST v1.1. A phase 3 clinical trial of pembrolizumab versus standard of care (methotrexate, docetaxel, or cetuximab) in recurrent or metastatic SCCHN subjects after treatment with platinum-based cetuximab therapy is being conducted (NCT02252042) with primary endpoint of OS. A third study of pembrolizumab alone versus pembrolizumab plus platinum plus 5-Fluorouracil versus cetuximab plus platinum plus 5-Fluorouracil for first line treatment of recurrent or metastatic SCCHN is currently being conducted (NCT02358031). The primary endpoint of this study will be PFS by

RECIST v1.1. For all three studies, subjects will receive pembrolizumab 200 mg intravenously on Day 1 of each 3 week cycle.

As existing data suggest 200 mg every 3 weeks as the appropriate dose for pembrolizumab and pembrolizumab is currently being tested at this fixed dose in ongoing head and neck cancer studies, this is the dose of pembrolizumab planned to be studied in this trial.

2.4 Rationale

Talimogene laherparepvec and pembrolizumab blockade likely play complementary roles in regulating adaptive immunity. Talimogene laherparepvec likely augments dendritic cell-mediated tumor antigen presentation through local expression of GM-CSF (Kaufman et al, 2010) and local antigen release by direct tumor lysis. PD-1 plays an important role in SCCHN. Pembrolizumab is a PD-1 regulator and prevents T-cell exhaustion in peripheral tissues. After evidence of activity in SCCHN, pembrolizumab is being evaluated in 2 phase 3 trials.

The combination of an agent that increases tumor-specific immune activation (talimogene laherparepvec) with one that blocks inhibitory T-cell checkpoints (pembrolizumab) could produce greater antitumor activity than either agent alone.

There are currently 2 ongoing combination immunotherapy studies with talimogene laherparepvec and a checkpoint inhibitor in advanced stage melanoma. The first is a phase 1b/2 study of ipilimumab with or without talimogene laherparepvec in unresected melanoma (NCT01740297). In the phase 1b portion, 18 of 19 subjects (more than half with stage IV M1b disease) received both talimogene laherparepvec and ipilimumab in combination. Full dose of talimogene laherparepvec and ipilimumab 3 mg/kg every 3 weeks starting at week 6 were tolerable. Per immune-related response criteria (data cutoff of 22 December 2014), the ORR in 18 evaluable subjects was 56% (33% complete responses [CRs]), and the durable response rate (DRR) was 44%. Median PFS was 10.6 months (2.6 to 19.3+ months). Median OS was not reached; 12-month and 18-month survival rates were 72.2% and 67%, respectively. On a lesion level, 8 and 5 of 16 uninjected index lesions regressed ≥ 50% and 100%, respectively. Grade 3/4 treatment-emergent A occurred in 32% of subjects, and grade 3/4 immune-related adverse events occurred in 2 subjects (grade 3 hypophysitis and adrenal insufficiency; and grade 4 amylase + lipase elevations). There were no treatment-related deaths (Puzanov et al, 2014). More recently, an interim analysis of the phase 2 portion of the study which was performed when 82 patients had ≥ 48 weeks of

follow up was reported (Chesney et al, 2016). One-hundred and seventy three subjects were randomized: 88 in the talimogene laherparepvec + ipilimumab arm and 85 in the ipilimumab arm. Characteristics for all subjects were similar: 54% stage IIIB-IVM1a, 45% IVM1b/c. Median follow up time for 82 subjects was 61.2 weeks (range: 0.14-113.9). Confirmed ORR was 35.7% in the combination arm and 17.5% in the ipilimumab arm with odds ratio for response of 2.6 (95% CI; 0.9-7.3). Unconfirmed ORR was 50% in the combination arm and 27.5% in the ipilimumab arm. Safety data in the analysis were as expected based on the phase 1b data; of 165 subjects in the safety set (85 in the combination arm and 80 in the ipilimumab arm), the incidences of grade 3 and 4 treatment related adverse events were similar in both arms (total of 20% in the combination arm and 19% in the ipilimumab arm) with the exception of diarrhea (4% in combination arm vs 0% in ipilimumab arm) and colitis (4% in combination arm vs 8% in ipilimumab arm). A grade 5 autoimmune hepatitis occurred in the combination arm which was attributed to ipilimumab per investigator.

The second study is a phase 1b/3 multicenter open-label trial of talimogene laherparepvec in combination with pembrolizumab for treatment of unresected, stage IIb to IVM1c melanoma (NCT02263508). In the phase 1b portion of the study, subjects with stage IIB-IV melanoma with injectable lesions and no prior systemic therapy received up to 4.0 mL of talimogene laherparepvec monotherapy for 2 doses followed by talimogene laherparepvec and pembrolizumab every 2 weeks thereafter. All 21 evaluable subjects had an adverse event: 29% grade 3, no grade 4 and 1 grade 5 (not treatment related). The most common adverse events by preferred term were fatigue (52%), pyrexia (48%), chills (43%), and rash (38%). Of 16 subjects evaluable for response, the unconfirmed response rate per investigator was 56%; DCR was 69% (12.5% CR, 44% partial response [PR], 12.5% stable disease [SD]) (Long et al, 2015).

This registrational study is intended to provide evidence that a regimen of an oncolytic immunotherapy (talimogene laherparepvec) and a checkpoint inhibitor (pembrolizumab) is safe and tolerable, and that the combination might enhance the clinical efficacy of single agent pembrolizumab in recurrent or metastatic SCCHN. The choice of PD-1 inhibitors for the control arm is based on the assumption that this class of agent may become the new standard of care in this indication. The study is an accelerated design leading from a phase 1b to a phase 3 study without a conventional phase 2 evaluation. However, activity of the combination will be evaluated at the end of the phase 1b study to support a decision to initiate the phase 3 study.

2.5 Clinical Hypotheses

Phase 1b:

Talimogene laherparepvec in combination with pembrolizumab will be safe and well tolerated in subjects with recurrent or metastatic SCCHN.

Phase 3:

The clinical hypothesis is that talimogene laherparepvec with pembrolizumab compared to placebo with pembrolizumab will improve OS. In addition to the hypothesis test for the primary endpoint, ORR, PFS, iORR, and iPFS in subjects given talimogene laherparepvec plus pembrolizumab versus placebo plus pembrolizumab will be compared.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a phase 1b/3, multicenter clinical trial. The study will be conducted in 2 parts (phase 1b and phase 3) as described below. The overall study design is described by a Study Design and Treatment Schema at the end of the protocol synopsis section.

The study endpoints are defined in Section 10.1.1.

3.1.1 Phase 1b Study Design

Phase 1b is a multicenter, single-arm study. Talimogene laherparepvec will be administered in combination with pembrolizumab to approximately 40 subjects with recurrent or metastatic SCCHN. DLT will be evaluated based on first 18 DLT-evaluable subjects. An expansion cohort of up to an additional 22 treated subjects will be enrolled to obtain a total of approximately 40 treated subjects to further evaluate the safety and to estimate the efficacy of the combination of talimogene laherparepvec with pembrolizumab to support a decision to initiate the phase 3 study.

3.1.1.1 Rules for DLT Evaluation in Phase 1b

A Dose Level Review Team (DLRT) will review the safety data to evaluate DLT. This team will recommend either to enroll more subjects for DLT evaluation in phase 1b, to prematurely stop enrollment into phase 1b, or to declare that the combination is tolerable based on the criteria described in Table 1 below.

The DLT evaluation period is 6 weeks from the initial administration of study treatment. To be evaluable for a DLT, subjects must have had the opportunity to be on treatment for at least 6 weeks from the initial dosing of study treatment and have received at least 2 doses of talimogene laherparepvec and 2 doses of pembrolizumab in combination, or

have a DLT during the DLT evaluation period after at least 1 dose of talimogene laherparepvec and pembrolizumab in combination. Subjects may be replaced if they are not evaluable for DLT to obtain 18 DLT-evaluable subjects (eg, a subject did not receive study treatment, or ended the study treatment before completion of DLT evaluation period for a reason other than experiencing a DLT).

Safety will be evaluated considering the incidence of DLTs among all DLT-evaluable subjects enrolled in the phase 1b. A sequential stopping rule is derived based on a hypothesis testing approach considering only the first 18 DLT-evaluable subjects (Goldman, 1987). There will be up to 3 planned safety interim analyses. The cumulative increments of DLT-evaluable subjects and corresponding acceptable maximum number and percentage of DLTs at each analysis are indicated in Table 1. The combination will not be declared safe if the number of DLTs exceeds the acceptable maximum number and phase 1b will stop.

Table 1. Cumulative Increments of DLT-evaluable Subjects and Corresponding Acceptable Maximum Number and Percentage of DLTs at Each Planned Interim Safety Analysis

Analysis	Number DLT Evaluable Subjects	Number DLT Evaluable	Acceptable Maximum Number (%) of DLTs
#1	First 4 to 6	4	2 (50)
		5	2 (40)
		6	2 (33)
		7[1]	2 (29)
#2	4 to 6 new after Analysis #1	8	2 (25)
		9	3 (33)
		10	3 (30)
		11	3 (27)
		12	3 (25)
		13[1]	3 (23)
#3	Exactly 18 total	18[2]	4 (22)

DLT = dose limiting toxicity
The design achieves a 7.7% 1-sided significance level and 81.6% power to test the null hypothesis of a DLT rate ≤ 10% versus the alternative hypothesis of a rate ≥ 33%.
[1] Although the target is 4 to 6 DLT-evaluable subjects at Analysis #1, and 4 to 6 new subjects at Analysis #2, all DLT-evaluable subjects will be included in each analysis.
[2] If > 18 subjects receive the combination they will contribute to the overall safety analysis, but only the first 18 DLT-evaluable will be considered in the decision to declare the combination safe.

3.1.1.2 Definition of DLT in Phase 1b

All toxicities will be graded using the CTCAE version 4.0 (Appendix A).

The occurrence of any of the following toxicities during DLT evaluation period (ie, 6-week period from the initial administration of talimogene laherparepvec and

pembrolizumab in combination) will be considered a DLT, if judged by the investigator to be related to the administration of talimogene laherparepvec and/or pembrolizumab:

- Grade 4 non-hematologic (non-laboratory) toxicity
- Grade 3 or higher pneumonitis
- Grade 3 non-hematologic (non-laboratory) toxicity lasting > 3 days despite optimal supportive care
- Grade 3 fatigue will not be classified as DLT, irrespective of duration
- Any grade 3 or higher non-hematologic laboratory value if:
  - medical intervention is required, or
  - the abnormality leads to hospitalization, or
  - the abnormality persists at grade 3 or higher for >1 week unless deemed not clinically important per both investigator and sponsor
- Grade 3 or grade 4 febrile neutropenia
- Thrombocytopenia < 25 x 10^9/L associated with bleeding event requiring intervention
- Serious herpetic event:
  - Herpetic encephalitis, encephalomyelitis, or disseminated herpetic infection
- Grade 5 toxicity (ie, death)
- Any other intolerable toxicity leading to permanent discontinuation of talimogene laherparepvec or pembrolizumab

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

An expansion cohort of up to 22 treated subjects will be enrolled so there will be approximately 40 treated subjects in total to estimate the efficacy of the combination of talimogene laherparepvec with pembrolizumab.

3.1.2 Phase 3 Study Design

Phase 3 is a multicenter, placebo-controlled, double-blind, randomized trial to evaluate the efficacy, as assessed by OS, of treatment with talimogene laherparepvec with pembrolizumab versus placebo with pembrolizumab in subjects with recurrent or metastatic SCCHN. Approximately 450 subjects will be randomized 1:1 to receive the following:

- Arm 1: talimogene laherparepvec plus pembrolizumab
- Arm 2: placebo plus pembrolizumab

Randomization will be stratified by HPV status at baseline (HPV- negative versus HPV-positive) and ECOG performance status (0 versus 1).

3.1.3 Tumor Assessment

3.1.3.1 Eligibility Assessment

Phase 1b

Conventional RECIST v1.1 (Eisenhauer et al, 2009) , with the following modification, will be used by the investigator to determine eligibility:

- Increased total target lesions to a maximum of 10 (up to a maximum of 5 per organ)

Phase 3

Conventional RECIST v1.1 (Eisenhauer et al, 2009) with no modifications will be used by the investigator to determine eligibility.

3.1.3.2 Response Assessment

For both phase 1b and phase 3, a variation of RECIST v1.1, irRECIST, will be used by the investigator to assess tumor response and make treatment decisions, and to assess the secondary tumor response related endpoints in the phase 1b and phase 3 portions of the study. In addition, for phase 3 only, investigators will also be asked to determine and document tumor responses per standard RECIST v1.1, although treatment decisions should NOT be made based on RECIST v1.1. Details for irRECIST can be found in Appendix D, and details for RECIST v1.1 can be found in Appendix E. Radiographic tumor assessments will be performed independent of treatment cycle at week 9 (±1 week), week 18 (±1 week), and then every 9 weeks (±1 week) or more frequently if clinically indicated until confirmed progressive disease per irRECIST (iPD) or start of a new anticancer treatment. Radiographic tumor assessments should not be adjusted for cycle initiation delays and performed according to the calendar. Radiographic tumor imaging assessment at screening (baseline) (computed tomography [CT] scan, positron emission tomography [PET]/contrast enhanced CT scan, or magnetic resonance imaging [MRI]) must include the neck, chest, abdomen and all other sites of disease. A CT scan or MRI of the brain should only be performed if signs or symptoms suggestive of central nervous system [CNS] metastases are present. The imaging modality selected (eg, CT or MRI) should remain constant for any individual subject.

3.1.4 Follow-up

3.1.4.1 Safety Follow-up

All subjects who receive investigational product will complete a safety follow-up visit approximately 30 (+7) days after the last dose of study treatment. Adverse events and

disease related events will be collected as described in Section 9.2. Serious adverse events and any concomitant medications associated with serious adverse events observed by the investigators or reported by the subjects that occur 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.

3.1.4.2 Long-term Follow-up

After the safety follow-up visit, all subjects will enter the long-term follow-up. Subjects will be followed for survival and subsequent anticancer therapies every 12 weeks (± 28 days) from safety follow-up for approximately 36 months after the last subject is enrolled. In addition, talimogene laherparepvec/placebo related adverse events that occur through the end of the long-term follow-up will be reported.

For subjects who discontinue study treatment without documented iPD and have not initiated a new anticancer therapy, every effort should be made to continue monitoring tumor response status by clinical and radiographic tumor assessments, and to complete PRO questionnaires as described in Section 7.7.

3.2 Number of Sites

The study will be conducted at approximately 140 sites in Australia, Europe, North America, Latin America, Asia, and other regions. Additional sites and countries may be added. Sites that do not enroll subjects within approximately 4 months of site initiation may be closed.

3.3 Number of Subjects

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

Approximately 490 subjects will be enrolled in this study: approximately 40 subjects will be enrolled in phase 1b and approximately 450 subjects will be enrolled in phase 3 Global Full Analysis Set (FAS[G]). Refer to Section 10.2 for sample size considerations.

3.4 Replacement of Subjects

Subjects enrolled in phase 1b may be replaced if they are not evaluable for DLT (eg, a subject did not receive study treatment, or ended the study treatment before completion of DLT evaluation period for a reason other than experiencing a DLT).

Subjects enrolled in phase 3 who are withdrawn or removed from treatment or from the study will not be replaced.

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

The duration of screening for each subject will be approximately 28 days. The duration of treatment will vary for each subject. Subjects enrolled (phase 1b)/randomized (phase 3) have an estimated median treatment period of 7 months, but can be treated for up to 24 months. All subjects will complete a safety follow-up visit approximately 30 (+7) days after the last dose of study treatment. After the safety follow-up visit subjects will enter the long-term follow-up. During this period, subjects will be followed for survival for approximately 36 months after the last subject is **enrolled**. The study duration for an individual subject is expected to be 45 months. The actual duration of the study for an individual subject may vary depending upon the time required to reach the study specified number of OS events.

3.5.2 End of Study

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

If a 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).

Primary Completion Phase 1b only: The time when the last phase 1b subject is assessed or receives an intervention for the purposes of final collection of data for the primary efficacy endpoint of phase 1b. The primary completion is anticipated to occur when the last phase 1b subject completes the week 9 tumor response assessment.

End of Study (end of trial): 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. This is anticipated to occur 36 months after the last subject is enrolled.**

4. SUBJECT ELIGIBILITY

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

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

4.1 Inclusion Criteria

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

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

103 Histologically confirmed diagnosis of metastatic or recurrent SCCHN of the oral cavity, oropharynx, hypopharynx, or larynx. Disease must be unsuitable for curative surgical resection and must not be amenable to curative radiotherapy.

104 Disease must have progressed after treatment with a platinum-containing regimen and should be defined as one of the following:

- disease progression or recurrence between 3 to 6 months of prior curatively intended multimodal therapy (which includes platinum therapy) for locoregionally advanced SCCHN.

Note: This criterion is only applicable for subjects who have not had treatment in the recurrent/metastatic setting.

- disease progression or recurrence after prior platinum therapy in the recurrent or metastatic setting

105 Subject must be candidate for intralesional therapy administration defined as one or more of the following:

- at least 1 injectable cutaneous, subcutaneous, or nodal SCCHN tumor ≥ 10 mm in longest diameter
- multiple injectable cutaneous, subcutaneous, or nodal SCCHN tumors that in aggregate have a longest diameter of ≥ 10 mm

Note: Mucosal surfaces of tumor lesions and visceral metastases should not be injected.

106 Subject must have radiographically measurable disease per RECIST v1.1 (Eisenhauer et al, 2009). Target lesions must not be chosen from a previously irradiated field unless there has been radiographically and/or pathologically documented tumor progression in that lesion prior to enrollment

107 ECOG performance status of 0 or 1

108 Adequate organ function determinedprior to enrollment, defined as follows:

- Hematological
  - ANC $\geq$ 1.5 x 10^9/L
  - platelet count $\geq$ 100 x 10^9/L
  - hemoglobin $\geq$ 9 g/dL

  Note: Subjects who have received transfusion of blood products (including platelets or red blood cells, or administration of colony stimulating factors [including G-CSF, GM-CSF, or recombinant erythropoietin) within 4 weeks prior to the first study treatment will be excluded.

- Renal
  - serum creatinine $\leq$ 1.5 x upper limit of normal (ULN), OR creatinine clearance $\geq$ 60 mL/min for a subject with creatinine levels > 1.5 x ULN. (Note: Creatinine clearance need not be determined if the baseline serum creatinine is within normal limits. Creatinine clearance should be determined per institutional standard).
- Hepatic
  - total bilirubin $\leq$ 1.5 x ULN OR direct bilirubin ≤ ULN for a subject with total bilirubin level > 1.5 x ULN
  - aspartate aminotransferase (AST) $\leq$ 2.5 x ULN OR $\leq$ 5 x ULN for a subject with liver metastases
  - alanine aminotransferase (ALT) $\leq$ 2.5 x ULN OR $\leq$ 5 x ULN for a subject with liver metastases
- Coagulation
  - international normalization ratio (INR) or prothrombin time (PT) $\leq$ 1.5 x ULN, unless the subject is receiving anticoagulant therapy, in which case PT and partial thromboplastin time (PTT)/activated PTT (aPTT) must be within therapeutic range of intended use of anticoagulants
  - PTT or aPTT $\leq$ 1.5 x ULN unless the subject is receiving anticoagulant therapy as long as PT and PTT/aPTT is within therapeutic range of intended use of anticoagulants

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

110 Phase 1b: Subject has a formalin fixed paraffin-embedded tumor sample from the primary or metastatic lesion that must be submitted within 4 weeks of enrollment for PD-L1, HPV-testing of oropharyngeal cancer (if not performed locally) and biomarker analyses.

Phase 3: Subject has a formalin fixed paraffin embedded tumor sample that is adequate for PD-L1 assessment prior to randomization (sites will be blinded to PD-L1 analysis). Tumor tissue from the subject must be submitted to a central laboratory during screening. Refer to the laboratory manual for more detailed tissue collection procedures.

111 Phase 3: Have results from local testing of HPV of tumor specimen for oropharyngeal cancer defined as p16 IHC testing using the CINtec® assay and a 70% cutoff point. If the assay is unavailable locally, sites must submit archived or recently biopsied formalin-fixed paraffin-embedded tumor tissue (block or unstained tumor slides) from either the primary or metastatic lesion for central laboratory testing. Note: HPV stratification in this trial will be performed using local or central testing of HPV status in subjects with oropharynx cancer. Oral cavity, hypopharynx, and larynx cancer are not required to undergo HPV testing by p16 IHC as by convention, they are assumed to be HPV negative. Please note that results from local testing of HPV of tumor specimen for oropharyngeal cancer patients are required for both phases of the study. Performing p16-IHC testing using the CINtec® assay is only required for phase 3.

4.2 Exclusion Criteria

201 Has known active CNS metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

202 Primary nasopharyngeal carcinoma.

203 Subject at risk of airway compromise in the event of postinjection tumor swelling/inflammation based on investigator judgment.

204 Phase 3: Previous treatment with 3 or more systemic regimens given for recurrent and/or metastatic disease.

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

207 History of interstitial lung disease (ILD).

208 Prior therapy with talimogene laherparepvec, pembrolizumab, other anti-PD-1, any other antibody or drug specifically targeting T-cell co-stimulation or immune check point pathway.

210 History or evidence of active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs).

Note: Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc) is not considered a form of systemic treatment.

211 Evidence of clinically significant immunosuppression such as the following:

- organ transplant/bone marrow transplant or other signs or symptoms of clinical immune system suppression
- any severe congenital or acquired cellular and/or humoral immune deficiency
- 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

Note: Subjects that require intermittent use of bronchodilators or local steroid injection are not excluded from the study.

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

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

214 Prior chemotherapy, radiotherapy, biological cancer therapy, targeted therapy, or major surgery within 28 days prior to enrollment or has not recovered to CTCAE grade 1 or better from adverse event due to cancer therapy administered more than 28 days prior to enrollment.

Note: Subjects with ≤ grade 2 neuropathy and/or alopecia are an exception to this criterion and may qualify for the study.

215 Currently participating or have participated in a study (treatment period only) of an investigational agent or used an investigational device within 28 days of enrollment/randomization.

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

217 Subject who is unwilling to forgo other investigational procedures during study treatment.

218 Known human immunodeficiency virus (HIV) disease.

219 Has acute or chronic active hepatitis B virus or hepatitis C virus infection or received treatment with nucleotide analogs such as those used in the treatment of hepatitis B virus (eg, lamivudine, adefovir, tenofovir, telbivudine, entecavir), ribavirin, or interferon alpha within 12 weeks of initiation of study treatment.

220 Received live vaccine within 28 days prior to enrollment/randomization.

221 Subject is pregnant or breast-feeding, or expecting to conceive or father children within the duration of the trial, starting with the screening visit and through 3 months after the last dose of talimogene laherparepvec/placebo or 4 months after the last dose of pembrolizumab, whichever is later.

222 Female subject of childbearing potential or male subject of reproductive potential who is unwilling to use acceptable method(s) of effective contraception during study treatment and through 3 months after the last dose of talimogene laherparepvec/placebo or 4 months after the last dose of pembrolizumab, whichever is later. Note: Women not of childbearing potential are defined as:

- Postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age 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. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient)

OR

- Have had a hysterectomy and/or bilateral oophorectomy, or bilateral salpingectomy at least 6 weeks prior to screening

OR

- Has a congenital or acquired condition that prevents childbearing

  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).Note: Acceptable methods of effective contraception are defined in the informed consent form. Additional country-specific contraception requirements may be defined in a country-specific protocol supplement at the end of the Appendix Section of the protocol as required by local laws and regulations.

  If there is any question that a subject of reproductive potential will not reliably comply with the requirements for contraception, that subject should not be enrolled into the study.

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

224 Subject has known sensitivity to any of the products or components to be administered during study treatment.

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

226 History or evidence of psychiatric, substance abuse, or any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or sponsor medical monitor, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.

227 Subject or subject's immediate family member (eg, spouse, parent/legal guardian, sibling, or child) is investigational site or sponsor staff directly involved in this trial.

Note: If prospective institutional review board (IRB)/independent ethics committee (IEC) approval (by chair or designee) is given, an exception to this criterion for a specific subject is permitted.

228 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 (eg, 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/placebo.

229 Has a known history of active bacillus tuberculosis.

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

231 Subjects with tumor that directly contacts or encases a major blood vessel AND there is ulceration and/or fungation onto the skin surface.

232 History of re-irradiation to a field which includes the carotid arteries.

5. SUBJECT ENROLLMENT

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

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

Each subject who enters into the screening period for the study (defined when the subject signs the informed consent) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification

number will be assigned by the Interactive voice response (IVR) system (referred to as IxRS throughout the protocol). 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. This number will not necessarily be the same as the randomization number assigned for the study.

5.1 Treatment Assignment Phase 1b

All subjects enrolled in the phase 1b of the study will receive open-label talimogene laherparepvec in combination with pembrolizumab. The treatment assignment date is to be documented in the subject's medical record and on the enrollment CRF.

5.2 Randomization/Treatment Assignment Phase 3

Upon confirmation of eligibility, the site staff will use the IVR system to randomize a subject. The IVR system will assign a randomization number. Approximately 450 subjects will be randomized 1:1 ratio to receive the following:

- Arm 1: talimogene laherparepvec plus pembrolizumab
- Arm 2: placebo plus pembrolizumab

Randomization will be stratified by HPV status at baseline (HPV- negative versus HPV-positive) and ECOG performance status (0 versus 1).

Following randomization via the IVR system, study treatment must commence within 5 days after enrollment.

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

The subject, site personnel, and sponsor study personnel and designees are blinded to the randomization treatment group assigned unless otherwise specified in the protocol.

A subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the subject on this study. If a subject discontinues study treatment due to documented disease progression and the knowledge of treatment assignment alters the subject's eligible treatment options outside of the trial, then the investigator may request to unblind the treatment assignment for that subject after discussion with the sponsor. All precaution and efforts will be taken to

ensure the sponsor and blinded site personal will remain blinded to the study treatment. Unblinding at the study site for any other reason will be considered a protocol deviation.

The investigator is strongly encouraged to contact the sponsor clinical study manager before unblinding any subject's treatment assignment, but must do so within 1 working day after the event and must document the unblinding in the subject's electronic CRF.

6. TREATMENT PROCEDURES

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

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

The Non-Amgen Investigational product(s) used in this study includes: pembrolizumab. The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of talimogene laherparepvec/placebo and pembrolizumab.

6.2 Investigational Product

6.2.1 Amgen Investigational Product: Talimogene Laherparepvec/Placebo

Talimogene laherparepvec/placebo will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures.

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

Placebo (talimogene laherparepvec formulation excipients as described in the Talimogene Laherparepvec Investigator's Brochure) will be supplied as sterile frozen liquid in the same presentation, packaging, and with blinded labeling as for talimogene laherparepvec.

Talimogene laherparepvec or placebo may be supplied as open-label or blinded. Where talimogene laherparepvec or placebo is supplied as open-label, the site pharmacist or designee will need to be unblinded to prepare blinded talimogene laherparepvec/placebo.

- For talimogene laherparepvec or placebo supplied as open-label investigational medicinal product, IxRS will confirm to the unblinded site pharmacist or designee, from which lot number(s) the vial(s) should be selected from each dosing visit. In no circumstances should an unblinded pharmacist reveal the treatment assignment to the other site staff.
- For talimogene laherparepvec or placebo supplied as a blinded investigational medicinal product, IxRS will confirm to the site pharmacist or designee from which box number(s) vial(s) should be selected from each dosing visit. All site personnel will be blinded to study treatment.

6.2.1.1 Dosage, Administration, and Schedule

Talimogene laherparepvec/placebo 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 CTCAE version 4 (Appendix A). Complete blood count with differential and chemistry panels including liver function laboratory tests (ALT, AST, and total bilirubin) should be obtained according to the Schedule of Assessments (Table 5 and Table 7) and the results should be checked before each treatment. For subjects on anticoagulant therapy, close monitoring of coagulation parameters is recommended during the study treatment phase. Dosing will occur only if these test values are acceptable per Section 6.2.1.2.

Talimogene laherparepvec/placebo will be administered by intralesional injection only into injectable cutaneous, subcutaneous, and nodal tumors, with or without image ultrasound (US) guidance. Talimogene laherparepvec/placebo must not be administered into the mucosal surface of tumor lesions or visceral metastases. For subjects with tumor(s) which directly contacts or encases a major vessel but does not have ulceration and/or fungation onto the skin surface, talimogene laherparepvec injections should be given no closer than 2 cm from the wall of the major vessel. This should be done under image guidance and by skilled personnel (eg, a surgeon).

For the first cycle, the dose of talimogene laherparepvec/placebo will be up to 8.0 mL of 10^6 PFU/mL administered on week 0, day 1. For the second cycle, subjects may receive up to 8.0 mL of talimogene laherparepvec 10^8 PFU/mL or placebo 3 weeks (+ 3 days) after the initial injection (ie, no sooner than day 22 but should not be delayed more than 3 days after the 3 week time point). All subsequent doses up to 8.0 mL of talimogene

laherparepvec10^8 PFU/mL or placebo will be administered every 3 weeks (± 3) days. If a delay of > 3 days is anticipated due to reasons other than toxicity, permission should be sought from the medical monitor. The treatment cycle interval may be increased due to toxicity as described in Section 6.2.1.2. It is recommended that talimogene laherparepvec/placebo be administered before pembrolizumab on treatment days.

The maximum volume of talimogene laherparepvec/placebo administered at any dose is 4.0 mL for any individual tumor lesion. The maximum volume at any treatment visit is 8.0 mL. Investigators are encouraged to use the maximum volume whenever lesions allow. The recommended volume of talimogene laherparepvec/placebo 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 2.

Table 2. Talimogene Laherparepvec Injection Volume Guideline Based on Tumor Size

Tumor Size (longest dimension)	Maximum Injection Volume
> 5.0 cm (50 mm)	4.0 mL
> 2.5 cm (25 mm) to 5.0 cm (50 mm)	2.0 mL
> 1.5 cm (15 mm) to 2.5 cm (25 mm)	1.0 mL
> 0.5 cm (5 mm) to 1.5 cm (15 mm)	0.5 mL
≤ 0.5 cm (5 mm)	0.1 mL

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

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

It is recommended that each lesion should receive the maximum amount possible to inject due to tumor properties at each visit before moving on the next lesion, using the prioritization model above and the injection volume guideline based on tumor size per Table 2. Tumor measurements for injection volume determination may be done by caliper measurements and/or by ultrasound guided measurements. Most recent prior radiographic tumor assessment measurements may be used to determine injection volume if caliper measurements and/or ultrasound guided measurements are not feasible and/or unavailable. The lesions injected will be recorded on the CRF.

Note: Continued injection into nodal lesions that have decreased to < 10 mm is up to the discretion of the investigator.

Subjects will be treated with talimogene laherparepvec/placebo until subjects have achieved a iCR, no injectable lesions, confirmed iPD (response per irRECIST), intolerance of study treatment, 24 months from the date of the first dose of talimogene laherparepvec/placebo, or end of study, 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 study therapy. The dose, start date, and lot number of talimogene laherparepvec/placebo are to be recorded on each subject's CRF.

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

Dose reductions of talimogene laherparepvec/placebo 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, 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

Talimogene laherparepvec should be withheld if subject experiences any adverse event which, in the opinion of the investigator, warrants withholding investigational product.

If the subject requires corticosteroid dosing of > 10 mg prednisone daily (or equivalent) for related toxicities, talimogene laherparepvec/placebo 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 6.9 shall be available to subjects. Talimogene laherparepvec/placebo treatment should be continued based on the potential benefit/risk assessment of the subject.

If talimogene laherparepvec/placebo dosing is delayed by more than 4 weeks from the date of the planned dose (ie, approximately 7 weeks since the previous dose) due to the occurrence of an adverse event that is considered related to talimogene laherparepvec/placebo, the subject must be permanently withdrawn from talimogene laherparepvec/placebo treatment. If talimogene laherparepvec/placebo dosing is delayed by more than 4 weeks from the date of the planned dose (ie, 7 weeks from the previous dose) for reasons other than treatment-related toxicity, the case must be reviewed by the sponsor medical monitor in conjunction with the investigator to determine if the subject can resume talimogene laherparepvec/placebo treatment.

Talimogene laherparepvec/placebo doses may be given no less than 15 days apart, if needed, for the purpose of re-aligning dosing schedules after a dose delay.

Talimogene laherparepvec in phase 1b or talimogene laherparepvec/placebo in phase 3 is to be permanently discontinued for subjects meeting any of the following criteria:

- Phase 1b subject developed DLT during the DLT evaluation period.
- The subject, for any reason, requires treatment with another anticancer therapeutic agent for treatment of the study disease (other than the exceptions noted in Excluded Treatments and/or Procedures During Study Period [Section 6.9]. In this case, discontinuation from the treatment occurs immediately upon introduction of the new agent.
- Confirmed iPD occurs as defined per the irRECIST (Appendix D).
- A grade 2 or greater immune-mediated adverse event (with the exception of vitiligo) or allergic reactions attributed to talimogene laherparepvec/placebo that would require a dose delay of greater than 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/placebo-related non-hematologic or hematologic toxicities grade 3 or greater occur that, in the opinion of the investigator, would require a dose delay of greater than 4 weeks from the date of the planned dose.
- 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/placebo dangerous for the subject.

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

In the event talimogene laherparepvec/placebo is delayed or permanently discontinued for talimogene laherparepvec/placebo-related toxicity, pembrolizumab may continue to be administered, as long as the toxicity is clearly not related to pembrolizumab. Likewise in the event pembrolizumab is delayed or permanently discontinued for pembrolizumab-related toxicity, talimogene laherparepvec/placebo may continue to be

administered, as long as the toxicity is clearly not related to talimogene laherparepvec/placebo.

6.2.2 Non-Amgen Investigational Product: Pembrolizumab

Non-Amgen investigational product, pembrolizumab, will also be used in this study. 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/4mL vials (25 mg/mL) solution for intravenous infusion.

Additional details regarding pembrolizumab are provided in the IPIM.

6.2.2.1 Pembrolizumab Dosage, Administration, and Schedule

Pembrolizumab 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 CTCAE version 4 (Appendix A). Complete blood count with differential and chemistry panels including liver function laboratory tests (ALT, AST, and total bilirubin) and thyroid function tests (triiodothyronine [T3] or free T3 [FT3] per local standard, free thyroxine [FT4], and thyroid stimulating hormone [TSH]) should be obtained according to the Schedule of Assessments (Table 5 and Table 7) and the results should be checked before each treatment. Dosing will occur only if these test values are acceptable per Section 6.2.2.2.

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.

Pembrolizumab at a dose of 200 mg will be administered intravenously every 3 weeks (± 3 days) after the initial dose. When talimogene laherparepvec/placebo and pembrolizumab are administered on the same day, it is recommended that talimogene laherparepvec/placebo be administered first. Pembrolizumab dosing will continue until a iCR is achieved, confirmed iPD (response per irRECIST), intolerance to treatment, 24 months from the date of the first dose of study treatment, or end of study, whichever occurs first.

Pembrolizumab infusion will be administered as a 30-minute intravenous infusion. Investigators 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 of -5 and +10 minutes is permitted (ie, infusion time is

30 minutes:-5 minutes/+ 10 minutes). A central catheter is not required for infusion; however if a subject has a central venous catheter in place, it is recommended that it be used for the infusion. A 0.2 or 0.22 µm in-line filter made of polyethersulfone must be used during administration to remove any adventitious particles. If the infusion set does not contain a 0.2 or 0.22 µm in-line filter, it is recommended to use an extension line containing the filter. Details on the dose calculation, preparation, and administration are provided the IPIM.

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

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

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening adverse events as per Table 3 below. See Section 6.2.3 for supportive care guidelines, including use of corticosteroids.

Table 3. Pembrolizumab-related Adverse Event Management

General instructions:

Corticosteroid taper should be initiated upon AE improving to grade 1 or less and continue to taper over at least 4 weeks.

For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks.

For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of pneumonitis Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		

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Table 3. Pembrolizumab-related Adverse Event Management

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Diarrhea / Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1-2 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.
	Grade 4	Permanently discontinue		

Table 3. Pembrolizumab-related Adverse Event Management

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
AST/ALT elevation or Increased bilirubin	Grade 2	Withhold **Permanently discontinue, if:** **AST or ALT > 3x ULN; and total bilirubin > 2 x ULN; and no other cause for the combination of laboratory abnormalities is immediately apparent (see Section 6.4.1)**	Administer corticosteroids (initial dose of 0.5- 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 or 4	Permanently discontinue	Administer corticosteroids (initial dose of 1-2 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 antihyperglycemic 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 discontinue1		

Table 3. Pembrolizumab-related Adverse Event Management

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
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 discontinue1		
Hypothyroidism	Grade 2-4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 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		

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Table 3. Pembrolizumab-related Adverse Event Management

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	Based on type and severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

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Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTES:

For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when adverse event resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

For myocarditis, in certain circumstances, pembrolizumab may be resumed at grade 1 only if the investigator believes that the myocarditis has clinically resolved and the investigator has obtained written permission from the medical monitor to resume therapy.

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase

In case of toxicity that does not resolve to grade 0 or 1 or baseline within 12 weeks after the last infusion of pembrolizumab, pembrolizumab treatment should be discontinued after consultation with the sponsor medical monitor. With the investigator and sponsor medical monitor agreement, subjects with laboratory adverse events still at grade 2 after 12 weeks may continue pembrolizumab treatment in the trial only if asymptomatic and controlled.

Subjects enrolled in phase 1b who develop a DLT during the DLT evaluation period will permanently discontinue pembrolizumab.

6.2.3 Rescue Medications and Supportive Care Guidelines for Pembrolizumab

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator.

Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other cases such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation the event is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Section 6.2.1.2 for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

6.2.3.1 Infusion Reactions

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 4.

Table 4. Infusion Reaction 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 subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours	Stop Infusion and monitor symptoms. 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 subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one 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 subject should be premedicated for the next scheduled dose. Subjects who develop grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.	Subject may be premedicated 1.5 hours (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg orally (or equivalent dose of antihistamine). Acetaminophen 500 - 1000 mg orally (or equivalent dose of antipyretic).
Grades 3 or 4	Stop Infusion.	No subsequent dosing
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)	Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine	
Grade 4: Life-threatening; pressor or ventilatory support indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. Subject is permanently discontinued from further trial treatment administration.	

Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.
CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NCI = National Cancer Institute; NSAID = nonsteroidal anti-inflammatory drug

6.2.3.2 Pembrolizumab Events of Clinical Interest

Events of Clinical Interest

Events of Clinical Interest that occur after the first dose of pembrolizumab through 30 (+7) days after the last dose of pembrolizumab must be reported to Amgen within 24 hours of the investigator's knowledge of the event regardless of attribution to pembrolizumab. Information on how to identify and report Events of Clinical Interest can be referenced in Section 9.5.

6.2.3.3 Diet and Other Considerations While Taking Pembrolizumab

6.2.3.3.1 Diet During Treatment With Pembrolizumab

Subjects should maintain a normal diet unless modifications are required to manage adverse events such as diarrhea, nausea or vomiting.

6.2.3.3.2 Contraception Requirements for Pembrolizumab

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use acceptable method(s) of effective contraception or are considered of non-childbearing potential. Female subjects of childbearing potential and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 4 months after the last dose of study drug by complying with one of the following:

1 Practice abstinence† from sexual activity;

OR

2 Use (or have their partner use) acceptable effective contraception, as defined in the informed consent form, during sexual activity

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and IRBs/IECs. Periodic abstinence (eg, calendar, ovulation, sympto-thermal, post-ovulation methods, etc) and withdrawal are not acceptable methods of contraception.

Refer to Section 4.2, exclusion criteria 221 and 222, for contraception requirements for men and women and definition of women of non-childbearing potential and men of reproductive potential for this study. Refer to the informed consent form for acceptable

method(s) of effective contraception for subjects to use in this study. Additional country-specific contraception requirements may be defined in a country-specific protocol supplement at the end of the Appendix Section of protocol as required by local laws and regulations.

Subjects should be informed that taking pembrolizumab may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, men and women of reproductive potential must adhere to the contraception requirements (described above) from the day of study medication initiation (or 14 days prior to the inititation of study medication for oral contraception) throughout the study period and for 4 months after the last dose of trial therapy. If there is any question that a subject of reproductive potential will not reliably comply with the requirements for contraception, that subject should not be enrolled into the study.

6.2.3.3.3 Use of Pembrolizumab in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. **The pregnancy and the outcome of the pregnancy will be reported to Amgen and followed as described in Section 9.3 (Pregnancy and Lactation Reporting).**

6.2.3.3.4 Use of Pembrolizumab in Nursing Women

It is unknown whether pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, female subjects who are breast-feeding are not eligible for enrollment in this study. **If a female subject breastfeeds while taking pembrolizumab, report the lactation case to Amgen as described in Section 9.3 (Pregnancy and Lactation Reporting).**

6.3 Other Protocol-required Therapies

All other protocol-required therapies, including topical anesthetic or an injectable local anesthetic medications used for pretreatment of the talimogene laherparepvec/placebo 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 the sponsor (except if required by local regulation). The investigator will be responsible for obtaining supplies of these protocol-required therapies.

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

6.4 Hepatotoxicity Stopping and Rechallenge Rules

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], AST, ALT, total bilirubin and/or international normalized ratio [INR] and/or signs/symptoms of hepatitis (as described in Sections 6.4.1 and 6.4.2) may meet the criteria for withholding or permanent discontinuation of investigational product as specified in the United States Food and Drug Administration Guidance for Industry Drug-Induced Liver Injury (DILI): Premarketing Clinical Evaluation, July 2009).

6.4.1 Criteria for Permanent Discontinuation of Investigational Products and Other Protocol-required Therapies Due to Potential Hepatotoxicity

Investigational product should be discontinued permanently and the subject should be followed according to the recommendations in Appendix A (Additional Safety Assessment Information and Drug-induced Liver Injury Reporting & Additional Assessments) for possible DILI, if ALL of the criteria below are met:

- Current total bilirubin > 2x ULN following baseline total bilirubin < ULN or INR > 1.5
- AND current AST or ALT > 3x ULN following baseline AST or ALT < ULN respectively
- AND no other cause for the combination of the above laboratory abnormalities is immediately apparent; important alternative causes for elevated AST/ALT and/or total bilirubin 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-one antitrypsin deficiency
  - Alcoholic hepatitis
  - Autoimmune hepatitis
  - Wilson's disease and hemochromatosis
  - Nonalcoholic Fatty Liver Disease including Steatohepatitis (NASH)
  - Non-hepatic causes (eg, rhabdomylosis, hemolysis)

If an alternative cause for hepatotoxicity is identified or less stringent conditions developed than what are noted above, determine (based on patient population and/or

severity of the hepatotoxicity or event) if investigational product should be withheld or permanently discontinued, as deemed appropriate for the safety of the subject.

6.4.2 Criteria for Conditional Withholding of Investigational Products and Other Protocol-required Therapies Due to Potential Hepatotoxicity

For subjects who do not meet the criteria for permanent discontinuation of investigational product outlined above and have no underlying liver disease, and eligibility criteria requiring normal transaminases and total bilirubin at baseline or subjects with underlying liver disease and baseline abnormal transaminases, the following rules are recommended for withholding of investigational product and other protocol-required therapies:

- Elevation of either AST or ALT according to the following schedule:

Baseline AST or ALT value	AST or ALT elevation
≤ 3 x ULN	> 5 x ULN for ≥ 2 weeks
≤ 3 x ULN	> 5 x ULN and unable to adhere to enhanced monitoring schedule
≤ 5 x ULN	> 8 x ULN at any time

- OR: total bilirubin > 3x ULN at any time
- OR: ALP > 8x ULN at any time

Investigational product should be withheld pending investigation into alternative causes of DILI. If investigational product(s) is withheld, the subject is to be followed according to recommendations in Appendix A for possible DILI. Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated total bilirubin, is discovered and the laboratory abnormalities resolve to normal or baseline (Section 6.4.3).

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

The decision to rechallenge the subject should be discussed and agreed upon unanimously by the subject, investigator, and sponsor medical monitor.

If signs or symptoms recur with rechallenge, then investigational product and other protocol-required therapies, as appropriate should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Section 6.4.1) should never be rechallenged without consulting with the sponsor medical monitor.

6.5 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.9.

Concomitant therapies are to be collected in the CRF from informed consent through 30 (+7) days after the last dose of talimogene laherparepvec/placebo or pembrolizumab, whichever is later. In addition, any concomitant medications associated with serious adverse events that occur 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 the sponsor and recorded in the CRF.

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

6.6 Other Treatment Procedures

Local radiation treatment to the site of bone and other metastasis will be permitted for palliative 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 and all study treatments should be withheld. Re-exposure to talimogene laherparepvec/placebo and pembrolizumab may occur post palliative radiation treatment only if the investigator and sponsor medical monitor agree that the subject's safety will not be compromised.

If a subject demonstrates evidence of new or worsening CNS metastases, all study treatments should be withheld. Subjects may be allowed to remain on study after discussion with the sponsor medical monitor provided the CNS metastases are adequately treated and the investigator determines the appropriateness of treatment resumption. In addition, in order to resume study treatment, the corticosteroid dose must not exceed 10 mg of prednisone or equivalent. Re-exposure to talimogene laherparepvec/placebo and pembrolizumab may occur only if the investigator and sponsor medical monitor agree that the subject's safety will not be compromised.

6.7 Medical Devices

Medical devices (eg, 0.2 or 0.22 µm in-line filter made of polyethersulfone, intravenous administration set, infusion pump syringes, sterile needles, alcohol prep pads) that are commercially available are not usually provided or reimbursed by the Sponsor (except,

for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

6.8 Product Complaints

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

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

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

6.9 Excluded Treatments and/or Procedures During Study Period

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

- other investigational agents or procedures concurrent experimental or approved antitumor therapies immunosuppressive agents with the exception of treatment for adverse events (see Sections 6.2.2.2 and 6.2.3)
- any live vaccine therapies used for the prevention of infectious disease within 28 days prior to enrollment/randomization and during treatment period. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines; non-live vaccines are allowed. Intranasal influenza vaccines (eg, Flu - Mist®) are live attenuated vaccines and are not allowed.
- systemic antiherpetic drugs (eg, acyclovir, valacyclovir, famciclovir)
- Note: Subjects may receive a topically administered antiherpetic drug more than 20 cm from the injection site.
- Any elective surgery or non-palliative definitive radiotherapy for SCCHN (refer to Section 6.6
- The exclusion criteria describe other medications and procedures which are prohibited in this study (refer to Section 4.2)

Subjects must not schedule any elective surgeries 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.

7. STUDY PROCEDURES

7.1 Schedule of Assessments

For Schedule of Assessments of phase 1b and phase 3 please refer to Table 5, Table 6, and Table 7 respectively.

Table 5. Schedule of Assessments for Phase 1b

	Screening			Treatment (week number)									Follow-up	
Study Procedures	≤ 28 days	≤ 14 days	≤ 72 hour	0	3	6	9	12	15	18	21	24[a]	Safety Within 30 days after last treatment	Long-term Every 3 months
General Assessments														
Informed Consent	X													
Review of Eligibility Criteria	X													
Demographics, Medical, Surgical and Medication History	X													
Recording of Concomitant Medications	X			X	X	X	X	X	X	X	X	X	X	X[b]
Physical Exam and Vital Signs	X			X	X	X	X	X	X	X	X	X	X	
Body Weight	X												X	
Height	X													
ECOG Performance Status	X			X	X	X	X	X	X	X	X	X	X	
12-lead ECG	X												X	
Review of adverse events, disease related events and serious adverse events	X			X	X	X	X	X	X	X	X	X	X	X[c]
Survival Assessment														X
Local Laboratory Tests														
Chemistry		X		X	X	X	X	X	X	X	X	X	X	
Hematology		X		X	X	X	X	X	X	X	X	X	X	
Hepatitis B surface antigen & and Hepatitis B core antibody		X												
Hepatitis C virus antibody		X												
Urinalysis[d]		X											X	
PT or INR and PTT or aPTT[e]		X												
T3 (or FT3), FT4, TSH		X		X		X		X		X		X	X	
Urine or Serum Pregnancy Test[f]			X										X	

Footnotes defined on the last page of the table.

Table 5. Schedule of Assessments for Phase 1b

	Screening			Treatment (week number)									Follow-up	
Study Procedures	≤ 28 days	≤ 14 days	≤ 72 hour	0	3	6	9	12	15	18	21	24[a]	Safety Within 30 days after last treatment	Long-term Every 3 months
Central Laboratory Tests														
Optional Blood for Pharmacogenetic Analysis[g]				X										
Blood for Biomarker Analyses[h]				X	X	X	X					X	X	
Blood for HSV-1 Serostatus				X	X	X	X							
Tumor tissue for biomarker analysis[i]				X										
Optional Tumor tissue for biomarker analyses[j]						X								
Archival Tumor Tissue (if applicable)[k]				X										
Swab of Herpetic Lesion for qPCR				Within 3 days of occurrence of suspected lesion of herpetic origin										
Radiographic Tumor/Response Assessments														
Radiographic (CT, PET/contrast enhanced CT or MRI,) Scans & Tumor Assessment[l,m]	X						X			X			X	X
Optional Photographs of Visible Tumor Lesions	Any Time													

Footnotes defined on the last page of the table.

Table 5. Schedule of Assessments for Phase 1b

	Screening			Treatment (week number)									Follow-up	
Study Procedures	≤ 28 days	≤ 14 days	≤ 72 hour	0	3	6	9	12	15	18	21	24[a]	Safety Within 30 days after last treatment	Long-term Every 3 months
Treatment Administration[l]														
Talimogene laherparepvec[n]				X	X	X	X	X	X	X	X	X		
Pembrolizumab[o]				X	X	X	X	X	X	X	X	X		
Reporting Exposure to Talimogene Laherparepvec														
Exposure of Subject's Household member of Caregiver	Anytime													
Exposure of Subject's Healthcare Provider	Anytime													

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CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; ECG = electrocardiogram; FT4 = free thyroxine; HSV-1 = herpes simplex virus type 1; INR = international normalized ratio; MRI = magnetic resonance imaging; PET = positron emission tomography; PT = prothrombin time; PTT/aPTT = partial thromboplastin time/activated partial thromboplastin time; qPCR = real-time polymerase chain reaction; T3/FT3=free triiodothyronine; TSH = thyroid stimulating hormone

[a] Repeat week 24 procedures and assessments every 3 weeks until end of study treatment, with the exceptions of thyroid function testing, which is required every 6 weeks unless otherwise indicated. Furthermore, blood for biomarker analysis is only required as indicated in the visit schedule, up to week 24. 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.

[b] Only subsequent anticancer treatment for SCCHN will be recorded.

[c] See Section 9.2 for long-term follow-up assessments and reporting.

[d] Urine samples for urinalysis will be collected at screening within 14 days prior to enrollment. During treatment urine samples for urinalysis will be collected if clinically indicated. Urine sample for urinalysis will also be collected at the safety follow-up visit.

[e] Blood sample for coagulation will be collected (PT/aPTT measured in seconds and INR as a ratio) at screening within 14 days prior to enrollment. During the treatment phase, close monitoring of coagulation parameters is recommended for subjects on anticoagulant therapy.

[f] Urine or serum pregnancy test to be performed on female of childbearing potential. A urine pregnancy test should be performed within 72 hour prior to enrollment and at the safety follow-up. Note: Additional blood or urine for pregnancy testing (for women of child-bearing potential) may be performed during treatment at the investigator's discretion or as defined in a country-specific protocol supplement at the end of the Appendix Section of the protocol as required per local country's laws and regulatory requirements. If urine pregnancy test result is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

[g] Optional pharmacogenetic blood sampling will be performed prior to study treatment administration.

[h] Blood samples for biomarker analyses will be collected prior to study treatment administration at the following time points: at day 1 of week 0, week 3, week 6, week 9 and either at time of initial unconfirmed iPR, confirmed **i**PD, or at 24 weeks for subjects with SD, whichever comes first. A blood sample should be collected at the safety follow-up visit.

[i] Subject has a formalin fixed paraffin embedded tumor sample from the primary or metastatic lesion that must be submitted within 4 weeks of enrollment for PD-L1, HPV testing **f**or oropharyngeal cancer (if not performed locally), and biomarker analyses. See Section 7.5.2 for more details. Refer to the Laboratory Manual for detailed tissue collection procedures.

[j] Optional tumor tissue biopsy via core needle within 3 days prior to day 1 of week 6, if subject has consented. Refer to laboratory manual for detailed tissue collection procedures.

[k] Archival tumor tissue, of any age since diagnosis, that is available in addition to the baseline sample, if applicable, should be submitted within 4 weeks after enrollment.

[l] At screening (baseline) and throughout the study, radiographic tumor imaging assessments (CT scan, PET/contrast enhanced CT scan or MRI) must include the neck, chest, abdomen, and all other sites of disease. A CT scan or MRI of the brain should only be performed if signs or symptoms suggestive of CNS metastases are present. The screening (baseline) scans must be done within 28 days prior to enrollment. During treatment, radiographic imaging will be performed independent of treatment cycle at week 9 (±1 week), week 18 (±1 week), and then every 9 weeks (±1 week) or more frequently if clinically indicated until confirmed iPD or start of new anticancer treatment. Imaging should not be adjusted for cycle initiation delays and performed according to the calendar. The imaging modality selected (eg, CT or MRI) should remain constant for any individual subject. Response or progression should be confirmed by repeated radiographic imaging ≥ 4 weeks after the first indication of response or progression. Radiographic imaging is required at the safety follow-up visit if the subject ended treatment prior to confirmed **i**PD and has not had radiographic tumor imaging performed within 9 weeks (+1 week) of the visit. During the long-term follow-up period, for subjects who discontinued treatment for any reason other than confirmed **i**PD, every effort should be made to complete radiographic assessments every 12 weeks (±1 week) or more frequently if clinically indicated until documentation of confirmed **i**PD, start of new anticancer therapy, or end of study whichever occurs first.

[m] Response (**i**CR, or **i**PR) or **i**PD to be confirmed by second consecutive radiographic assessments no less than 4 weeks from the date of the first documented response or **i**PD.

[n] Talimogene laherparepvec will be administered on day 1 of week 0, day 1 of week 3 (+ 3 days), and every 3 weeks (± 3 days) thereafter. The initial dose of talimogene laherparepvec is up to 8.0 mL of 10^6 PFU/mL. Subsequent doses of talimogene laherparepvec are up to 8.0 mL of 10^8 PFU/mL.

[o] Pembrolizumab will be administered at a dose of 200 mg starting at day 1 of week 0, day 1 of week 3 (+ 3 days), and every 3 weeks (± 3 days) thereafter. When alimogene laherparepvec and pembrolizumab are administered on the same day, it is recommended that talimogene laherparepvec be administered first.

Table 6. Schedule of Assessments for Biodistribution and Shedding of Talimogene Laherparepvec for Phase 1b Only

	Study Treatment [a]													Follow-up Period
Week	0	0	0	1	2	3	3	3	4	5	6	7	9	Safety Follow-up
Talimogene Laherparepvec Cycle	1	1	1	1	1	2	2	2	2	2	3	3	4	Day 30 Safety Follow-up Visit
Day	1	2	3	8	15	1	2	3	8	15	1	8	1	30 (+ 7) days after end of treatment
Blood [a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine [a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Swab of Surface of Exterior of Occlusive Dressing[b]		X	X	X	(X)	(X)	X	X	X	(X)	(X)	X	(X)	(X)
Swab of Surface of Injected Lesion [b]		X	X	X	X	X	X	X	X	X	X	X	X	X
Swab of Oral Mucosa [c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] Blood and urine sample for real-time polymerase chain reaction (qPCR) testing of talimogene laherparepvec DNA will be performed at the following time points: Cycle 1: day 1 (prior to and approximately 1 hour [± 15 minutes], 4 hours [± 30 minutes], after talimogene laherparepvec administration), day 2 (24 [± 4] hours after talimogene laherparepvec administration), day 3 (48 [± 4] hours after talimogene laherparepvec administration), day 8 (± 2 days), and day 15 (± 2 days). Cycle 2: day 1 (prior to and approximately 1 hour [± 15 minutes], 4 hours [± 30 minutes], after talimogene laherparepvec administration), day 2 (24 [± 4] hours after talimogene laherparepvec administration), day 3 (48 [± 4] hours after talimogene laherparepvec administration), and day 8 (± 2 days), and day 15 (± 2 days). Cycle 3: day 1 (prior to talimogene laherparepvec administration) and day 8 (± 2 days). Cycle 4: day 1 (prior to talimogene laherparepvec administration). Blood and urine samples for qPCR testing will also be collected at the 30-day safety follow-up visit (+7 days). Please refer to the Central Laboratory Manual for instructions regarding sample collection, storage, and shipment procedures.

[b] Swabs of the exterior of the occlusive dressing and the surface of injected lesions for qPCR testing of talimogene laherparepvec DNA and if positive, a TCID50 assay will be performed. The occlusive dressing can be removed 7 days after the talimogene laherparepvec injection (see Injection Site Care Instructions for details). However, an occlusive dressing should be kept on longer if the lesions at the injection sites are weeping or oozing. During treatment: Select the largest injected lesion at baseline (ie, on day 1 of cycle 1).. The exterior of the selected occlusive dressing and the surface of the selected injected lesion will be swabbed starting on day 2 of cycle 1, at the following time points and only re-swabbed if the lesion is injected subsequently up to and including day 1 of cycle 4. The outside of the occlusive dressing will be swabbed first. The occlusive dressing will thereafter be removed and the surface of the injected lesion will be swabbed. Swabs of the exterior of the occlusive dressing will also be collected at day 1 of cycles 2, 3, and 4 and day 15 (± 2 days) at cycles 1 and 2, as well as at the 30-day safety follow up visit (+ 7 days) if the lesion is ulcerated or weeping that requires the occlusive dressing to be kept on for more than 7 days after the injection (as marked with parentheses in Table 6).

Cycle 1: day 2 (24 [± 4] hours after talimogene laherparepvec administration), day 3 (48 [± 4] hours after talimogene laherparepvec administration), day 8 (± 2 days) and day 15 (± 2 days). Cycle 2: day 1 (prior to talimogene laherparepvec administration), day 2 (24 [± 4] hours after talimogene laherparepvec administration), day 3 (48 [± 4] hours after talimogene laherparepvec administration), day 8 (± 2 days) and day 15 (± 2 days). Cycle 3: day 1 (prior to talimogene laherparepvec administration) and day 8 (± 2 days). Cycle 4: day 1 (prior to talimogene laherparepvec administration). During safety follow-up: Swabs of the surface of the injected lesion(s) (if a lesion is in complete response [CR], the place of the prior injection will be swabbed) will also be collected at the 30-day safety follow-up visit (+7 days). At each time point only if qPCR of talimogene laherparepvec DNA testing is positive, then a TCID50 assay will be performed to evaluate whether the presence of infective talimogene laherparevec virus is detectable in the sample. Please refer to the Central Laboratory Manual for instructions regarding sample collection, storage, and shipment procedures.

[c] Swabs of oral mucosa for qPCR of talimogene laherparepvec DNA testing and TCID50 assay will be collected at the following timepoints: Cycle 1: day 1 (prior to talimogene laherparepvec administration), day 2 (24 [± 4] hours after talimogene laherparepvec administration), day 3 (48 [± 4] hours after talimogene laherparepvec administration), day 8 (± 2 days), and day 15 (± 2 days). Cycle 2: day 1 (prior to talimogene laherparepvec administration), day 2 (24 [± 4] hours after talimogene laherparepvec administration, day 3 (48 [± 4] hours after talimogene laherparepvec administration), day 8 (± 2 days) and day 15 (± 2 days). Cycle 3: day 1 (prior to talimogene laherparepvec administration) and day 8 (± 2 days). Cycle 4: day 1 (prior to talimogene laherparepvec administration). If qPCR testing of talimogene laherparepvec DNA is positive, then a TCID50 assay will be performed to evaluate whether the talimogene laherparepvec virus is detectable in the sample. During safety follow-up: swab of oral mucosa for qPCR testing will be collected at the 30 day safety follow-up visit (+ 7 days). Please refer to the Central Laboratory Manual for instructions regarding sample collection, storage, and shipment procedures.

Table 7. Schedule of Assessments for Phase 3

	Screening			Treatment (Week Number)									Follow-up	
Study Procedures	≤ 28 days	≤ 14 days	≤ 72 hour	0	3	6	9	12	15	18	21	24[a]	Safety Within 30 days after last treatment	Long-term (Every 3 months)
General Assessments														
Informed Consent	X													
Review of Eligibility Criteria	X													
Demographics, Medical, Surgical and Medication History	X													
Recording of Concomitant Medications	X			X	X	X	X	X	X	X	X	X	X	X[b]
Physical Exam and Vital Signs	X			X	X	X	X	X	X	X	X	X	X	
Body Weight	X												X	
Height	X													
ECOG Performance Status	X			X	X	X	X	X	X	X	X	X	X	
12-lead ECG	X												X	
Review of Adverse Events, Disease Related Events and Serious Adverse Events	X			X	X	X	X	X	X	X	X	X	X	X[c]
EORTC QLQ H&N35, EORTC QLQ C30[d]				X	X	X	X	X	X	X			X	X
EQ-5D-5L[e]				X	X	X	X	X	X	X			X	X
Survival Assessment														X
Local Laboratory Tests														
Chemistry		X		X	X	X	X	X	X	X	X	X	X	
Hematology		X		X	X	X	X	X	X	X	X	X	X	
Hepatitis B Surface Antigen and Hepatitis B Core Antibody		X												
Hepatitis C virus antibody		X												
Urinalysis[f]		X											X	

Footnotes defined on the last page of the table

Table 7. Schedule of Assessments for Phase 3

	Screening			Treatment (Week Number)									Follow-up	
Study Procedures	≤ 28 days	≤ 14 days	≤ 72 hour	0	3	6	9	12	15	18	21	24[a]	Safety Within 30 days after last treatment	Long-term (Every 3 months)
PT or INR and PTT or aPTT[g]		X												
T3 (or FT3), FT4, TSH		X		X		X		X		X		X	X	
Urine or Serum Pregnancy Test[h]			X										X	
Central Laboratory Tests														
Optional Blood for Pharmacogenetic Analysis[i]				X										
Blood for Biomarker Analyses[j]				X	X	X	X					X	X	
Blood for HSV-1 Serostatus				X	X	X	X							
Tumor Tissue for PD-L1, HPV Testing and Biomarker Analyses[k]	X													
Optional Tumor Tissue for Biomarker Analyses[l]						X								
Archival Tumor Tissue (if applicable)[m]				X										
Blood for Anti-Pembrolizumab Antibody[n]				X	X		X		X		X		X	X
Blood for Pembrolizumab PK[o]				X	X		X		X		X		X	X
Swab of Herpetic Lesion for qPCR				Within 3 days of occurrence of suspected lesion of herpetic origin										

Footnotes defined on the last page of the table

Table 7. Schedule of Assessments for Phase 3

	Screening			Treatment (Week Number)									Follow-up	
Study Procedures	≤ 28 days	≤ 14 days	≤ 72 hour	0	3	6	9	12	15	18	21	24[a]	Safety Within 28 days after last treatment	Long-term (Every 3 months)
Radiographic Tumor/Response Assessments														
Radiographic (CT, PET/contrast enhanced CT or MRI) Scans and Tumor Assessment by RECIST v1.1[r]	X						X			X			X	X
Radiographic (CT, PET/contrast enhanced CT or MRI) Scans and Tumor Assessment **by irRECIST**[p,q]							X			X			X	X
Optional Photographs of Visible Tumor Lesions	Any Time													
Talimogene Laherparepvec/Placebo[s]				X	X	X	X	X	X	X	X	X		
Pembrolizumab[t]				X	X	X	X	X	X	X	X	X		
Reporting Exposure to Talimogene Laherparepvec														
Exposure of Subject's Household Member or Caregiver	Anytime													
Exposure of Subject's Healthcare Provider	Anytime													

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iCR = complete response (per irRECIST); CNS = central nervous system; EQ-5D-5L = EuroQoL-5D; HPV = human papilloma virus irRECIST = immune-related Response Evaluation Criteria in Solid Tumors; iPD = progressive disease (per irRECIST); PD-L1 = programmed death ligand 1; ECOG = Eastern Cooperative Oncology Group; ECG = electrocardiogram; PT = prothrombin time; INR = international normalized ratio; PTT/aPTT = partial thromboplastin time/activated partial thromboplastin time; T3/FT3 = free tri-iodothyronine; FT4 = free thyroxine; TSH = thyroid stimulation hormone; HSV-1 = herpes simplex virus type 1; PK = pharmacokinetics; qPCR = real-time polymerase chain reaction; CT = computed tomography; PET = positron emission tomography; MRI = magnetic resonance imaging; iPR = partial response (per irRECIST); PRO = patient reported outcomes; SCCHN = squamous cell carcinoma of the head and neck; iSD = stable disease (per irRECIST)

[a] Repeat week 24 procedures and assessments every 3 weeks until end of study treatment, with the exceptions of the thyroid function testing which is required every 6 weeks unless otherwise indicated. Furthermore, blood for biomarker analysis is only required up to week 24 as indicated in the schedule of assessments. 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.

[b] Only subsequent anticancer treatment for SCCHN will be recorded.

[c] See Section 9.2 for long-term follow-up assessments and reporting

[d] Completion of the EORTC QLQ-H&N35 and EORTC QLQ-C30 questionnaires prior to study treatment administration at day 1 of weeks 0, 3, 6, 9, 12, 15, 18, and then every 9 weeks until end of study treatment, and at the safety follow-up visit. During long-term follow-up, for subjects who discontinued treatment for any reason other than confirmed iPD, every effort should be made to complete the questionnaires every 3 months until documentation of confirmed iPD, start of new anticancer therapy, or end of study, whichever occurs first.

[e] The EQ-5D-5L questionnaire will be completed at weeks 0, 3, 6, 9, 12, 15, 18, and then every 9 weeks. until end of study treatment and at safety follow-up visit. For subjects who discontinued treatment for any reason other than confirmed iPD, every effort should be made to complete the questionnaires every 3 months until documentation of confirmed iPD, start of new anticancer therapy, or end of study, whichever occurs first. For subjects with confirmed disease progression, EQ-5D-5L will be collected within 1 to 3 weeks of confirmed disease progression, at safety follow-up, and every 3 months thereafter in long-term follow-up. During long-term follow-up after confirmed iPD or start of new anticancer therapy, if subjects are too ill to self-complete the EQ-5D-5L, collection of EQ-5D-5L can be via telephone interview conducted by trained study staff using a standardized script.

[f] Urine samples for urinalysis will be collected at screening within 14 days prior to enrollment. During treatment urine samples for urinalysis will be collected if clinically indicated. Urine sample for urinalysis will also be collected at the safety follow-up visit.

[g] Blood sample for coagulation will be collected (PT/aPTT measured in seconds and INR as a ratio) at screening within 14 days prior to enrollment. During the treatment phase, close monitoring of coagulation parameters is recommended for subjects on anticoagulant therapy.

[h] Urine or serum pregnancy test to be performed on female of childbearing potential. A urine pregnancy test should be performed within 72 hour prior to enrollment and at the safety follow-up. Note: Additional blood or urine for pregnancy testing (for women of child-bearing potential) may be performed during treatment at the investigator's discretion or as defined in a country-specific protocol supplement at the end of the Appendix Section of the protocol as required per local country's laws and regulatory requirements. If urine pregnancy test result is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

[i] Optional pharmacogenetic blood sampling will be performed prior to study treatment administration if subject has consented to the pharmacogenetics substudy..

[j] Blood samples for biomarker analyses will be collected prior to study treatment administration at the following time points: at day 1 of week 0, week 3, week 6, week 9 and either at time of initial unconfirmed PR, confirmed iPD, or at 24 weeks for subjects with iSD, whichever comes first. A blood sample should be collected at the safety follow-up visit. Refer to Laboratory Manual for blood sample procedures.

[k] Tumor tissue from the primary or metastatic lesion and the associated pathology report must be submitted within 28 days before randomization to the central laboratory for PD-L1, HPV testing, and biomarker analyses, See Section 7.5.2 for further details. Refer to the Laboratory Manual for detailed tissue collection procedures.

[l] Optional tumor tissue biopsy via core needle within 3 days prior to day 1 of week 6 if subject has consented. Refer to Laboratory Manual for detailed tissue collection procedures.

[m] Archival tumor tissue, of any age since diagnosis, that is available in addition to the required baseline tumor sample (Section 7.5.2) should be submitted within 4 weeks after randomization.

[n] Blood for anti-pembrolizumab antibody (also termed immunogenicity) will be collected at week 0 (ie, cycle 1 of pembrolizumab), week 3 (ie, cycle 2 of pembrolizumab), week 9 (ie, cycle 4 of pembrolizumab), week 15 (ie, cycle 6 of pembrolizumab), week 21 (ie, cycle 8 of pembrolizumab) and every 12 weeks (4 cycles of pembrolizumab) thereafter starting at week 33 (ie, cycle 12 of pembrolizumab), at safety follow-up visit (30 [+7] days after discontinuation of study treatment), and again 3 and 6 months after discontinuation of study treatment or until the subject starts new anticancer treatment, whichever is first. All samples should be drawn within 24 hours before infusion of pembrolizumab and at the same time as pre dose trough blood collection for the PK sample.

[o] Blood for PK of pembrolizumab: Predose trough and post-dose peak PK samples will be collected at week 0 (ie, cycle 1 of pembrolizumab). Pre-dose trough samples only will be collected at week 3 (ie, cycle 2 of pembrolizumab), week 9 (ie, cycle 4 of pembrolizumab), week 15 (ie, cycle 6 of pembrolizumab), week 21 (ie, cycle 8 of pembrolizumab) and every 12 weeks (4 cycles) thereafter, starting at week 33 (ie, cycle 12 of pembrolizumab), at safety follow-up visit (30 [+7] days after discontinuation of study treatment), and again 3 and 6 months after discontinuation of study treatment or until the subject starts new anticancer treatment, whichever is first. All trough samples should be drawn within 24 hours before infusion of pembrolizumab. The peak sample should be drawn within 30 minutes after the end of the infusion. A one-time PK sample should also be drawn between 48 to 168 hours after week 0 (ie, cycle 1) dosing.

[p] Throughout the study, radiographic imaging assessments (CT scan, PET/contrast enhanced CT scan, or MRI) must include the neck, chest, abdomen, and all other sites of disease. A CT scan or MRI of the brain should only be performed if signs and symptoms suggestive of CNS metastases are present. During treatment, radiographic imaging will be performed independent of treatment cycle at week 9 (±1 week), week 18 (± 1 week), and then every 9 weeks (±1 week) or more frequently if clinically indicated until confirmed iPD or start of new anticancer treatment. Imaging should not be adjusted for cycle initiation delays and performed according to the calendar. The imaging modality selected (eg, CT or MRI) should remain constant for any individual subject. Radiographic imaging is required at the safety follow-up visit if the subject ended treatment prior to confirmed iPD and has not had radiographic tumor imaging performed within 28 days (+1 week) of the visit. During long-term follow-up, 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 until documentation of confirmed iPD, start of new anticancer therapy, or end of study whichever occurs first. The radiologic imaging assessments are performed locally.

[q] Response (iCR, or iPR) or iPD to be confirmed by second consecutive radiographic assessments no less than 28 days from the date of the first documented response or iPD.

[r] RECIST v1.1 assessments done at screening for eligibility and throughout the study.

[s] Talimogene laherparepvec/placebo will be administered on day 1 of week 0, day 1 of week 3 (+ 3 days), and every 3 weeks (± 3 days) thereafter. The initial dose of talimogene laherparepvec/placebo is up to 8.0 mL of 10^6 PFU/mL. Subsequent doses of talimogene laherparepvec/placebo are up to 8.0 mL of 10^8 PFU/mL. The maximum volume of talimogene laherparepvec administered at any dose is 4.0 mL for any individual lesion. The maximum volume at any treatment visit is 8.0 mL.

[t] Pembrolizumab will be administered at a dose of 200 mg starting at day 1 of week 0, day 1 of week 3 (+ 3 days), and every 3 weeks (± 3 days) thereafter. When talimogene laherparepvec/placebo and pembrolizumab are administered on the same day, it is recommended that talimogene laherparepvec/placebo be administered first.

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Refer to the applicable supplemental (eg, laboratory, imaging,) manuals for detailed collection and handling procedures.

7.2 General Study Procedures

The procedures performed and timing of each study visit are outlined in the Schedule of Assessments (Table 5, Table 6, and Table 7). Details regarding each type of procedure are provided in subsequent subsections. Procedures that are part of routine care are not considered study specific procedures and may be used at screening to determine eligibility.

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

7.2.1 Screening and Enrollment

Informed consent must be obtained before completing any screening procedures ensue. After signing the written informed consent form, the site will register the subject in the IVR system and screen the subject in order to assess eligibility for participation. Screening procedures are to be completed during the screening period within 4 weeks prior to enrollment or randomization. If a subject has not met all eligibility criteria at the end of the 4 week window, the subject will be registered as a screen failure. Screen fail subjects may be eligible for re-screening once as described in Section 7.2.2. Prior to enrollment, subject eligibility must be confirmed with screening procedures. Subjects satisfying eligibility requirements will be enrolled.

7.2.2 Rescreening

Subjects who are unable to complete or meet eligibility requirements on initial screening will be permitted to rescreen once. Rescreened subjects must first be registered as screen failed in the IVR system and subsequently registered as rescreened. Subjects will retain the same subject identification number assigned at the original screening. Once the subject is registered as rescreened, a new 4 week screening window will begin. If the rescreening period begins more than 4 weeks after the original signing of the informed consent form, all screening procedures, including informed consent, must be repeated. If the rescreening occurs less than 4 weeks after the original signing of the informed consent, then only those criteria that were originally failed are required to be repeated.

7.2.3 Treatment

The date of the first dose of talimogene laherparepvec/placebo is defined as day 1 (week 0). All subsequent doses and study visits will be scheduled based on the day 1 date. During treatment, assessments and procedures can be performed within 3 days of the planned visit. It is recommended that dosing occur on the same day of the week (eg, if first dose is administered on Monday, all subsequent doses should be administered on a Monday), however, a ± 3 day dosing and study procedure window is allowed unless otherwise specified (eg, second dose window is + 3 days). Study treatment administration should begin as soon as possible after enrollment via the IVR system but no later than 5 days after enrollment. Study treatment is to be administered after all required study procedures are completed for each visit.

Phase 1b:

The first dose of talimogene laherparepvec will be up to 8.0 mL of 10^6 PFU/mL. The second injection, up to 8.0 mL of 10^8 PFU/mL, will be administered 3 weeks (+3 days) after the initial injection (ie, no sooner than day 22 but should not be delayed more than 3 days after the 3 week time point). All subsequent injections, up to 8.0 mL of 10^8 PFU/mL, will be administered 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 volume at any treatment visit is 8.0 mL.

When talimogene laherparepvec and pembrolizumab are administered on the same day, it is recommended that talimogene laherparepvec be administered first. Refer to Section 6.2.1.

Phase 3:

The initial dose of double-blind treatment is up to 8.0 mL of 10^6 PFU/mL talimogene laherparepvec/placebo (talimogene laherparepvec formulation excipients as described in the Talimogene Laherparepvec Investigator's Brochure). The second dose up to 8.0 mL of 10^8 PFU/mL talimogene laherparepvec/placebo should be administered 21 (+ 3) days after the initial dose. Subsequent doses up to 8.0 mL of 10^8 PFU/mL talimogene laherparepvec/placebo should be given every 3 weeks (± 3 days). The maximum volume of talimogene laherparepvec/placebo administered at any dose is 4.0 mL for any individual tumor lesion. The maximum volume at any treatment visit is 8.0 mL. When talimogene laherparepvec/placebo and pembrolizumab are administered on the same day, it is recommended that talimogene laherparepvec/placebo be administered first.

Phase 1b/3:

Pembrolizumab at a dose of 200 mg will be administered intravenously every 3 weeks (± 3 days). See Section 6.2.2.2 for additional information regarding dosage and administration of pembrolizumab.

7.2.4 Follow-up

7.2.5 Safety Follow–up

All subjects who receive investigational product will complete a safety follow-up visit approximately 30 (+ 7) days after the last dose of study treatment.

7.2.6 Long term Follow-up

After the safety follow-up visits, subjects will enter the long-term follow-up. Subjects will be contacted to assess survival, initiation of additional anticancer treatment and EQ-5D-5L (for phase 3).

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/randomized that is included in the primary OS analysis, whichever comes first. Anticancer therapies for SCCHN and talimogene laherparepvec/placebo related adverse events that occur through the end the long term follow-up will be reported. **The phase 1b subjects will be followed for approximately 36 months after the last subject is enrolled.**

For subjects who discontinued treatment for any reason other than confirmed PD, every effort should be made to collect PROs for phase 3 subjects (QLQ-C30, QLQ-HN35, and EQ-5D-5L), perform radiographic scans for tumor imaging every 12 weeks (± 1 week) until documentation of confirmed iPD (response per irRECIST), start of new anticancer therapy, or end of study, whichever occurs first.

For those subjects who are randomized but do not receive any doses of investigational product, every effort should be made to continue monitoring tumor response status by clinical and radiographic assessments as described in Table 5 and Table 7. They should continue into the long-term follow-up and be followed for survival and subsequent anticancer therapies every 12 weeks (± 28 days) for approximately 36 months after the last subject is enrolled.

7.3 Description of Study Procedures

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

7.3.1 Informed Consent

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

7.3.2 Demographic Data

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

7.3.3 Medical History

The investigator or designee will collect complete medical and surgical history. Medical history will include information on the subject's concurrent medical conditions, clinically significant diseases, surgeries, cancer history (including HPV status if known), reproductive status, smoking history, use of alcohol, and drugs of abuse. The current toxicity grade will be collected for each condition that has not resolved. Squamous cell carcinoma of the head and neck history must date back to original diagnosis. All findings are to be recorded on the medical history Case Report Form (CRF).

7.3.4 Prior Therapies

Prior therapies (eg, prescription drugs, over the counter drugs, herbal or homeopathic remedies, nutritional supplements) that were being taken from 4 weeks prior to screening through informed consent should be collected.

Therapy name, indication, dose, unit, frequency, and start and stop dates will be collected for prior therapies taken for current or prior malignancies.

7.3.5 Concomitant Therapy

All concomitant medications that are administered after the subject has signed informed consent through 30 (+ 7) days after the last administration of study treatment will be recorded in the CRF. Concomitant medications should be assessed on an ongoing basis and recorded at each subject visit. Only subsequent anticancer therapy for SCCHN will be recorded during the long-term follow-up period. Please see Section 6.5 for additional details.

7.3.6 Adverse Events, Disease Related Events, and Serious Adverse Events

Safety event reporting procedures are described in Section 9.2.

7.3.7 Physical Examination

A physical examination will be performed at screening per standard of care. At subsequent visits (or as clinically indicated), limited symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded as adverse events on the adverse event CRF. Physical examination findings should be recorded on the appropriate CRF (eg, medical history, event).

7.3.8 Vital Signs

Vital signs include systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature. It is recommended that subjects 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 the most recumbent position possible. The position selected and temperature location for a subject should be the same that is used throughout the study and document on the vital sign CRF. All measurements are to be recorded on the vital signs CRF.

Vital signs should be obtained prior to study treatment administration, and if necessary, during and after administration of study treatment.

7.3.9 Physical Measurements

Body weight will be recorded in kilograms. Height will be collected in centimeters.

7.3.10 ECG

A 12-lead ECG will be performed per standard of care. Subject must be in a 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 the most recumbent position possible. The ECG must include the following measurements: heart rate, PR interval, QRS, QT, and QTc intervals. The investigator or designated site physician will review all ECGs. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to the sponsor.

7.3.11 ECOG Performance Status

ECOG performance status will be collected as outlined in **Appendix F**.

7.3.12 Exposure to Talimogene Laherparepvec

If a household member, caregiver, or healthcare provider who has had close contact with a subject treated with talimogene laherparepvec/placebo on this study is suspected to have been exposed to talimogene laherparepvec (eg, have or who have had signs or

symptoms suspected to be herpetic in origin or who have been accidentally exposed to talimogene laherparepvec) while the subject is taking talimogene laherparepvec/placebo, the exposure must be reported to the sponsor. Refer to Section 9.4.

7.3.13 Radiographic Tumor Assessment

At screening (baseline) and throughout the study, radiographic tumor imaging assessments must include CT scan, PET/contrast enhanced CT scan, or MRI of the neck, chest, abdomen, and other relevant sites of disease. A CT scan or MRI of the brain will only be performed if signs or symptoms suggestive of CNS metastasis are present. A spiral CT scan of the chest may be obtained but is not a requirement. An MRI or non-contrast CT scan may be used in subjects for whom CT scans with contrast are contraindicated (ie, subjects with contrast allergy or impaired renal clearance.

Imaging will be performed per the Schedule of Assessments (Table 5 and Table 7) or more frequently if clinically indicated until confirmed iPD (response per irRECIST), or start of new anticancer treatment. Response (iCR, or iPR) or iPD is to be confirmed by second consecutive assessments no less than 4 weeks from the date of the first documented response or iPD. Imaging should not be adjusted for cycle initiation delays and performed according to the calendar. The imaging modality selected (eg, CT scan or MRI) should remain constant for any individual subject

Furthermore, the same radiographic procedure used to assess disease sites at screening (baseline) should be used throughout the study (eg, the same contrast protocol for CT scans). All known sites of disease must be documented at screening and re-assessed at each subsequent tumor evaluation. The radiographic tumor imaging assessments and measurements are performed locally and the response will be assessed by the investigator using irRECIST criteria (Appendix D). For phase 3 only, investigators will also be asked to assess and document tumor responses using the standard RECIST v1.1 criteria (Appendix E). However, treatment decisions should NOT be made based on RECIST v1.1.

7.4 Laboratory Assessments

On-treatment tests can be performed within 3 days of the planned visit. Results should be reviewed prior to the administration of study treatment. All tests (except for real-time polymerase chain reaction [qPCR], HSV-1 antibody, tumor biopsy, pembrolizumab PK and ADAs, and blood for biomarkers) are to be performed at the local laboratory. See Table 8 for laboratory analytes to be assessed.

Table 8. Laboratory Analytes

Chemistry	Coagulation	Thyroid Function	Hematology	Other Labs
Sodium	PT (seconds) or INR (ratio)	TSH	Red blood cell	Urine or serum pregnancy test
Potassium	PTT or aPTT (seconds)	T3 (or FT3 per local standard)	Hemoglobin	Urinalysis
Chloride		FT4	Hematocrit	Blood
Calcium			Platelets	Glucose
Magnesium			White blood cell	Protein
Phosphorus			Differential	Specific gravity
Uric acid			• Neutrophils	Microscopic exam (only reflexively for abnormal urinalysis results)
Total protein			• Eosinophils	Hepatitis B surface antigen and Hepatitis B core antibody
Albumin			• Basophils	Hepatitis C virus antibody
Blood urea nitrogen			• Lymphocytes	qPCR for talimogene laherparepvec DNA
Creatinine[a]			• Monocytes	HSV-1 antibody
Total bilirubin				HPV-testing
Direct bilirubin				PD-L1 testing
Alkaline-phosphatase				Anti-pembrolizumab antibody
AST				Pembrolizumab PK
ALT				Biomarker blood
Glucose				Archived tumor tissue
				Fresh tumor biopsy tissue

AST = aspartate aminotransferase; ALT = alanine aminotransferase ; PT = prothrombin time; INR = international normalization ratio; PTT/aPTT = partial thromboplastin time/activated partial thromboplastin time; TSH = thyroid stimulating hormone; T3/FT3=free triiodothyronine ; FT4 = free thyroxine; qPRC = real-time polymerase chain reaction; HSV-1 = herpes simplex virus type-1; HPV = Human papillomavirus; PD-L1 = programmed cell death-1 ligand 1.

[a] Creatinine clearance should be determined per institutional standard. Creatinine clearance need not be determined if the baseline serum creatinine is within normal limits per protocol.

7.4.1 qPCR for Biodistribution and Shedding Samples

At each time point, only if qPCR testing is positive, a TCID50 assay will be performed to evaluate whether the talimogene laherparepvec virus is detectable in the sample. Please refer to the Laboratory Manual for more details.

7.4.2 qPCR for Suspicious Herpetic Lesions

Swab of cold sore, vesicles, and other lesions suspected to be herpetic in origin (if any) must be collected for qPCR testing of talimogene laherparepvec DNA. Subjects 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-1 infection is suspected. A qPCR analysis will be performed on the swab sample by the central laboratory to evaluate whether talimogene laherparepvec DNA is detectable in the sample. Refer to the Laboratory Manual for more details.

7.4.3 Optional Photography Substudy (Selected Phase 1b Sites And Phase 3 Sites)

For sites selected to participate in the photography substudy, photographs of visible lesions may be taken at any time during the study period, or copies of pre-existing photographs may be collected if available. . The sponsor may use, copy, and/or distribute the photographs for educational purposes, in scientific lectures, journal articles, and textbooks. The sponsor may also use the photographs for general commercial purposes and may have the photographs published, circulated, or presented in any way either alone or with other written, printed, graphic, or audio matter to members of the medical, nursing, pharmaceutical and related progressions, as well as to the public at large. The subjects' identity will not be disclosed in any photographs. The sponsor would only show the photographs of subjects without identifying the subject facial characteristics. Any tattoos or other body marks that may identify the subjects will be covered. The sponsor may edit, reduce, enlarge, or otherwise change the photographs. The photographs may have commercial value to the sponsor. Neither the sponsor nor the investigator will compensate the subject for the photographs or the use of the photographs. Refer to the Photography Manual for further instructions.

7.5 Biomarker Sample Collection

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

The sponsor may attempt to develop test(s) designed to identify subjects most like to respond positively or negatively to investigational product(s) (eg, Amgen or non-Amgen investigational product or protocol required therapies).

7.5.1 Blood Samples

Blood samples are to be collected for biomarker analysis prior to study treatment at the following time points: at day 1 of weeks 0, 3, 6, 9, and either at the time of initial unconfirmed **i**PR, confirmed **i**PD, or at week 24 for subjects with **i**SD, whichever comes first. A blood sample should be collected at the safety follow-up visit. Refer to the Laboratory Manual for blood sample procedures.

7.5.2 Tumor Tissue Samples

Tumor tissue biopsies are to be collected and CD8 and PD-L1 will be evaluated to explore molecular mechanisms associated with response or resistance to treatment.

Baseline Tumor Tissue Samples

Phase 1b

Formalin fixed paraffin embedded tumor tissue and associated pathology report sample from the primary or metastatic lesion should be submitted within 4 weeks of enrollment to the central laboratory

Phase 3

Formalin fixed paraffin embedded tumor tissue and associated pathology report from the primary or metastatic lesion will be collected and must be submitted within 28 days before randomization to the central laboratory.

Both Phases

Tissue prioritization is as follows:

(1) Whenever possible fresh tissue from newly obtained biopsy is preferred. If not available, archival tissue may be submitted.

(2) When submitting a previously archived tissue sample, the most recent tissue available is preferred.

(3) Tissue samples from metastatic sites are preferred over those from the primary tumor.

(4) Tissue sample should be from outside of the field of maximum radiation dose delivered, whenever possible.

Note: If no tumor sample is available, the subject should be willing to undergo and submit tissue from a new biopsy. Biopsies should be obtained outside of the field of maximum radiation dose delivered, whenever possible. Subjects with an unevaluable tumor sample for PD-L1 expression testing may obtain a new biopsy and subjects with an unevaluable newly obtained biopsy may undergo re-biopsy at the discretion of the

investigator. If repeat sample is also unevaluable and the subject is otherwise eligible, the investigator may enroll the subject with or without a second re-biopsy.

Week 6 Optional Tumor Tissue Samples

There will be an optional tumor biopsy at week 6 for phase 1b and phase 3 subjects who have consented for the procedure.

Archival tumor tissue

Whenever possible for phase 1b and phase 3 subjects, it is asked that an additional archival sample of any age, preferably predating the baseline tumor tissue by greater than 6 months be submitted to assess for potential changes in biomarkers that may result from cancer progression over time. If archival tumor samples are submitted in addition to required samples for enrollment/randomization, a block of formalin-fixed paraffin-embedded tumor tissue is to be sent to the central laboratory along with the corresponding pathology report within 4 weeks after randomization/enrollment. The tumor block is to be carefully selected by a pathologist or a skilled experience histology associate to include generous tumor tissue using the pathology report as a guide. In lieu of a block, approximately 20 to 25 unstained sections on charged slides from the same block can be submitted. When the samples of tumor tissues are available, analyses of tumor specific mutations or epigenetic changes may be performed (eg, somatic mutations).

7.5.3 HPV Testing

Both phases

HPV status in subjects with oropharyngeal cancer is required.

Oral cavity, hypopharynx, and larynx cancer are not required to undergo HPV testing by p16 IHC as by convention, they are assumed to be HPV-negative.

HPV p16 testing, defined as p16 IHC testing using the CINtec® assay and a 70% cutoff point, can be done at a local laboratory (if the test can be performed locally per standard of care).

Phase 1b

Results of HPV testing performed at a local laboratory and the assay that was used should be recorded on the CRF form.

If previously performed HPV result is not available, sites should be willing to submit for central laboratory HPV testing using the baseline tumor tissue sample submitted.

Phase 3

Results of HPV testing for all subjects with oropharyngeal cancer will be required for stratification. HPV stratification in this trial will be performed using local or central testing of HPV status on tumor tissue samples that were obtained during the screening period. The testing of HPV of tumor specimen for oropharyngeal cancer in this study is defined as p16 IHC testing using the CINtec® assay and a 70% cutoff point. If this assay is unavailable locally, central laboratory HPV testing should be done using the tumor tissue sample submitted within 28 days of randomization. Pembrolizumab PK and Anti-Drug Antibodies (ADA) Testing

Pembrolizumab PK and ADA testing should be collected per the timepoints listed in the Schedule of Assessments (Table 5 and Table 7).

7.6 Optional Pharmacogenetic Studies

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 these optional pharmacogenetic studies include the use of genetic markers to help in the investigation of cancer and/or to identify subjects who may have positive or negative response to talimogene laherparepvec and/or pembrolizumab. For this optional pharmacogenetics analysis, 1 additional **blood** sample will be collected prior to study treatment

7.7 Patient Reported Outcomes (Phase 3 only)

PROs will be assessed using the following 3 questionnaires: EORTC QLQ-C30, QLQ-H&N35, and EQ-5D-5L. The three questionnaires are commonly used, uniformly accepted and validated instruments to evaluate health outcomes in subjects with cancer. PRO questionnaires will be administered to subjects where translations are available.

Subjects should be given sufficient space and time to complete the questionnaire. Family members or friends should not assist the subject in completing the questionnaire. The time required to complete the questionnaire will be less than 10 minutes.

The study coordinator should check the responses for completeness and encourage the subject to complete any missing responses. Detailed instructions relating to the administrative procedures of the questionnaires will be provided to the sites. Subject's

refusal (including reason for refusal) to complete all or any part of the questionnaire should be documented in the study data capture system.

The study coordinator should not interpret any items or the response options. If a subject asks what an item means then repeat the item to them verbatim. Ask the subject to answer the item according to what they think the question means. If they have trouble deciding on an answer, ask them to choose the response that comes closest to how they feel. Subjects have the option of not answering a question if they truly do not understand the question.

PRO questionnaires will be collected via paper. During long-term follow-up, EQ-5D may be collected via telephone (upon identification of the subject).

7.7.1 EORTC QLQ-C30

The EORTC QLQ-C30 Version 3.0 is a 2-page, self-reporting 30-item generic instrument for use in cancer subjects across tumor types (Bjordal et al., 2000). It assesses 15 domains consisting of 5 functional domains (physical, role, emotional, cognitive, social), 9 symptom domains (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties), and a global health status or QOL scale (Aaronson et al, 1993).

7.7.2 EORTC QLQ-H&N35

EORTC QLQ-H&N35 is a head and neck–specific questionnaire designed to assess the quality of life of patients with head and neck cancer. The questionnaire contains 35 items, which can be condensed into 7 multi-item and 11 single-item scales. The questionnaire results in scales that score from 0 to 100. For the function scales, a score of 100 means perfect quality of life, whereas for the symptom scales it would indicate heavy burden.

7.7.3 Health State Utility Estimates

HSU estimates for the purpose of inclusion in a health economic model will be derived using the EQ-5D-**5**L.

The EQ-5D-**5**L questionnaire is a 2-page, generic preference-based QOL measure comprised of a 5-item health status measure and a visual analogue scale (VAS) (Kind, 1996; Rabin and de Charro, 2001) and is used to generate 2 scores. The EQ-5D-**5**L utility score is based on answers to 5 questions that evaluate mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D-**5L** VAS generates a single health status index an analogue scale ranges from 0 to 100 in which

subjects are asked to rate their current health state by drawing a line from a box marked, "Your health today."

7.8 Sample Storage and Destruction

Any blood, swabs, or tumor sample collected according to the Schedule of Assessments (Table 5, Table 6, and Table 7) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure that analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

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

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

Since the evaluations are not expected to benefit the subject directly or alter the treatment course, the results of pharmacogenetics, biomarker development, or other exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

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

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such a project and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See Section 11.3 for subject confidentiality.

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw

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

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments (Table 5, Table 6, and Table 7) including different options for follow-up (eg, in person, by phone/email, through family/friends, in correspondence/communication with other treating physicians, the review of medical records) and collection of data, including endpoints and adverse events. Subjects that have discontinued investigational product and/or protocol required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on study to undergo safety surveillance and/or collection of outcome data. The investigator must document the change to the Schedule of Assessments (Table 5, Table 6, and Table 7) 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).

For subjects who discontinue investigational product without documented iPD and have not initiated a new anticancer therapy, every effort should be made to continue monitoring tumor response status by clinical and radiographic assessments, and to complete PRO questionnaires as described in Table 5 and Table 7.

Those subjects who discontinue investigational product should continue into the long-term follow-up. Subjects will be followed for survival and subsequent anticancer therapies every 12 weeks (± 28 days) for approximately 36 months after the last subject is enrolled. In addition, talimogene laherparepvec- or placebo-related adverse events that occur through the end of the long-term follow-up will be reported.Withdrawal of full consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publically available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

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

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

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

8.3 Reasons for Removal From Treatment or Study

8.3.1 Reasons for Removal From Treatment

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

- subject request
- safety concern (eg, due to an adverse event, ineligibility determined, protocol deviation, non-compliance, requirement for alternative therapy, pregnancy)
- other protocol specified criteria see Sections 6.2.1.1, 6.2.1.2, 6.2.2.1 and 6.2.2.2).
- death
- lost to follow-up
- decision by sponsor (other than subject request, safety concern, lost to follow-up)
- disease progression
- subject's treatment assignment is unblinded during the double-blind phase of the study via the IVR system for the future management of the subject, and subject is not allowed to continue treatment (see Section 5.2)

8.3.2 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

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definition of Safety Events

9.1.1 Disease Related Events

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

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

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

9.1.2 Adverse Events

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

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition or underlying disease (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration more than would be expected, and/or has an association with a significantly worse outcome than expected. A pre-existing condition that has not worsened more than anticipated (ie, more than usual fluctuation of disease) during the study or involves

an intervention such as elective cosmetic surgery or a medical procedure while on study, is not considered an adverse event.

Note: For situations where adverse events are due to SCCHN, the primary tumor type (eg, metastatic SCCHN) should be used, rather than the term “disease progression”.

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

9.1.3 Serious Adverse Events

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

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

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

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

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

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of “other medically important serious event”. Examples of such events could include a new cancer that is not a condition of the study, events associated with an overdose, allergic bronchospasm, convulsions, blood dyscrasias, DILI (see Appendix A

for DILI reporting criteria), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

9.2 Safety Event Reporting Procedures

9.2.1 Reporting Procedures for Disease Related Events

The investigator is responsible for ensuring that all Disease Related Events (serious or non-serious) observed by the investigator or reported by the subject that occur after the first dose of talimogene laherparepvec/placebo or pembrolizumab through the safety follow-up visit (ie, 30 [+7] days after the last dose of talimogene laherparepvec/placebo or pembrolizumab, whichever is later), are recorded on the Event CRF as a Disease Related Event.

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

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

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

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

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

9.2.2 Adverse Events

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

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after the first dose of talimogene laherparepvec/placebo or pembrolizumab through the safety follow-up visit (ie, 30 [+7] days after the last dose of talimogene laherparepvec/placebo or pembrolizumab, whichever is later) are reported using the Event CRF.

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

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

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

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

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

9.2.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events, follow-up to a serious adverse event, including death due to any cause other than progression of the cancer under study, observed by the investigator or reported by the subject that occur after signing of the informed consent through 90 (+7) days after the last dose of talimogene laherparepvec or pembrolizumab, or 30 (+7) days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, are recorded in the subject's medical record and are submitted to Amgen. Additionally, all study drug-related serious adverse events that occur during the long-term safety follow-up period until the

end of study should also be captured in the Event CRF although these events will not be considered treatment-emergent adverse events.

All serious adverse events must be submitted to the sponsor within 24 hours following the investigator's knowledge of the event via the Event CRF.

If the electronic data capture (EDC) system is unavailable to the site staff to report the serious adverse event, the information is to be reported to the sponsor via an electronic Serious Adverse Event Contingency Report Form within 24 hours of the investigator's knowledge of the event. See Appendix B for a sample of the Serious Adverse Event Worksheet /electronic Serious Adverse Event Contingency Report Form. **T**he data must be entered into the EDC system when the system is again available.

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

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

All **n**ew information relating to a previously reported serious adverse event must be submitted to the sponsor within 24 hours following knowledge of the new information. The investigator may be asked to provide additional follow-up information, which may include a discharge summary or extracts from the medical record. Information provided about the serious adverse event must be consistent with that recorded on the Event CRF.

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

To comply with worldwide reporting regulations for serious adverse events, the treatment assignment of subjects who develop serious, unexpected, and related adverse events may be unblinded by the sponsor before submission to regulatory authorities.

The sponsor will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and IRBs/IECs in compliance with all reporting requirements according to local regulatory requirements and procedures.

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

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

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after end of study. However, these serious adverse events can be reported to the sponsor. In some countries (eg, European Union [EU] member states), investigators are required to report serious adverse events that they become aware of after end of study. If serious adverse events are reported, the investigator is to report them to the sponsor within 24 hours following the investigator's knowledge of the event.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting.

9.3 Pregnancy and Lactation Reporting

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

In addition to reporting any pregnancies occurring during the study, investigators should report pregnancies that occur 3 months after the last dose of talimogene laherparepvec or 4 months after the last dose of pembrolizumab.

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

If a female subject becomes pregnant during the study, the investigator should attempt to obtain information regarding the birth outcome and health of the infant.

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

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

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

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

9.4 Reporting of Exposure to Talimogene Laherparepvec/Placebo

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

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

9.5 Pembrolizumab Events of Clinical Interest

Selected adverse events known as Pembrolizumab Events of Clinical Interest (ECI) must be reported to the sponsor within 24 hours of the investigator's knowledge of the event regardless of attribution to pembrolizumab.

For the time period beginning when the consent form is signed until treatment enrollment/randomization, any pembrolizumab ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment, or a procedure.

For the time period beginning at treatment enrollment/randomization through 30 (+7) days following cessation of pembrolizumab treatment, any Pembrolizumab ECI, or follow-up to a Pembrolizumab ECI, whether or not related to pembrolizumab, must be reported within 24 hours to the sponsor.

Pembrolizumab Events of Clinical Interest for this trial include:

- an overdose of pembrolizumab, as defined in Section 9.6
- potential drug-induced liver injury (DILI) from pembrolizumab as defined in Section 9.7

Subjects should be assessed for possible Pembrolizumab ECI prior to each dose.

9.6 Definition of an Overdose of Pembrolizumab for this Protocol and Reporting of Pembrolizumab Overdose

For the purpose of this trial, an overdose of pembrolizumab will be defined as any dose of pembrolizumab equal to or greater than 1000 mg. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, pembrolizumab should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate 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 the sponsor as described in Section 9.2.2. In addition, the adverse event(s) or serious adverse event(s) associated with ("result from") the overdose of pembrolizumab should be reported as an ECI as described in Section 9.5.

9.7 Definition and Reporting of Pembrolizumab Drug-induced Liver Injury

For the purpose of this trial, potential DILI associated with ("resulting from") pembrolizumab will be defined as:

- elevated AST or ALT ≥ 3 x ULN
- AND elevated total bilirubin ≥ 2 x ULN

- AND ALP < 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 found in the separate guidance document entitled, the pembrolizumab Event of Clinical Interest Guidance for Potential DILI in Clinical Trials.

To facilitate appropriate monitoring for signals of DILI associated with pembrolizumab, cases of concurrent DILI according to the criteria specified above require the following:

- The event is to be reported to the sponsor as an adverse event of potential DILI within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate CRF (eg, Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed.
- Workup to confirm DILI should be immediately initiated as described in the pembrolizumab Event of Clinical Interest Guidance for Potential DILI in Clinical Trials document. Any confirmed event of DILI is to be reported as a serious adverse event within 24 hours after confirmation of the event.

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 9.2.2.2.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

10.1.1.1 Primary Endpoints

Phase 1b

- Subject incidence of DLT

Phase 3

- Overall survival (OS): Time from randomization date to the date of death from any cause

10.1.1.2 Secondary Endpoints

Phase 1b

- iORR (iCR+iPR), iCRR, iBOR, iDOR, iDCR, and iPFS (response evaluation by investigator using irRECIST)
- OS
- Subject incidence of treatment-emergent and treatment-related adverse events (all adverse events, grade ≥ 3 adverse events, serious adverse events, fatal adverse events, adverse events and serious adverse events leading to discontinuation of

treatment, and adverse events defined as events of interest) and laboratory abnormalities.

Phase 3

- ORR and PFS (response evaluation by investigator using RECIST v1.1)
- iORR and iPFS (response evaluation by investigator using irRECIST)
- iCRR, iBOR; iDOR, and iDCR (response evaluation by investigator using irRECIST)
- CRR, BOR, DOR, and DCR (response evaluation by investigator using RECIST v1.1)
- 1-year, 2-year, and 3-year survival
- Subject incidence of treatment-emergent and treatment-related adverse events (all adverse events, grade ≥ 3 adverse events, serious adverse events, fatal adverse events, adverse events and serious adverse events leading to discontinuation of treatment, and adverse events defined as events of interest) and laboratory abnormalities.
- Summary scores at each assessment and changes from baseline of PROs as assessed by the EORTC QLQ-C30 GHS/QoL

10.1.1.3 Exploratory Endpoints

Phase 1b

- ORR, CRR, BOR, DCR, and DOR (response evaluation by investigator using modified RECIST v1.1)
- Incidence of clearance of talimogene laherparepvec DNA from blood and urine
- Rate of detection and subject incidence of talimogene laherparepvec DNA and virus from blood, urine, exterior of occlusive dressing, surface of injected lesions, and oral mucosa
- Response rates in injected and uninjected lesions: evaluable lesion incidence of a ≥ 30% decrease in lesion length for ≥ 4 weeks
- Incidence of detection of talimogene laherparepvec DNA in lesions suspected to be herpetic in origin

CCI

Phase 3

- Response rates in injected and uninjected lesions
- Incidence of detection of talimogene laherparepvec DNA in lesions suspected to be herpetic in origin
- Subject incidence of anti-pembrolizumab antibodies
- Serum concentration of pembrolizumab

CCI

- iORR, iCRR, iBOR, iDOR, iDCR, and iPFS (response evaluation by investigator using irRECIST) by baseline PD-L1 status.
- ORR, CRR, BOR, DOR, DCR, and PFS (response evaluation by investigator using RECIST v1.1) by baseline PD-L1 status
- OS, 1-year, 2-year, and 3-year survival by baseline PD-L1 status
- iORR, iCRR, iBOR, iDOR, iDCR, and iPFS (response evaluation by investigator using irRECIST), by baseline HPV status
- ORR, CRR, BOR, DOR, DCR, and PFS (response evaluation by investigator using RECIST v1.1) by baseline HPV status
- OS 1-year, 2-year, and 3-year survival by baseline HPV status

CCI

- Mean scores and changes from baseline of PRO as assessed by EORTC QLQ-H&N35, and EORTC QLQ-C30.
- HSU estimates derived via EQ-5D-**5**L at each assessment in phase 3 and post-progression

10.1.2 Analysis Sets

10.1.2.1 DLT Analysis Set

The DLT analysis set will include DLT-evaluable subjects who have had the opportunity to be on treatment for at least 6 weeks from the initial dosing of study treatment and have received at least 2 doses of talimogene laherparepvec and 2 doses of pembrolizumab in combination, or have a DLT during the DLT evaluation period after at least 1 dose of talimogene laherparepvec and pembrolizumab in combination.

10.1.2.2 Efficacy Analysis Set

The Efficacy Analysis Set (EAS) will be used for the primary efficacy analysis of the phase 1b. It is a subset of the Safety Analysis Set (SAS) where subjects with locoregionally advanced disease with a recurrence < 3 months after prior platinum-containing curatively intended multimodal therapy are excluded.

10.1.2.3 Full Analysis Set

Secondary efficacy analysis for efficacy endpoints of phase 1b part of the study will be conducted on the Full Analysis Set (FAS) defined as all subjects who have received at

least 1 dose of talimogene laherparepvec and 1 dose of pembrolizumab in combination. Efficacy will be analyzed with the FAS overall and excluding subjects in the EAS.

The primary analysis of all efficacy endpoints for phase 3 part of the study, unless noted otherwise, will be conducted on the Global Full Analysis Set (FAS[G]) defined as all randomized subjects as of the date of the last subject randomized from a country other than Japan. All subjects will be analyzed according to treatment to which they are randomized.

10.1.2.4 Safety Analysis Set

The Safety Analysis Set (SAS) will include all enrolled/randomized subjects who received at least 1 dose of talimogene laherparepvec/placebo or pembrolizumab. The Global Safety Analysis Set (SAS[G]) will include all randomized subjects in the FAS(G) that received at least 1 dose of talimogene laherparepvec/placebo or pembrolizumab. These analysis sets will be defined separately for the phase 1b and phase 3. For phase 3 all subjects will be analyzed according to the treatment they received. Note: if applicable, any subjects who did not receive their first dose of pembrolizumab in combination with talimogene laherparepvec but received it later will be analyzed in the talimogene laherparepvec plus pembrolizumab arm.

10.1.2.5 PD-L1 Analysis Set

The PD-L1 positive analysis set will include all randomized subjects that have PD-L1 positive status at baseline. The PD-L1 not positive analysis set will include all randomized subjects that have a PD-L1 not positive status at baseline.

10.1.2.6 HPV Analysis Set

The HPV-negative analysis set will include all randomized subjects that are HPV-negative at baseline. The HPV-positive analysis set will include all randomized subjects that are HPV-positive at baseline.

CCI

10.1.2.8 PRO Analysis Set

The analysis used for EORTC QLQ-C30, EORTC QLQ-HN35, and EQ-5D-5L will be performed using the PRO FAS(G) population, which constitutes randomized subjects defined by the FAS(G) population who have at least 1 PRO assessment available and have received at least 1 dose of the study medication. Subjects in the PRO FAS(G) population will be included in the treatment group to which they are randomized.

10.1.3 Covariates and Subgroups

To explore the robustness of efficacy signal in phase 1b, iORR may also be estimated separately by PD-L1 status (positive/not positive) or other covariates listed below.

Besides the stratification factors for randomization in phase 3 of HPV status at baseline (HPV- negative vs HPV-positive) and ECOG performance status (0 vs 1), the following covariates will be used to examine efficacy and safety in subgroups or in multivariate analyses as appropriate:

- Region (South America vs North America vs. EU vs. Asia vs Other or phase 1b; South America vs North America vs EU vs Japan vs Other Asia vs Other for phase 3)
- Age at baseline: < 50, ≥ 50; < 65, ≥ 65; < 75, ≥ 75 years
- Sex (female vs male)
- Prior smoking (never vs former vs current)
- HSV-1 serostatus (positive vs negative)
- **HPV status (positive vs negative vs unknown) (phase 1b)**
- The sum of diameters of target lesions
- Weight loss >5% in the previous 6 months
- Primary tumor site(oral cavity vs oropharynx vs hypopharynx vs. larynx)
- Brain metastasis status (baseline brain metastasis vs no baseline brain metastasis)
- Prior radiotherapy for the treatment of SCCHN
- Extent of disease (metastatic vs locoregionally recurrent only)
- Prior lines of therapy in recurrent/metastatic setting (0, 1 or 2)
- PD-L1 status at baseline (PD-L1 positive vs PD-L1 not positive)
- Baseline CD8 + T cell density
- Maximum blinded investigational product total volume per treatment administration ≥ 4 mL at highest concentration (yes, no)

10.2 Sample Size Considerations

10.2.1 Sample Size Considerations for Phase 1b

In testing for the null hypothesis H0 that the combination of talimogene laherparepvec and pembrolizumab has a DLT rate ≤ 10% versus the alternative hypothesis (Ha) that the true DLT rate is ≥ 33%, the sample size goal is to have ≥ 80% power for a 1-sided ≤ 10% significance level test to reject H0 when Ha is true (Goldman AI, 1987).

With up to 3 safety interim analyses, the sequential stopping rules shown in Table 1 (Section 3.1.1) gives 81.6% power for a 7.7% 1-sided significance level test. A maximum of 18 DLT-evaluable subjects will be enrolled. If > 18 subjects receive the combination they will contribute to the overall safety analysis, but only the first 18 DLT-evaluable will be considered in the decision to declare the combination safe. Subjects may be replaced if they are not evaluable for DLT to obtain 18 DLT-evaluable subjects (eg, a subject did not receive study treatment, or ended the study treatment before completion of DLT evaluation period for a reason other than experiencing a DLT). The null hypothesis may be accepted and the combination declared safe prior to 18 DLT-evaluable subjects if it can be definitively determined that the stopping rule will not be exceeded with additional subjects.

An expansion cohort of up to an additional 22 treated subjects will be enrolled so there will be 40 treated subjects in total. The decision to proceed to phase 3 will consider safety data in all treated subjects and efficacy among all treated subjects excluding those with locoregionally advanced disease with disease progression or recurrence < 3 months after prior platinum-containing curatively intended multimodal therapy. The efficacy analysis is expected to include approximately 27 subjects. The decision to proceed to phase 3 will consider, for example, long-term tolerability and minimum efficacy consistent with pembrolizumab monotherapy historical data.

The main efficacy endpoint in the phase 1b for the phase 3 decision will be the iORR (response per irRECIST by investigator assessment) with or without confirmation of response. Given the observed iORR, the Bayesian posterior probability will be calculated that the true combination iORR exceeds the expected iORR for pembrolizumab by an absolute amount (delta). The expected iORR for pembrolizumab in the study population with 9 weeks minimum potential follow-up is approximately 11% and will be represented by a beta(2.2,17.8) distribution with mean 0.11 and precision 20.0. The iORR for the combination will be represented by a beta(0.2,1.8) distribution with mean 0.11 and precision 2.0. Figure 1 provides the posterior probability

of a delta increase from 0% to 30% in 5% increments for an observed iORR ranging from 11.1% (3/27) to 51.9% (14/27). Figure 2 provides the delta mean and 90% credible region of the absolute iORR increase of combination over pembrolizumab.

Figure 1. Probability of a Combination Delta Absolute Objective Response Rate Increase Over Pembrolizumab

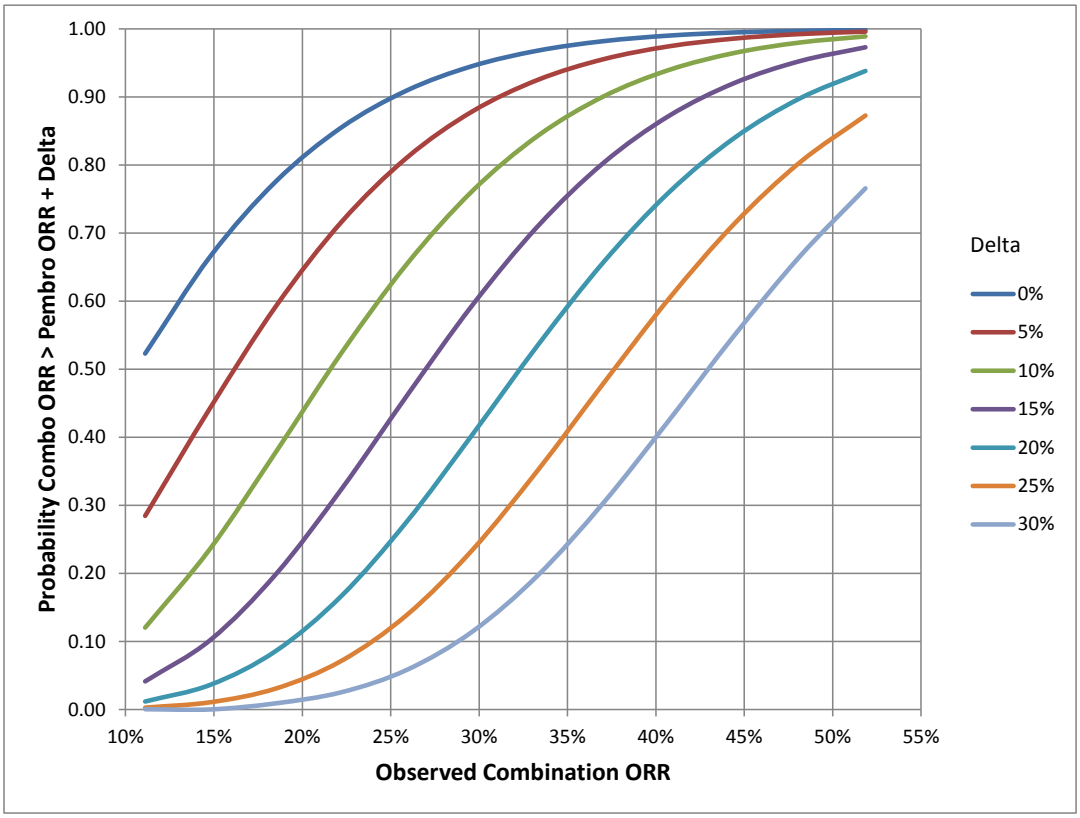
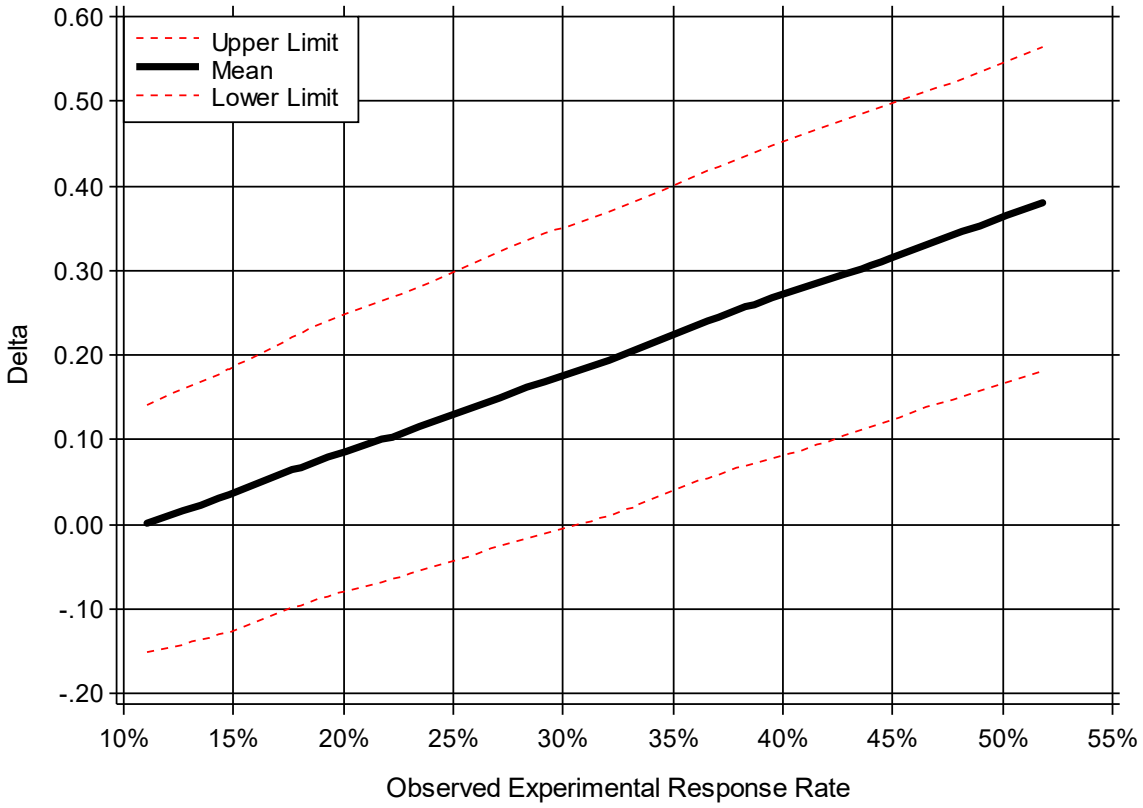


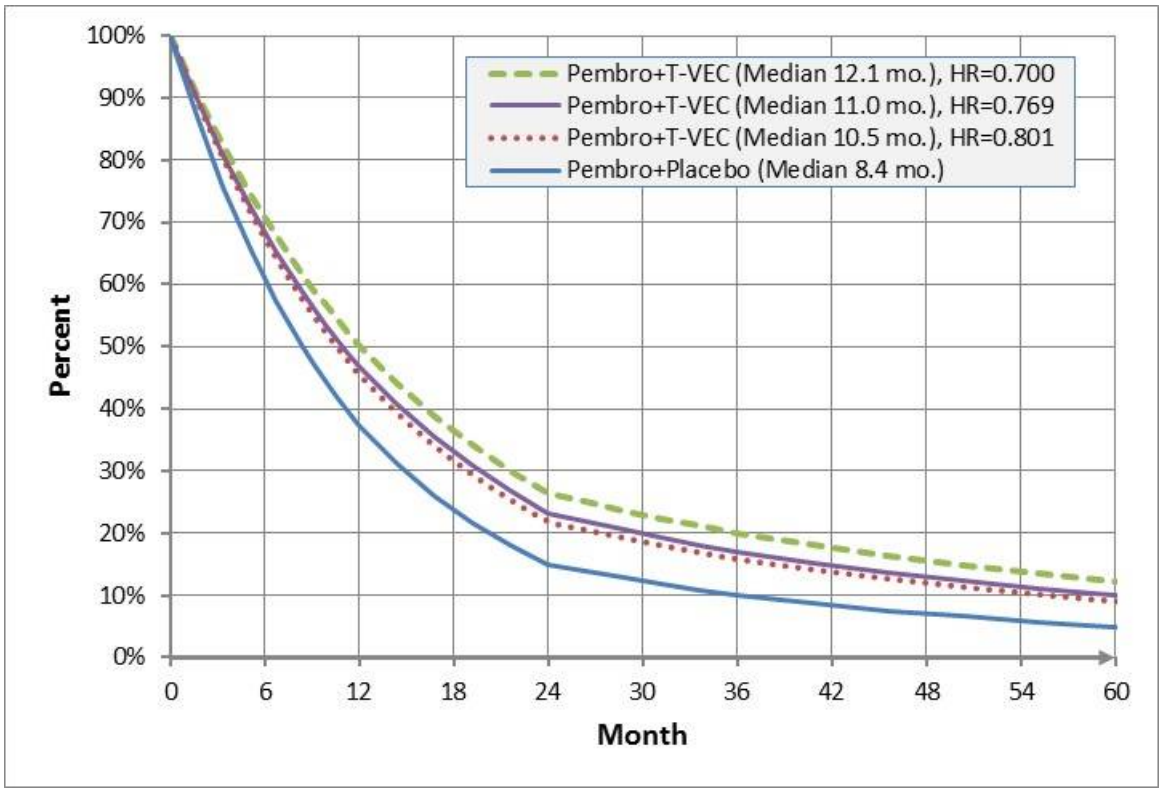
Figure 2. Delta Mean and 90% Credible Region of Absolute Objective Response Rate Increase of Combination Over Pembrolizumab



10.2.2 Sample Size Considerations for Phase 3

The primary endpoint for phase 3 is OS. A hazard ratio (HR) (talimogene laherparepvec with pembrolizumab/placebo with pembrolizumab) of 0.7 for OS is hypothesized in the FAS(G). Assuming OS follows a piece-wise exponential distribution (Figure 3), the hypothesized HR translates into a relative increase of 43% (absolute increase of 3.7 months) in median OS from 8.4 to 12.1 months. The minimum statistically significant OS effect corresponds to an HR of 0.769 (increase of median OS of 2.6 months, 8.4 to 11.0) at the OS interim analysis and 0.801 (increase of 2.1 months, 8.4 to 10.5) at the OS primary analysis.

Figure 3. Overall Survival Assumptions



HR = hazard ratio; pembro = pembrolizumab; T-VEC = talimogene laherparepvec

Median OS (pembrolizumab) = 8.4 months; p(t) = **survival** rate at month t; p(12) = 0.373, p(24)= 0.15, p(36)=0.10, p(60)=0.05, and p(80)=0.04 constant hazard in each interval between 5 consecutive pieces; a constant hazard ratio across all pieces.

The overall Type 1 error rate is 2-sided 0.05. The event goal for OS to achieve 90% power for a 2-sided 0.05 significance level test is 336 (Lan and DeMets, 1983). Assuming approximately 75% of subjects have an OS event at the time of OS primary analysis, the sample size is estimated to be 450 (225 per arm). The OS event goal is adjusted for the interim efficacy analysis but not for the interim futility assessment; however, the power loss due to futility is < 1% if considered binding. Assuming 50% of cumulative enrollment is accrued after 2/3 of total enrollment period (that is, a concave shape of the cumulated enrollment curve) and exponential distributions for loss to follow-up with an annual rate of 5% per year for OS, Table 9 displays the timing of analyses based on an average enrollment rates at 21 subjects per month.

Table 9. Timing of Primary Analysis for OS (at 336 events) in the Phase 3 Study

Average Enrollment Rate	Enrollment Duration (month)	OS Interim Analysis DCO (month)	OS Primary Analysis DCO (month)
21 /month	21	**30**	**38**

OS = overall survival; DCO = data cut-off**, interim and primary after 280 and 336 events, respectively**

In addition to the hypothesis test for the primary endpoint, statistical tests for the secondary endpoints of ORR, PFS, iORR, and iPFS will be performed conditional on rejecting the OS null hypothesis. Table 10 shows event goals (or analysis time) based on hypothesized effect sizes and simulated powers for testing 5 endpoints. The simulated powers are based on the Maurer-Bretz graphical multiple testing procedure (Maurer and Bretz, 2013) assuming a concurrent primary analysis of all hypotheses. Details of the multiple testing procedure are described in Section 10.5.1.

Table 10. Hypothesized Effect Sizes and Hypothesis Test Powers

Hypothesis	Effect Size	Primary Analysis Timing	Simulated Power[a]
H_1 (OS)	HR = 0.70	336 events in FAS(G)	90%
H_2 (ORR): 20% vs 40%	OR = 2.67	FAS(G) with 19 weeks minimum potential follow-up	90%
H_3 (PFS)	HR = 0.70	360 events in FAS(G)	84%
H_4 (iORR): 20% vs 45%	OR = 3.27	FAS(G) 19 weeks minimum potential follow-up	90%
H_5 (iPFS)	HR = 0.65	336 events in FAS(G)	88%

FAS(G) = Global Full Analysis Set; H = hypothesis; HR = hazard ratio; iPFS = progression-free survival (per irRECIST); iORR = objective response rate (per irRECIST); OR = odds ratio; OS = overall survival; ORR = objective response rate; PFS = progression-free survival

[a] Simulated power (10,000 repetitions) using version 0.8.10 qMCP R package with a correlation of 0.67 between H1/H2, H1/H3, H2/H4, and a correlation of 0.25 between H1/H3, H1/H5, H2/H5, H2/H3, H3/H4, and H4,H5 test statistics.

Assuming exponential PFS, the hypothesized PFS HR of 0.70 translates into a relative increase of 43% (absolute increase of 1.6 months) in median PFS time from 3.8 to 5.4 months. Odds ratios of 2.67 and 3.27 are hypothesized for ORR and iORR, respectively, in the phase 3 part of the study assuming a 20% rate in the placebo with pembrolizumab arm and 40% and 45%in the talimogene laherparepvec with pembrolizumab arm. Assuming exponential iPFS, the hypothesized iPFS HR of 0.65

translates into a relative increase of 54% (absolute increase of 2 months) in median iPFS time from 3.8 to 5.8.

10.3 Access to Individual Subject Treatment Assignments by Sponsor or Designees

Unblinding and potentially unblinding information for subjects and investigators should not occur prior to the study being formally unblinded (eg, the formal unblinding may occur at the final analysis rather than at the interim or primary analysis) except as specified (eg, Section 5.2 and Section 9.2.2). The study team, with exceptions noted above, will remain blinded until either results of the OS interim analysis are communicated or otherwise the OS primary analysis. To support the review of unblinded safety and efficacy data by the Data Monitoring Committee (DMC), an external biostatistics group will be responsible for analyzing the data per the DMC charter. The sponsor study personnel will remain blinded with exceptions where necessary for study conduct (eg, processing and analyzing biomarkers, regulatory safety reporting requirements).

10.4 Planned Analyses

10.4.1 Interim Analyses

DLT interim safety analyses are planned and conducted by the study team for the phase 1b, with data being review by a DLRT.

Interim analysis of safety monitoring and futility analysis based on OS prior to the primary analysis of OS in phase 3 will be conducted by an external independent biostatistics group and reviewed by the DMC per the DMC charter. The study team is responsible for conducting the primary analysis of OS and all subsequent analyses.

10.4.1.1 DLT Safety Analysis (Phase 1b)

The planned interim safety data reviews in phase 1b to evaluate DLT will be conducted according to timing/rules described in Table 1 (Section 3.1.1). Data will be reviewed by a DLRT.

10.4.1.2 Interim Safety Analysis (Phase 3)

Two planned interim safety data reviews will occur after approximately 40 and 100 subjects have been enrolled in phase 3 and have had an opportunity to be followed up for at least 6 weeks after receiving study treatment and approximately every 6 months after the DMC meeting for the OS interim analysis. Survival data may be reviewed by the DMC from a safety perspective, therefore no multiplicity adjustment is needed. Monitoring guidelines will be provided in the DMC charter. An interim safety

data review will also occur that includes the first 8 subjects enrolled with 3 or more randomized into treatment arm from Japan in the phase 3 part of the study and have had the opportunity to be followed for at least 6 weeks after receiving study treatment. Additional analyses may be conducted for Japan enrolled subjects as needed for regulatory or safety.

An additional, interim safety data review will occur when at least 10 subjects have received at least one treatment with a total volume >4 ml of 10^8 PFU/mL talimogene laherparepvec plus pembrolizumab and have had the opportunity to be followed up to 6 weeks after receiving the > 4 mL dose of 10^8 PFU/mL. Data will be reviewed by the DLRT if it includes phase 1b subjects only, otherwise it will be reviewed by the DMC.

It is not planned for the enrollment/randomization to be suspended during these ongoing phase 3 safety analyses.

10.4.1.3 Interim OS Efficacy and Futility Analysis (Phase 3)

OS Efficacy

An OS interim efficacy analysis is planned when approximately 280 events have been observed. The OS null hypothesis H_1 will be tested at a nominal alpha level determined by the Lans DeMets type spending function approximating the O'Brien-Fleming stopping boundary (O'Brien and Fleming, 1979). Assuming exactly 280 and 336 events at the interim and primary analysis, the interim and primary analysis nominal alpha levels will be 2.81% and 4.19%, respectively. The timing of the interim analysis was selected to ensure approximately 70% power in a potential scenario in which there is a non-constant OS effect with HR = 0.95 prior to 3 months and HR = 0.618 thereafter. The expected observed HR for this lag effect scenario is 0.718 and 0.700 at 280 and 336 events. Overall power for the lag effect scenario is about 89% whether or not futility is considered binding. If the OS treatment effect is constant with HR = 0.700, then the interim power will be about 78%.

OS Futility

If the null OS hypothesis H_1 is not rejected at the interim analysis, then OS futility will be evaluated by the DMC. The futility criterion will be an observed HR > 0.92. If there is no treatment effect on OS (HR of 1.0), there is a 76% probability of declaring OS futile; however, the probability of falsely declaring futility is only about 1% given a **constant** OS HR of 0.70 and it is about 2% for the above lag effect scenario. The futility analysis in the phase 3 study will be non-binding.

The null hypothesis tests for ORR, PFS, iORR, and iPFS will be tested if the OS null hypothesis H_1 is rejected at either the OS interim or primary analysis. The analysis of ORR and iORR will include the subset of the FAS(G) with at least 19 weeks minimum potential follow-up (ie, week 18 response assessment +1 week window). If the null OS Hypothesis, H_1, is rejected at the interim analysis, the study will continue to the OS primary analysis (ie, follow-up continued), if required, to perform the primary analysis for any secondary hypothesis that had an interim analysis at the OS interim analysis with its null not rejected.

At the time of the interim analysis, Amgen senior management will make the decision to unblind the study team based on the DMC's recommendation.

Interim versus Primary Efficacy Analysis of Secondary Hypothesis

The earliest planned OS analysis will be considered primary for ORR and iORR that includes at least 390 subjects in the ORR and iORR analyses; otherwise, interim analyses of ORR and iORR will be performed with an O'Brien-Fleming nominal alpha level and the primary analysis of ORR and iORR will be performed at the first subsequent planned OS analysis that includes all FAS(G) subjects in the ORR and iORR analyses (ie, the OS primary or final analysis).

The earliest planned OS analysis will be considered primary for PFS that includes at least 330 PFS events; otherwise, an interim analysis of PFS will be performed with an O'Brien-Fleming nominal alpha level and the primary analysis of PFS will be performed at the first subsequent planned OS analysis with at least 360 PFS events.

The earliest planned OS analysis will be considered primary for iPFS that includes at least 300 iPFS events; otherwise an interim analysis of iPFS will be performed with an O'Brien-Fleming nominal alpha level and the primary analysis of iPFS will be performed at the first subsequent planned OS analysis with at least 336 iPFS events.

Table 11. Possible Hypothesis Tests at the Two-planned Analyses

Planned Efficacy Analyses for OS Primary Endpoint			Testing of Secondary Hypothesis					
	Trigger		ORR/iORR		PFS		iPFS	
Analysis	# of events[a]	Analysis Type	N[a]	Analysis Type	# of events[a]	Analysis Type	# of events[a]	Analysis Type
#1	280	IA	< 390	IA	< 330	IA	< 300	IA
#2	336	PA	≥ 390	PA	≥ 330	PA	≥ 300	PA

ORR = objective response rate (per RECIST v1.1); iORR = objective response rate (per irRECIST); OS = overall survival; PFS = progression-free survival (per RECIST v1.1); iPFS = progression-free survival (per irRECIST); IA = interim analysis; PA = primary analysis
[a] In the Global Full Analysis Set (FAS[G]).

10.4.2 Blinded Independent Central Review for Secondary Endpoints

A blinded Independent Central Review (BICR) by a third party imaging laboratory of the tumor imaging data will be considered in the event of a statistically and clinically significant investigator assessed RECIST v1.1 ORR and/or PFS effect. An initial audit will be performed with approximately 116 (26%) randomly selected subjects from the FAS(G).

The investigator assessed estimate of the ORR effect in the FAS(G) will be considered consistent with a BICR assessed estimate if a high degree of concordance is observed at the subject level in the initial audit sample for achievement of an objective response pooling all subjects. Specifically, consistency will be declared if the null hypothesis of a kappa concordance statistic of 0.65 or less for an objective response is rejected at a 1-sided 2.5% significance level. Assuming an overall ORR of 30% and a true kappa of 0.90, the initial audit size will provide approximately 90% power and rejection of the null hypothesis will require and observed kappa statistic of at least 0.77, 89% agreement, and a maximum investigator versus BICR ORR absolute difference about 11% in the audit sample.

The consistency of the investigator-assessed estimate of the PFS effect in the FAS(G) with a BICR-assessed estimate will be evaluated with a 2-stage procedure (Dodd et al 2011). The PFS consistency criterion will be achievement of a 1-sided 95% CI for the BICR-assessed PFS log HR below zero. The initial audit sample would provide a greater than 80% probability of achieving the PFS consistency criterion for Stage 1 of the procedure if the investigator-assessed PFS HR is 0.70 in the FAS(G) with 360 events and the correlation is 0.85 between the

investigator- and BICR-assessed PFS log-HR. The audit size for Stage 1, however, will be re-calculated based on a bootstrap estimate of the correlation obtained from the initial audit and the observed investigator-assessed PFS HR in the FAS(G). Stage 1 will be considered with a complete-case BICR if the final audit size exceeds 300 subjects, 67% of the FAS(G). Stage 1 may alternatively be assessed with the initial audit if it is not feasible to achieve an 80% probability of consistency.

10.4.3 Dose Level Review Team

A DLRT consisting of the Sponsor study team, including at least one medical monitor, safety representative, and biostatistician, at least one representative of the Merck study team, and at least one investigator participating in the study who has recruited subjects into the phase 1b part of the study, will review the safety data to evaluate possible drug effects and DLT. The DLRT will recommend either to enroll more subjects for DLT evaluation in phase 1b, to prematurely stop enrollment into phase 1b, or to declare that the combination is tolerable based on the criteria described in Table 1.

10.4.4 Data Monitoring Committee

An independent, external to the sponsor, multidisciplinary DMC consisting of a biostatistician and 2 clinicians that collectively have experience in the management of subjects with SCCHN and in the conduct and monitoring of randomized clinical trials will be established before the start of the phase 3 part of the trial. The DMC will monitor the overall conduct of the phase 3 trial including OS futility based on the criterion in Section 10.4.1.3.

10.4.5 Primary Analysis

10.4.5.1 Primary Analysis Phase 1b

For the phase 1b part of the study, the primary analysis will occur when the last subject enrolled has had the opportunity to complete the 9-week response assessment.

10.4.5.2 Primary Analysis Phase 3

For the phase 3 part of the study, the timing for the primary analysis of OS will be event-driven based on the FAS(G). The event goal for OS is 336. Detailed approximate timings of the analyses are shown in Table 9.

10.4.6 Follow-Up Analysis for Phase 1b

For the phase 1b part of the study, the primary analysis will be repeated 1 year after the last subject enrolled.

10.4.7 Final Analysis

The final analysis of the study will be conducted after the last subject enrolled has had the opportunity to complete the long-term follow-up (ie, 36 months after the last subject is **enrolled** in the FAS.

10.5 Planned Methods of Analysis

10.5.1 General Considerations

For the phase 1b part of the study, the DLT analysis set will be used to summarize the subject incidence of DLT and, unless specified otherwise, the SAS will be used for all analyses of safety. The EAS, FAS, and the FAS excluding subject in the EAS will be used for all efficacy analyses.

For the phase 3 part of the study, the efficacy analyses will be conducted on the FAS(G). Treatment effects on efficacy endpoints will be evaluated and compared between the 2 treatment arms according to the treatment as randomized. Formal treatment comparisons will be performed on the primary endpoints and the 4 key secondary endpoints. The SAS(G), unless specified otherwise, will be used for all analyses of safety in the phase 3. Descriptive efficacy and safety analyses of subjects randomized after the global last subject enrolled (LSE[G]) will be provided separately at the time of the OS interim and primary analyses.

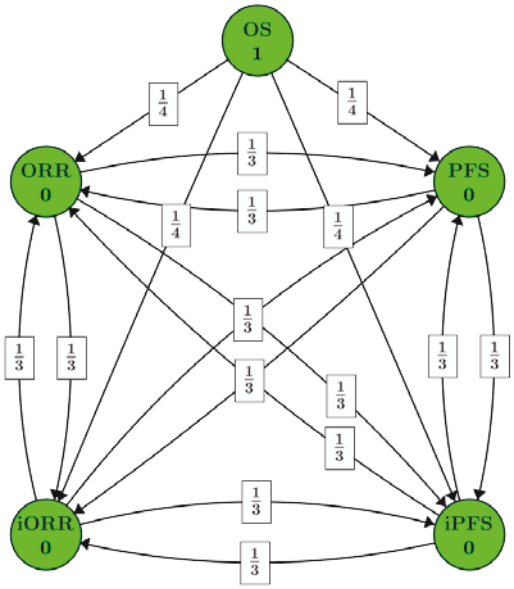
In principle, summary statistics including mean, standard deviation, median, first and third quartiles, will be provided for continuous variables. Frequency and percentage will be summarized by treatment arm for binary and categorical variables. Proportions and the corresponding 95% confidence intervals will be based on normal approximations and the treatment comparison will be based on a Cochran-Mantel-Haenszel test. Exact tests will be considered for subgroup analyses when the cell size is considered small. Time-to-event endpoints will be estimated using the K-M method. Stratified Log-rank test statistics and associated p-values will also be calculated. Hazard ratios will be estimated using stratified Cox PH models.

Descriptive statistics will be provided for efficacy, safety, talimogene laherparepvec DNA, and biomarker endpoints as appropriate.

Multiple statistical hypothesis tests will be conducted which include testing for the primary endpoint of OS and the 4 secondary endpoints (ORR, PFS, iORR, and iPFS response evaluation by investigator using RECIST v1.1 and irRECIST) at multiple analysis time points. To control the study-level overall Type I error, a graphical multiple

testing procedure for group-sequential tests will be utilized (Maurer and Bretz, 2013). No updated information (eg, additional events or subjects) will be used if a hypothesis is re-tested after its primary analysis. A hypothesis can be re-tested repeatedly with a different nominal level that is propagated from rejecting other hypothesis test(s). Figure 4 illustrates the Maurer-Bretz multiple testing procedure with initial α allocation specified as a fraction of the overall study α level. Each hypothesis is represented by a circle. A 0 fraction in the circle indicates a hypothesis that is tested conditional on rejection of another hypothesis. The fractions on the directed arrows connecting 4 hypotheses indicate the proportion of α propogated from one hypothesis to the other when its hypothesis is rejected. Hypotheses are rejected sequentially based on the smallest p-value.

Figure 4. Initial Graph of Maurer-Bretz Multiple Testing Procedure



iORR = objective response rate per irRECIST; iPFS = progression-free survival by irRECIST; ORR = objective response rate; OS = overall survival; PFS = progression-free survival

Further details regarding the derivation of nominal significance levels for each hypothesis test at the planned analyses will be provided in the Statistical Analysis Plan.

10.5.2 Primary Efficacy Endpoint

Phase 1b

The subject incidence of DLT will be summarized using the DLT analysis set.

Phase 3

The efficacy analyses will be conducted on the FAS(G). Treatment effects on efficacy endpoints will be evaluated and compared between the 2 treatment arms according to the treatment as randomized.

For analysis of the primary endpoint OS, a stratified log-rank test will be used as the primary method for testing the null hypothesis of no treatment difference. The randomization factors, along with PD-L1 status at baseline (PD-L1 positive vs PD-L1 not positive), will be used as stratification factors. A hazard ratio will be estimated using the Cox proportional hazards (PH) model stratified by the randomization factors per IVR and PD-L1 status at baseline with Efron's method (Efron 1977) used to handle ties. Kaplan-Meier time to event curves will be presented based on randomized treatment arm.

Statistical testing of OS will follow the multiple hypothesis testing procedure described in Section 10.5.1.

Covariates to define subgroups for analysis of efficacy endpoints will include, but not be limited to, the randomization stratification factors.

10.5.3 Secondary Efficacy Endpoints

All endpoints of the phase 1b will be descriptively analyzed.

ORR and iORR will be treated as binary endpoints and summarized by treatment arm as randomized with associated 95% CIs, and with treatment comparisons based on the Cochran-Mantel-Haenszel test stratified by the randomization stratification factors and PD-L1 at baseline. Following the intent-to-treat principle, subjects who do not have any follow up tumor assessments will be determined to be non-complete responders. Analysis of PFS and iPFS will follow the analysis described for the primary endpoint of OS.

Hypothesis testings for ORR, PFS, iORR, and iPFS are described in the multiple testing procedure in Section 10.5.1. Analyses of the remaining secondary endpoints in phase 3 will be descriptive.

CRR, iCRR, DCR, and iDCR will be summarized by treatment arm as randomized (phase 3). Subjects who do not have any follow-up tumor assessments will be determined to be non-responders for CRR and iCRR or to not have had a response of

stable or better for DCR and iDCR. DOR and iDOR among responders will be analyzed and estimated using the Kaplan-Meier method.

10.5.4 Safety Endpoints

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

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

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

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

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. Summaries and statistical analyses of ECG measurements are not planned.

The qPCR analysis result of talimogene laherparepvec DNA in swab samples taken from exterior of occlusive dressing, surface of injected lesions, and oral mucosa suspected to be herpetic in origin (if any) in phase 1b samples will be summarized. The incidence and percentage of subjects who develop anti-pembrolizumab antibodies (binding and if positive, neutralizing) at any time will be tabulated.

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

10.5.5 PRO Endpoints

The PRO analyses will be conducted on FAS(G) population. Summary scores at each assessment and changes from baseline of PROs as assessed by EORTC QLQ-H&N35,

EORTC QLQ-C30 questionnaire subscales will be reported. The calculation of scores will be based on the questionnaire's standard scoring guidelines. Methods for assessing and handling missing data together with the full details the PRO analyses will be provided in a supplemental statistical analysis plan (SSAP). Comparisons between groups for the QLQ-C30 GHS/QoL subscale (secondary endpoint) and select subscales from the QLQ-C30 and QLQ-HN35 will be analyzed as per the PRO SSAP.

10.5.6 Health State Utility Estimates

For the EQ-5D-5L questionnaire, two scores will be estimated; the utility score calculated from the 5 domains using a scoring algorithm and the VAS score based on the 0-100 feeling thermometer. Changes from baseline will be summarized and at specified time points of interest, differences between treatment groups for each defined score will be analyzed. The calculation of scores and methods for handling missing data will be based on the questionnaire's standard scoring guidelines. Details for deriving the HSU estimates and the full analysis plan will be provided in the PRO SSAP.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

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

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

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

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

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

11.2 Institutional Review Board/Independent Ethics Committee

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

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

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

11.3 Subject Confidentiality

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

Subjects are to be identified by a unique subject identification number.

Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.

On the CRF demographics page, in addition to the unique subject identification number, include the age at time of enrollment/randomization.

For Serious Adverse Events reported to the sponsor, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).

Documents that are not submitted to the sponsor(eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

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

11.4 Investigator Signatory Obligations

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

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

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

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

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

The sponsor reserves the right to terminate the study at any time. Both the sponsor and the Investigator reserve the right to terminate the Investigator's participation in the study according to the study contract. The investigator is to notify the IRB/IEC in writing of the

study's completion or early termination and send a copy of the notification to the sponsor.

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

12.2 Study Documentation and Archive

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

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

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

CRF entries may be considered source data if the CRF is the site of the original recording (ie, there is no other written or electronic record of data). In this study, EQ-5D-5L, QLQ-C30, and QLQ-H&N35 can be used as source documents.

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 the sponsor and/or applicable regulatory authorities.

Elements to include:

- Subject files containing completed CRFs, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and the sponsor

- Investigational product-related correspondence including Proof of Receipts (POR), Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable.
- Non-investigational product(s) and or medical device(s) documentation, as applicable.

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

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

12.3 Study Monitoring and Data Collection

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

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

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

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

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the CRFs must be maintained and readily available.
- Updates to CRFs will be automatically documented through the software's "audit trail".

- To ensure the quality of clinical data across all subjects and sites, a clinical data management review is performed on subject data received by the sponsor. During this review, subject data are checked for consistency, omissions, and any apparent discrepancies. In addition, the data are reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries are created in the EDC system database for site resolution and subsequently closed by the EDC system or by a sponsor reviewer.
- The investigator signs only the Investigator Verification Form for this EDC study or the investigator applies an electronic signature in the EDC system if the study is set up to accept an electronic signature. This signature indicates that investigator inspected or reviewed the data on the CRF, the data queries, and agrees with the content.

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

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (Table 5, Table 6, and Table 7) the investigator can search publically available records [where permitted]) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

12.5 Language

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood. CRFs must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language.

12.6 Publication Policy

To coordinate dissemination of data from this study, Amgen encourages the formation of a publication committee consisting of several investigators and appropriate Amgen staff,

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

Authorship of any publications resulting from this study will be determined on the basis of the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (International Committee of Medical Journal Editors, 2013, updated 2014), which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, and 3.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

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

12.7 Compensation

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

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14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

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

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

Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of Drug Induced Liver Injury (DILI), cases of concurrent AST or ALT and total bilirubin and/or INR elevation according to the criteria specified in Section 6.4 require the following:

- The event is to be reported to the sponsor 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 CRF (eg, Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to the sponsor.

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 9.2.2.2.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) is/are withheld (either permanently or conditionally) due to potential DILI as specified in Section 6.4.1 and Section 6.4.2 or who experience AST or ALT elevations > 3 x ULN 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 total bilirubin > 2x ULN or INR > 1.5, retesting of liver tests, bilirubin (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 total bilirubin:
  - Obtain complete blood count with differential to assess for eosinophilia
  - Obtain serum total immunoglobulin IgG, Anti-nuclear antibody, Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 to assess for autoimmune hepatitis
  - Obtain serum acetaminophen (paracetamol) levels
  - Obtain 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
  - Obtain viral serologies
  - Obtain CPK, haptoglobin, LDH, and peripheral blood smear
  - Perform appropriate liver imaging if clinically indicated
- Obtain appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Obtain hepatology consult (liver biopsy may be considered in consultation with an hepatologist)
- Follow the subject and the laboratory tests (ALT, AST, total bilirubin, INR) until all laboratory abnormalities return to baseline or normal. 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 corresponding CRFs.

Appendix B. Sample Serious Adverse Event Report Form

AMGEN Study # XXXXXXXX AMG XXX	**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 death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Is event serious?	If serious, enter Serious Criteria code (See codes below)	Relationship Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP? <Device> No ☐ Yes ☐ / <Device> No ☐ Yes ☐ / <Device> No ☐ Yes ☐ / <Device> No ☐ Yes ☐	Outcome of Event 1-Resolved 2-Not resolved 3-Fatal 4-Unknown	Check only if event is related to study procedure eg, biopsy
				☐ Yes ☐ No				
				☐ Yes ☐ No				
				☐ Yes ☐ No				

Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required/prolonged hospitalization; 04 Persistent or significant disability /incapacity; 06 Congenital anomaly / birth defect; 08 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 #
<<IP/Device>>	☐blinded ☐open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<<IP/Device>>	☐blinded ☐open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

AMGEN Study # XXXXXXXX AMG XXX	**Electronic Serious Adverse Event Contingency Report Form** For Restricted Use

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 # XXXXXXXX AMG XXX	**Electronic Serious Adverse Event Contingency Report Form** For Restricted Use

Site Number	Subject ID Number

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

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

Appendix C. Pregnancy and Lactation Notification Worksheets

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: _____

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

2. Contact Information

Investigator Name _____ Site # _____

Phone (____)_____ Fax (____)_____ Email _____

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

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

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

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

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

5. Pregnancy Information

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

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

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

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

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

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

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

_____

_____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

Effective Date: March 27, 2011

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Print Form

AMGEN® Lactation Notification Worksheet

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

1. Case Administrative Information

Protocol/Study Number: _____

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

2. Contact Information

Investigator Name _____ **Site #** _____

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

Institution _____

Address _____

3. Subject Information

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

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

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

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

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: 03 April 2012, version 2.

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Appendix D. Radiological Guidance for Assessment of Disease Response

Initially developed in 2000 and modified in 2009, RECIST guidelines provide a standard approach to solid tumor measurement and definitions for objective assessment of change in tumor size in adult and pediatric cancer clinical trials. More recently, however, to account for the unique tumor response characteristics seen with treatment with immunotherapeutic agents, standard RECIST v1.1 will be adapted (irRECIST) to assess tumor responses in this study for treatment decisions only. Immunotherapeutic agents such as pembrolizumab and talimogene laherparepvec may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST v1.1 therefore may not be the optimal method for response assessment of immunotherapeutic agents. Immune-related RECIST (irRECIST) is RECIST v1.1 adapted to account for the unique tumor response seen with immuno-therapeutics. irRECIST will be used by local site investigators to assess tumor response and progression, and make treatment decisions. Adaptations for irRECIST include the following:

- For initial progressive disease (PD), tumor assessment should be repeated ≥4 weeks later in order to confirm PD with the option of continuing treatment per below while awaiting radiologic confirmation of progression.
- If repeat imaging shows < 20% tumor burden compared to nadir, stable or improved previous new lesion (if identified as cause for initial PD), and stable/improved non-target disease (if identified as cause for initial PD), treatment may be continued/resumed.
- In determining whether or not the tumor burden has increased or decreased, all target lesions as well as non-target lesions should be considered.

Note: For phase 3 only, investigators will also be asked to assess and document tumor response per standard RECIST v1.1. However, RECIST v1.1 response assessment should NOT be used in treatment decisions.

Method of Measurement of Tumor Lesions:

<u>CT scans (or MRI):</u>

Computed tomography (CT) scans by contrast-enhanced or spiral scan (or magnetic resonance imaging [MRI] scan) will be performed to evaluate tumor response for visceral

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

Positron Emission Tomography (PET)/CT Scans:

If a combined PET/CT scan is performed at the discretion of the investigator, the CT portion of that exam should not be substituted for the dedicated CT exams required by this protocol. The PET portion of the CT may introduce additional data which may bias the investigator assessment of response if it is not routinely or serially performed. However, if the investigator or the site radiologist can document that the CT performed as part of a PET/CT is of identical diagnostic quality to a diagnostic CT (with intravenous and oral contrast) then the CT portion of the PET/CT can be used for tumor measurements.

Ultrasound:

Ultrasound (US) should not be used as a primary method to assess lesion measurements in response to treatment.

Baseline Lesions

Measurable Lesions:

Measurable lesions are defined at baseline as lesions that can be accurately measured in at least one 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 short axis when assessed by CT scan or MRI.

Non-Measurable Lesions:

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 mm but < 15 mm short axis) and other truly non-measurable lesions are considered non-measurable. Examples of non-measurable lesions include some bone lesions, ascites, pleural/pericardial effusion, lymphangitic involvement of the

skin or (lymphangitis cutis/pulmonis), cystic lesions, and groups of lesions that are small and numerous.

Documentation of "Target", "Non-Target" and "New" Lesions:

Baseline evaluations will be used to prospectively identify all sites of disease present as close as possible to the enrollment and never greater than or equal to 28 days before the enrollment date. Sites of disease will be characterized as either target, non-target lesions or new lesions.

Baseline Documentation of Target Lesions:

Up to 10 target lesions with a maximum of 5 per organ (phase 1b) and up to 5 target lesions with a maximum of 2 per organ (phase 3) will be chosen to measure over the course of therapy. Pathological lymph nodes that are defined as measurable must meet the criterion of a short axis of ≥ 15 mm by CT scan in order to be identified as target lesions.

Target lesions should be selected on the basis of their size (lesions with longest diameter) and suitability for accurate repeated measurements by radiographic imaging. In situations where larger lesions cannot be accurately measured repeatedly (eg, near the diaphragm where respiratory changes may affect measurements), smaller lesions that meet criteria for measurability may be selected instead. Target lesions must not be chosen from a previously irradiated field unless there has been documented tumor progression in that field prior to enrollment. The distribution of the target lesions should be representative of the subject's overall disease (eg, largest lesions per organ).

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum of diameters will be used as reference by which to characterize the objective tumor response.

Baseline Documentation of Non-Target Lesions:

Any measurable lesions that were not chosen as target lesions and pathological lymph nodes with short axis ≥ 10 mm but < 15 mm, as well as non-measurable lesions should be identified as non-target lesions. Non-target lesions are evaluated at each timepoint but measurements are not required.

Documentation of New Lesions:

Any new lesion that appears during the course of study will be categorized as a new lesion. New lesions are evaluated at each timepoint but measurements are not required.

Follow-up Assessment of Tumor Lesions:

At each subsequent tumor assessment, the sum of diameters of target lesions will contribute to the total tumor burden.

Tumor Burden = sum of diameter of target lesions

New lesions and non-target lesion measurements are not required and these lesions should be followed qualitatively.

For radiographically assessed non-nodal disease the convention will be used that if a lesion being measured decreases in size to ≤ 5 mm in diameter or if it is believed to be present and faintly seen but too small to measure, a value of 5 mm will be assigned. If the non-nodal lesion subsequently increases in size to greater than or equal to 5 mm in one dimension, its true size will be recorded. If it is in the opinion of the radiologist that the non-nodal lesion has likely disappeared, the measurement should be recorded as "0 mm". If a lymph node is nonpathological (< 10 mm), dimensions should be recorded as 5 mm.

Response Evaluation:

Evaluation of Objective Response:

The subject response will be assessed based on tumor burden (the sum of diameters of target lesions) and qualitative assessment of non-target lesions per the definitions in Table 12. The overall response is derived from time-point response assessments as described in Table 14. Treatment decisions based on initial progressive disease are described in Table 13.

Table 12. Definition of Measurable Tumor Response (Baseline Target, Non-target, and New Lesions) per irRECIST

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 is required. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm.
Partial Response (iPR):	Decrease in tumor burden* ≥ 30% relative to baseline. Confirmation by a consecutive assessment at least 4 weeks (28 days) after first documentation required.
Progressive Disease (iPD):	Increase in tumor burden* ≥ 20 % and at least 5 mm absolute increase compared to nadir (minimum recorded tumor burden) or qualitative worsening of non-target lesions or a new lesion. For irRECIST, confirmation by a repeat, consecutive assessment no less than 4 weeks (28 days) from the date first documented progressive disease is required.
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 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)	Radiographic imaging was not performed at this time point to evaluate the response of measurable lesions

irRECIST = immune-related Response Evaluation Criteria in Solid Tumors
* Tumor Burden = sum of diameter of target lesions
Diameters used:
For nodal disease, shortest axis
For non-nodal disease, longest diameters

Table 13. Imaging and Treatment After First Radiologic Evidence of PD per irRECIST

	Clinically Stable		Clinically Unstable/Rapid Clinical Deterioration	
	Imaging	Treatment	Imaging	Treatment
1st radiologic evidence of iPD (progressive disease by irRECIST)	Repeat imaging at ≥ 4 weeks at site to confirm iPD	May continue study treatment at the local site Investigator's discretion while awaiting confirmatory tumor imaging by site by irRECIST.	Repeat imaging at ≥ 4 weeks to confirm iPD per investigator discretion*	Discontinue treatment
Repeat tumor imaging confirms iPD (progressive disease by irRECIST) at the local site	No additional imaging required	Discontinue treatment (exception is possible upon consultation with sponsor)	No additional imaging required	N/A
Repeat tumor imaging shows iSD, iPR or iCR by the local site	Continue regularly scheduled imaging assessments	Continue study treatment at the local site Investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion.

iCR = complete response per irRECIST; iPD = progressive disease per irRECIST; iPR = partial response per irRECIST; irRECIST = immune-related Response evaluation Criteria in Solid Tumors; PD = progressive disease

*Note: Clinically unstable patients are not required to undergo confirmation of PD. This decision is left to the discretion of the investigator.

Confirmation of Disease Progression:

In subjects who have initial evidence of radiological **i**PD, it is at the discretion of the PI whether to continue a subject on study treatment until repeat imaging is obtained based on their assessment of clinical stability. Subjects may receive study treatment and tumor assessment should be repeated ≥ 4 weeks later in order to confirm **i**PD by per site assessment.

Clinical stability is defined as the following:

1) absence of symptoms and signs indicating clinically significant progression of disease, including worsening of laboratory values

2) no decline in ECOG performance status

3) absence of rapid progression of disease

4) absence of progressive tumor at critical anatomical sites (eg, compression) requiring urgent alternative medical intervention

In determining whether or not the tumor burden has increased or decreased per irRECIST, the local site investigator should consider all target and non-target lesions as well as any incremental new lesion(s).

iPD is confirmed at repeat imaging if ANY of the following occur by irRECIST:

- Tumor burden remains ≥ 20% and at least 5 mm absolute increase compared to nadir
- Non-target disease resulting in initial PD is worse (qualitative assessment)
- New lesion resulting in initial PD is worse (qualitative assessment)
- Additional new lesion(s) since last evaluation
- Additional new non-target progression since last evaluation (i.e non-target progression following initial **i**PD in which **i**PD was due to either increased target lesion tumor burden or a new lesion but was not confirmed on repeat imaging).

Note: Rapid clinical deterioration does not require confirmation of **i**PD

If repeat imaging confirms **i**PD due to <u>any</u> of the scenarios listed above, subjects will be discontinued from study therapy.

NOTE: If a subject has confirmed radiographic progression (ie, 2 scans at least 4 weeks apart demonstrating progressive disease) per irRECIST, but the subject is achieving a clinically meaningful benefit, and there is no further increase in the tumor burden at the confirmatory tumor imaging, an exception to continue treatment may be considered following consultation with the sponsor.

iPD is not confirmed at repeat imaging if ALL of the following occur by irRECIST:

- Tumor burden is < 20 % or < 5 mm absolute increase compared to nadir
- Non-target disease resulting in initial **i**PD is stable or improved (qualitative assessment)
- New lesion resulting in initial **i**PD is stable or improved (qualitative assessment)
- No incremental new lesion(s) since last evaluation
- No incremental new non-target progression since last evaluation

If repeat imaging does not confirm **i**PD by irRECIST and the subject continues to be clinically stable, treatment may continue and follow the regular imaging schedule. If **i**PD is confirmed by a consecutive assessment, the first date of **i**PD documented should be the date of **i**PD. However, if **i**PD is not confirmed by a consecutive assessment but is

again noted at a subsequent assessment, the date of **i**PD documented should be the second date of **i**PD to capture incremental benefit.

When feasible, subjects should not be discontinued until progression is confirmed by the local site investigator/radiographic assessment. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. New lesions will be documented on the CRF form.

Confirmation of Response (**i**CR or **i**PR):

To be assigned a status of **i**CR or **i**PR changes in tumor measurements must be confirmed by consecutive repeat assessments performed no less than 4 weeks (28 days) after the criteria for response are first met.

The confirmatory assessments for complete response (CR)/partial response (PR) should be completed as close to the 28 day period without waiting for the next scheduled assessment (ie, 9 weeks later in case of subjects on treatment and 12 weeks later for subjects in long term follow-up (LTFU) who have ended treatment for reasons other than PD.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of **i**CR depends on this determination, it is recommended that the residual lesion be investigated (ie, biopsy) to confirm the **i**CR status.

Subjects who have had Complete or Partial Removal/Reduction of the Lesion will be Evaluated as Follows:

The procedure itself and all post-procedure lesion assessments should always be recorded in the CRF. A completely resected lesion should be assigned a default code of 0 mm (for target lesions) or “absent” (for non-target lesions). A partially resected lesion should be assigned its measurement post-procedure (for target lesions) or “present” (for non-target lesions). If the resected lesion contains no cancer under pathology evaluation, subsequent tumor assessments post-procedure may be used for tumor burden calculations and/or determination of response. If the resected lesion contains cancer or pathology results are unknown, the recorded tumor assessments post-procedure may be used for tumor burden calculations, but determination of visit overall response will be considered unable to evaluate (iUE or UE) for response except in the case of iPD or PD. Similarly, the visit overall response will be considered **iUE and**

UE, respectively, due to an incomplete tumor response assessment unless the criteria for iPD and PD, respectively, is met based on the subset of lesions assessed.

If the new tumor burden post-procedure is lower than the nadir before the procedure, then the new nadir will be set to the post procedure tumor burden. Otherwise, the previous pre-procedure nadir will be retained as the nadir. Subsequent assessments for iPD and PD will be determined from the nadir.

Merging Lesions

When two or more target lesions merge, the smaller lesion should have 0 mm recorded for the current and all future assessments, and the larger lesion should have the longest diameter of the merged lesion recorded for the current assessment and be followed for future assessments. When two or more non-target lesions merge, the smaller lesion should be recorded as absent for the current and all future assessments, and the larger lesion should be recorded as present for the current assessment and followed for future assessments. If a target lesion merges with a non-target lesion, the non-target lesion should be absent for the current visit and all future assessments, and the target lesion should include both merged lesions for recording measurements. New lesions and enlarging non-target lesions are measured qualitatively.

Separating Lesions

When a target lesion splits into 2 or more lesions, the largest measurable part of the split lesion should be considered to be the previously recorded target lesion with measurements provided for the current assessment and followed for future assessments. The dimensions of the split parts would still be target lesions. When a non-target lesion splits into 2 or more lesions, the split parts remain non-target lesions for the duration of the study. Any new lesions that result from separating should be documented as lesions that were generated by separating and not truly new lesions.

Table 14. Matrix for Determining the Overall Response at Each Assessment Point for irRECIST

Target Lesions (tumor burden)[a]	Non-target Lesions	New Lesions	Visit Overall Response	Subject Overall Response
↓ 100%	Absent / NA	Absent	iCR	iCR[b]
	Stable	Absent	iPR	iPR[b]
	Qualitatively worse	Absent	iPD	iPR if no further worsening of non-target lesions[b,c]
	Absent / Stable / NA	Present	iPD	iPR if stable new lesions and no additional new lesions[b,c]
↓ ≥ 30%	Absent / Stable / NA	Absent	iPR	iPR[b]
	Qualitatively worse	Absent	iPD	iPR if no further worsening of non-target lesions[bc]
	Absent / Stable / NA	Present	iPD	iPR if news lesions stable and no additional new lesions[b,c]
↓ < 30% to ↑ < 20%	Absent / Stable / NA	Absent	iSD	iSD if ≥ 8 weeks from start of study therapy; otherwise, UE
	Qualitatively worse	Absent	iPD	iSD if no further worsening of non-target lesions[c]
	Absent / Stable / NA	Present	iPD	iSD if stable new lesions and no additional new lesions[c]
↑ ≥ 20% and ↑ ≥ 5 mm absolute	Any	Any	iPD	iPD[c]
UE	Absent / Stable / NA	Absent	iUE	iUE
	Qualitatively worse	Absent	iPD	iPD[c]
	Absent / Stable / NA	Present	iPD	iPD[c]
iCR/iPR/iSD	ND/iUE	Absent	iUE	iUE
	ND/iUE	Present	iPD	iPD

iCR = complete response (per irRECIST); NA = not applicable; ND = not done; iPD = progressive disease (per irRECIST); iPR = partial response (per irRECIST); iSD = stable disease (per irRECIST); iUE = unable to evaluate (per irRECIST)

[a] Decrease relative to baseline; increase relative to nadir.

[b] Confirmation or iCR/iPR required by a repeat consecutive assessment no less than 4 weeks (28 days) from the date first documented. For iCR, any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. The subject overall response will be iSD if iCR/iPR is not confirmed.

[c] In the absence of clinical instability, an initial visit overall response of iPD must be consecutively confirmed no less than 4 weeks (28 days) from the date first documented for a subject overall response of iPD. The onset of iPD will be at the initial visit overall response of iPD when it is confirmed. If the initial visit overall response of iPD is not confirmed, then a subsequent iPD does not need to be confirmed for a subject overall response of iPD.

Appendix E. RECIST v1.1 Guidelines for Assessment of Disease Response

(Phase III Only)

For phase III only, investigators will be asked to obtain and document tumor responses per standard RECIST v1.1 along with those per irRECIST at every scheduled and unscheduled tumor assessment following the same target and non-target lesions determined for irRECIST tumor response assessment. Clinical decisions for treatment, however, should only be made based on tumor assessment using irRECIST.

Method of Measurement of Tumor Lesions:

Note: Imaging scans obtained for irRECIST tumor response assessment should also be used for RECIST v1.1 assessment

CT scans (or MRI):

Computed tomography (CT) scans by contrast-enhanced or spiral scan (or magnetic resonance imaging [MRI] scan) will be performed to evaluate tumor response for visceral or nodal/soft tissue disease (including lymph nodes). The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. A switch from contrast enhanced CT to noncontrast CT or to MRI (or vice versa) should not preclude response assessment if, in the judgment of the site radiologist, there is no significant difference in the assessment by changing modalities. This may occur if a subject has developed a medical contraindication to intravenous contrast for CT scans while on trial. This change would require the preapproval of the sponsor medical monitor.

Positron Emission Tomography (PET)/CT Scans:

If a combined PET/CT scan is performed at the discretion of the investigator, the CT portion of that exam should not be substituted for the dedicated CT exams required by this protocol. The PET portion of the CT may introduce additional data which may bias the investigator assessment of response if it is not routinely or serially performed. However, if the investigator or the site radiologist can document that the CT performed as part of a PET/CT is of identical diagnostic quality to a diagnostic CT (with intravenous and oral contrast) then the CT portion of the PET/CT can be used for tumor measurements.

Ultrasound:

Ultrasound (US) should not be used as a primary method to assess lesion measurements in response to treatment.

Note: Tumor Lesions designated for irRECIST response assessment should also be used for RECIST v1.1.

Baseline Lesions

Measurable Lesions:

Measurable lesions are defined at baseline as lesions that can be accurately measured in at least one 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 short axis when assessed by CT scan or MRI.

Non-Measurable Lesions:

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 mm but < 15 mm short axis) and other truly non-measurable lesions are considered non-measurable. Examples of non-measurable lesions include some bone lesions, ascites, pleural/pericardial effusion, lymphangitic involvement of the skin or (lymphangitis cutis/pulmonis), cystic lesions, and groups of lesions that are small and numerous.

Documentation of “Target”, “Non-Target” and “New” Lesions:

Baseline evaluations will be used to prospectively identify all sites of disease present as close as possible to the enrollment and never greater than or equal to 28 days before the enrollment date. Sites of disease will be characterized as either target, non-target lesions or new lesions.

Baseline Documentation of Target Lesions:

Up to 5 target lesions (a maximum of 2 per organ) will be chosen to measure over the course of therapy (Phase III). Pathological lymph nodes that are defined as measurable must meet the criterion of a short axis of ≥ 15 mm by CT scan in order to be identified as target lesions.

Target lesions should be selected on the basis of their size (lesions with longest diameter) and suitability for accurate repeated measurements by radiographic imaging.

In situations where larger lesions cannot be accurately measured repeatedly (eg, near the diaphragm where respiratory changes may affect measurements), smaller lesions that meet criteria for measurability may be selected instead. Target lesions must not be chosen from a previously irradiated field unless there has been documented tumor progression in that field prior to enrollment. The distribution of the target lesions should be representative of the subject's overall disease (eg, largest lesions per organ).

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum of diameters will be used as reference by which to characterize the objective tumor response.

Baseline Documentation of Non-Target Lesions:

Any measurable lesions that were not chosen as target lesions and pathological lymph nodes with short axis ≥ 10 mm but < 15 mm, as well as non-measurable lesions should be identified as non-target lesions. Non-target lesions are evaluated at each timepoint but measurements are not required.

Documentation of New Lesions:

Any new lesion that appears during the course of study will be categorized as a new lesion. New lesions are evaluated at each timepoint but measurements are not required.

Tumor Assessment per RECIST v1.1:

At each subsequent tumor assessment after baseline, the sum of diameters of target lesions (longest for non-nodal lesions and short axis for nodal) will contribute to the total tumor burden.

Tumor Burden = sum of diameter of target lesions

New lesions and non-target lesion measurements are not required and these lesions should be followed qualitatively.

Response Evaluation:

Evaluation of Objective Response:

The subject response will be assessed based on tumor burden (the sum of diameters of target lesions) and qualitative assessment of non-target lesions per the definitions in Table 15.

Table 15. Definition of Tumor Response for RECIST v1.1

Evaluation of Target Lesions	
Complete Response (CR)	Disappearance of all non-nodal target lesions. Any pathological lymph nodes (whether target or non-target) must have 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 smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression)
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study
Unable to Evaluate (UE)	Any non-target lesion present at baseline which was not assessed or was unable to be evaluated leading to an inability to determine the status of that particular tumor for that time point
Not Done (ND)	Scans were not performed at this time point to evaluate target lesions
Evaluation of Non-target Lesions	
Complete Response (CR)	Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10mm short axis)
Non-CR/Non-PD	Persistence of one or more non-target lesion(s).
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).
Unable to Evaluate (UE)	Any non-target lesion present at baseline which was not assessed or was unable to be evaluated leading to an inability to determine the status of that particular tumor for that time point
Not Done (ND)	Scans were not performed at this time point to evaluate target lesions

RECIST = Response Evaluation Criteria in Solid Tumors

Target Lesions:

- All target lesions (nodal or non-nodal) should have the actual measurements recorded at each subsequent evaluation even when very small (eg, 2 mm) if possible.
- Any non-nodal target lesion that become ‘too small to measure’ a default value of 5 mm should be assigned. If the lesion has disappeared, 0 mm should be recorded.
- Any nodal target lesion that become ‘too small to measure’ a default value of 5 mm should be assigned for its short axis.

- Coalescing lesions: If a plane is maintained in aiding the demarcation of the 2 lesions, then the maximal diameter of each individual lesion should be recorded. If the lesions have truly coalesced, then the longest diameter should be used for the coalesced lesion and assigned to the largest of the coalesced lesions. The smaller of the lesions then should be recorded as 0 mm. If target lesion(s) coalesces with non-target lesion(s), the longest diameter should be used for the coalesced lesions and assigned to the largest of the coalesced target lesion(s). If a target lesion merges with a non-target lesion, the non-target lesion should be absent from the current visit and all future assessments, and the target lesion should include both merged lesions for recording measurements. New lesions and enlarging non-target lesions are measured qualitatively.
- Splitting lesions: When a target lesion splits into 2 or more lesions, the largest measurable part of the split lesion should be considered to be the previously recorded target lesion with measurements provided for the current assessment and followed for future assessments. The dimensions of the split parts would still be target lesions. Any new lesions that result from separating should be documented as lesions that were generated by separating and not truly "new" lesions.

Non-Target Lesions

- Coalescing lesions: When 2 or more non-target lesions merge, the smaller lesion should be recorde as absent for the current and all future assessments, and the larger lesion should be recorded as present for the current assessment and followed for future assessments.
- Splitting lesions: When a non-target lesion splits into 2 or more lesions, the split parts remain non-target lesions for the duration of the study. Any new lesions that result from separating should be documented as lesions that were generated by separating and not truly new lesions.
- In contrast to irRECIST, to achieve progression of disease of non-target lesions, 'unequivocal progression' of these lesions must be documented on the basis that there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size or "qualitative worsening" as described for irRECIST assessment would not suffice to achieve 'unequivocal progression' status per RECIST v1.1.

New Lesions

- A new lesion should be unequivocal. If a new lesion is equivocal, continued therapy and follow-up evaluation should ensue until it is clear that it represents a new lesion, then progression should be declared using the date of the initial scan.
- Appearance of new malignant lesions on a follow up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

Subjects who have had Complete or Partial Removal/Reduction of the Lesion will be Evaluated as Follows:

- The procedure itself and all post-procedure lesion assessments should always be recorded in the CRF. A completely resected lesion should be assigned a default code of 0 mm (for target lesions) or "absent" (for non-target lesions). A partially resected lesion should be assigned its measurement post-procedure (for target lesions) or "present" (for non-target lesions). If the resected lesion contains no cancer under pathology evaluation, subsequent tumor assessments post-procedure may be used for tumor burden calculations and/or determination of response. If the resected lesion contains cancer or pathology results are unknown, the recorded tumor assessments post-procedure may be used for tumor burden calculations, but determination of response will be considered unable to evaluate (UE) for response except in the case of PD. If the new tumor burden post-procedure is lower than the nadir before the procedure, then the new nadir will be set to the post procedure tumor burden. Otherwise, the previous pre-procedure nadir will be retained as the nadir. Subsequent assessments for PD will be determined from the nadir.

Evaluation of visit overall response

A summary of the overall response determination at each evaluation time point is provided in Table 16.

Table 16. Matrix for Determining the Overall Response at Each Assessment Point for RECIST v1.1

Target Lesions	Non-target Lesions	New Lesions	Visit overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	UE/ND	No	PR
CR	NA	No	CR
PR	Non-PD/NA/UE/ND	No	PR
SD	Non-PD/NA/UE/ND	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
UE	Non-PD/NA	No	UE
ND	Non-PD/NA	No	UE

CR = complete response; NA = no non-target lesions at baseline; PD = progressive disease; PR = partial response; SD = stable disease
Non-/CR/Non-PD : Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits; UE = unevaluable

Appendix F. Eastern Cooperative Oncology Group (ECOG) Performance Status

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

Amendment 4

Protocol Title: A Phase 1b/3 Multicenter, Randomized Trial of Talimogene Laherparepvec in Combination With Pembrolizumab for the Treatment of Subjects With Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck

Amgen Protocol Number TVEC 20130232

EudraCT number 2015-003011-38

Amendment Date: 11 May 2018

Rationale:

This protocol is being amended to:

- Add language to clarify long term follow-up for subjects in phase 1b due to decision to not proceed to the phase 3 part of the study
- Remove PK and ADA samples from phase 1b portion of protocol per discussion with FDA, EMA, and PDMA (Merck request).
- Update End of Study language to align with most recent Amgen template text and to include the definition of Primary Completion and End of Trial for subjects who completed phase 1b
- Include a follow-up analysis for phase 1b
- Add text providing guidance about latex allergies to exclusion criteria no. 223
- Update serious adverse event reporting procedures to align with current safety language
- Update pembrolizumab safety language regarding pregnancy reporting and breastfeeding
- Update Key Sponsor Contacts
- Make administrative and editorial changes

Description of Changes:

Section: Global

Change: Date changed from 25 October 2017 to **11 May 2018**.

Section: Global

Change: Editorial and administrative edits throughout.

Section: Title Page

Replace:

PPD, MD
Clinical Research Senior Medical Scientist
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
Telephone: PPD
Email: PPD
PPD
Global Clinical Trial Manager
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
Telephone: PPD
Email: PPD

With:

PPD, **PhD**
Clinical Research Senior Medical Scientist
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Thousand Oaks, CA 91320-1799
Telephone: PPD
Email: PPD
PPD
Global Clinical Trial Manager
ICON Clinical Research UK Ltd
Marlow International (3rd Floor)
Parkway,
Marlow,
Buckinghamshire, SL7 1
Telephone: PPD
Email: PPD

Section: Title Page

Add:

Amendment 4 **11 May 2018**

Section: Synopsis, Study Design, paragraph 3

Replace:

Subjects will be followed for survival, subsequent anticancer therapies and talimogene laherparepvec/placebo related adverse events every 12 weeks from safety follow-up visit (± 28 days) for approximately 36 months after the last subject is randomized in phase 3.

With:

Subjects will be followed for survival, subsequent anticancer therapies and talimogene laherparepvec/placebo related adverse events every 12 weeks from safety follow-up visit (± 28 days) for approximately 36 months after the last subject is **enrolled**.

Section: Synopsis, Statistical Considerations, paragraph 3

Delete:

Summaries of the incidence of DLTs will be provided. Descriptive statistics will be provided for efficacy, safety, ~~PK, antibodies,~~ talimogene laherparepvec DNA, and biomarker endpoints as appropriate.

Section: Synopsis, Statistical Considerations, paragraph 10

Add:

For the phase 1b part of the study, the primary analysis will be repeated 1 year after the last subject enrolled.

Section: Phase 3 Study Design and Treatment Schema, footnote d

Delete:

[d] Long-term follow-up every 12 weeks (± 28 days) from safety follow-up visit until approximately 36 months after last subject enrolled ~~in phase 3~~. Talimogene laherparepvec/placebo related adverse events that occur after the safety follow-up visit through the end of the long-term follow-up will be reported.

Section: Study Glossary

Replace:

End of Study (primary completion)	defined as when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary endpoint of phase 3. The primary completion is anticipated to occur when approximately 336 deaths occur in phase 3.

With:

End of Study (primary completion)	**Primary Completion:** defined as when the last subject is assessed or receives an intervention for the purposes of final collection of data for the **primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early.** **Primary Completion Phase 1b only: The time when the last phase 1b subject is assessed or receives an intervention for the purposes of final collection of data for the primary efficacy endpoint of phase 1b. The primary completion is anticipated to occur when the last phase 1b subject completes the week 9 tumor response assessment.**

Section: Study Glossary

Replace:

End of Study (end of trial)	defined as when the last subject is assessed or receives an intervention for evaluation in the study. This is anticipated to occur 36 months after the last subject is randomized in phase 3.

With:

End of Study (end of trial)	defined as 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**. This is anticipated to occur 36 months after the last subject **is enrolled**.

Section: 1.3 Exploratory

Delete:

- ~~To evaluate the incidence of anti-pembrolizumab antibodies when pembrolizumab is administered in combination with talimogene laherparepvec~~
- ~~To evaluate the pharmacokinetics (PK) of pembrolizumab when administered in combination with talimogene laherparepvec~~

Section: 3.1.4.2 Long-Term Follow-up, paragraph 1

Delete:

Subjects will be followed for survival and subsequent anticancer therapies every 12 weeks (± 28 days) from safety follow-up for approximately 36 months after the last subject is enrolled ~~in phase 3~~.

Section: 3.5.1 Study Duration for Subjects

Replace:

During this period, subjects will be followed for survival for approximately 36 months after the last subject is randomized in phase 3.

With:

During this period, subjects will be followed for survival for approximately 36 months after the last subject is **enrolled**.

Section: 3.5.2 End of Study

Replace:

Primary Completion: The time when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary analysis; the primary completion is anticipated to occur when approximately 336 deaths occur in phase 3 among subjects included in the primary OS analysis.

End of Trial: The time when the last subject is assessed or receives an intervention for evaluation in the study. This is anticipated to occur 36 months after the last subject included in the primary OS analysis is randomized in phase 3.

With:

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

If a 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).

Primary Completion Phase 1b only: The time when the last phase 1b subject is assessed or receives an intervention for the purposes of final collection of data for the primary efficacy endpoint of phase 1b. The primary completion is anticipated to occur when the last phase 1b subject completes the week 9 tumor response assessment.

End of Study (end of trial): 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. This is anticipated to occur 36 months after the last subject is enrolled.**

Section: 4.2 Exclusion Criteria, Criterion no. 223

Add:

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

Section: 6.2.2.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation, Table 3

Add:

AST/ALT elevation or Increased bilirubin	Grade 2	Withhold **Permanently discontinue, if:** **AST or ALT > 3x ULN; and total bilirubin > 2 x ULN; and no other cause for the combination of laboratory abnormalities is immediately apparent (see Section 6.4.1)**	Administer corticosteroids (initial dose of 0.5- 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

Section: 6.2.3.3.3 Use of Pembrolizumab in Pregnancy

Replace:

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the sponsor without delay and within 24 hours if the outcome is a serious adverse experience (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the sponsor.

With:

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. **The pregnancy and the outcome of the pregnancy will be reported to Amgen and followed as described in Section 9.3 (Pregnancy and Lactation Reporting).**

Section: 6.2.3.3.4 Use of Pembrolizumab in Nursing Women

Add:

If a female subject breastfeeds while taking pembrolizumab, report the lactation case to Amgen as described in Section 9.3 (Pregnancy and Lactation Reporting).

Section: Table 5. Schedule of Assessments for Phase 1b

Delete

~~Blood for Anti-Pembrolizumab antibody[l]~~				~~X~~	~~X~~		~~X~~		~~X~~		~~X~~		~~X~~	~~X~~
~~Blood for Pembrolizumab PK[m]~~				~~X~~	~~X~~		~~X~~		~~X~~		~~X~~		~~X~~	~~X~~

Section: Table 5. Schedule of Assessments for Phase 1b, abbreviations

Delete:

~~PK = pharmacokinetics~~

Section: Table 5. Schedule of Assessments for Phase 1b, footnotes l and m

Delete:

[l] ~~Blood for anti-pembrolizumab antibody (also termed immunogenicity) will be collected at week 0 (ie, cycle 1 of pembrolizumab), week 3 (ie, cycle 2 of pembrolizumab), week 9 (ie, cycle 4 of pembrolizumab), week 15 (ie, cycle 6 of pembrolizumab), week 21 (ie, cycle 8 of pembrolizumab) and every 12 weeks (4 cycles of pembrolizumab) thereafter starting at week 33 (ie, cycle 12 of pembrolizumab), at safety follow-up visit (30 [+7] days after discontinuation of study treatment), and again 3 and 6 months after discontinuation of study treatment or until the subject starts new anticancer treatment, whichever is first. All samples should be drawn within 24 hours before infusion of pembrolizumab and at the same time as pre dose trough blood collection for the PK sample.~~

[m] ~~Blood for PK of pembrolizumab: Predose trough and post-dose peak PK samples will be collected at week 0 (ie, cycle 1 of pembrolizumab). Pre-dose trough samples only will be collected at week 3 (ie, cycle 2 of pembrolizumab), week 9 (ie, cycle 4 of pembrolizumab), week 15 (ie, cycle 6 of pembrolizumab), week 21 (ie, cycle 8 of pembrolizumab) and every 12 weeks (4 cycles) thereafter, starting at week 33 (ie, cycle 12 of pembrolizumab), at safety follow-up visit (30 [+7] days after discontinuation of study treatment), and again 3 and 6 months after discontinuation of study treatment or until the subject starts new anticancer treatment, whichever is first. All trough samples should be drawn within 24 hours before infusion of pembrolizumab. The peak sample should be drawn within 30 minutes after the end of the infusion. A one-time PK sample should also be drawn between 48 to 168 hours after week 0 (ie, cycle 1) dosing.~~

Section: 7.2.6 Long term Follow-up, paragraph 2

Add:

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/randomized that is included in the primary OS analysis, whichever comes first. Anticancer therapies for SCCHN and talimogene laherparepvec/placebo related adverse events that occur through the end the long term follow-up will be reported. **The phase 1b subjects will be followed for approximately 36 months after the last subject is enrolled.**

Section: 7.2.6 Long term Follow-up, paragraph 4

Delete:

They should continue into the long-term follow-up and be followed for survival and subsequent anticancer therapies every 12 weeks (± 28 days) for approximately 36 months after the last subject is enrolled ~~in phase 3~~.

Section: 8.1 Subjects' Decision to Withdraw, paragraph 4

Delete:

Those subjects who discontinue investigational product should continue into the long-term follow-up. Subjects will be followed for survival and subsequent anticancer therapies every 12 weeks (± 28 days) for approximately 36 months after the last subject is enrolled ~~in phase 3~~.

Section: 9.2.2.2 Reporting Procedures for Serious Adverse Events, paragraph 1

Replace:

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

With:

The investigator is responsible for ensuring that all serious adverse events, follow-up to a serious adverse event, including death due to any cause other than progression of the cancer under study, observed by the investigator or reported by the subject that occur after signing of the informed consent through 90 (+7) days after the last dose of talimogene laherparepvec or pembrolizumab, or 30 (+7) days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, are recorded in the subject's medical record and are submitted to Amgen. Additionally, all study drug-related serious adverse events that occur during the long-term safety follow-up period until the

end of study should also be captured in the Event CRF although these events will not be considered treatment-emergent adverse events.

All serious adverse events must be submitted to the sponsor within 24 hours following the investigator's knowledge of the event via the Event CRF.

Section: 10.1.1.3 Exploratory Endpoints, Phase 1b

Delete:

- ~~Subject incidence of anti-pembrolizumab antibodies~~
- ~~Serum concentration of pembrolizumab~~

Section: 10.1.3 Covariates and Subgroups

Add:

- **HPV status (positive vs negative vs unknown) (phase 1b)**

Section: 10.2.2 Sample Size Considerations for Phase 3, paragraph 2

Replace:

Median OS (pembrolizumab) = 8.4 months; p(t) = event rate at month t; p(12) = 0.373, p(24)= 0.15, p(36)=0.10, p(60)=0.05, and p(80)=0.04 constant hazard in each interval between 5 consecutive pieces; a constant hazard ratio across all pieces.

With:

Median OS (pembrolizumab) = 8.4 months; p(t) = **survival** rate at month t; p(12) = 0.373, p(24)= 0.15, p(36)=0.10, p(60)=0.05, and p(80)=0.04 constant hazard in each interval between 5 consecutive pieces; a constant hazard ratio across all pieces.

Section: 10.4.6 Follow-Up Analysis for Phase 1b

Add:

10.4.6 Follow-Up Analysis for Phase 1b

For the phase 1b part of the study, the primary analysis will be repeated 1 year after the last subject enrolled.

Section: 10.4.7 Final Analysis

Replace:

10.4.6 Final Analysis

The final analysis of the study will be conducted after the last subject enrolled in phase 3 has had the opportunity to complete the long-term follow-up (i.e, 36 months after the last subject is randomized in the FAS(G).

With:

10.4.**7** Final Analysis

The final analysis of the study will be conducted after the last subject enrolled has had the opportunity to complete the long-term follow-up (ie, 36 months after the last subject is **enrolled** in the FAS.

Section: 10.5.1 General Considerations, paragraph 4

Delete:

Descriptive statistics will be provided for efficacy, safety, ~~PK, antibodies,~~ talimogene laherparepvec DNA, and biomarker endpoints as appropriate ~~for phase 1b and phase 3 part of the study~~.

Amendment 3

Protocol Title: A Phase 1b/3 Multicenter, Randomized Trial of Talimogene Laherparepvec in Combination With Pembrolizumab for the Treatment of Subjects With Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck

Amgen Protocol Number (Talimogene Laherparepvec) 20130232

EudraCT number 2015-003011-38

Rationale:

This protocol is being amended to:

- Add the investigator-assessed RECIST v1.1 secondary tumor response endpoints of objective response rate (ORR) and progress-free survival (PFS) as secondary endpoints and remove Complete Response Rate (CRR) per irRECIST as a secondary endpoint. Complete Response Rate (CRR) per irRECIST was removed as a secondary endpoint.
- Replace EQ-5D-3L with EQ-5D-5L to utilize the most recent PRO version
- Revised exclusion criteria regarding re-irradiation
- Replaced modified RECIST v1.1 of 10 maximum lesions with 5 per organ with standard RECIST v1.1 for screening (5 maximum lesions with 2 per organ) to align with the use of standard RECIST v1.1 introduced for key secondary endpoints.
- Added RECIST v1.1 assessment in addition to irRECIST assessment for response assessment.
- The set of secondary hypotheses to be tested with the Maurer-Bretz procedure was revised to potentially generate more robust efficacy conclusions. Testing of CRR was replaced with ORR. Testing was added for RECIST v1.1 ORR and PFS. The total number of potential hypotheses tested as a result increased from 3 to 5.
- The number of events at the OS interim analysis was increased from approximately 255 to 280 to preserve 70% power in the event of a potential treatment lag effect.
- Sample size considerations were revised due to the OS interim analysis change and to discuss the power for the revised secondary hypothesis tests.
- The OS futility criterion at the interim analysis was changed from a conditional power < 10% given a true HR of 0.70 to an observed HR > 0.92 considering a potential treatment lag effect.
- An audit-based Blind Independent Central Review (BICR) was added to assess the consistency of investigator- and BICR-assessed treatment effects for RECIST v1.1 ORR and PFS.

- The definition of the phase 3 primary efficacy and safety analysis sets, primary completion, and end of trial were revised to maintain the study's statistical considerations.
- Updated language on disease related events and reporting procedures – per internal Amgen recommendations.
- Updated language on disease related events and reporting procedures to align across program.
- Made minor administrative changes, text clarifications, and edits throughout the protocol.

Amendment 2

Protocol Title: A Phase 1b/3 Multicenter, Randomized Trial of Talimogene Laherparepvec in Combination With Pembrolizumab for the Treatment of Subjects With Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck

Amgen Protocol Number (Talimogene Laherparepvec) 20130232

Rationale:

This protocol is being amended to:

- Update eligibility criteria triggered by recent safety signal – carotid blowout syndrome, and efficacy signal – lack of benefit in primary refractory patients with progressive disease within 3 months of curative intent multimodality therapy.
- Remove progression free survival as a primary endpoint for phase 3 and make it a secondary endpoint, along with CRR
    - The decision to forego of PFS as a dual primary endpoint hinged upon a few factors which included: the recent outcome of CHECKMATE 141 which led to approval of nivolumab based upon OS and also the final approval or pembrolizumab which is dependent upon OS from KEYNOTE 040. Considering the fact that OS is a superior outcome measure of a treatment over PFS especially in a poor prognosis disease and that PFS is not always a surrogate for OS, combined with the precedent set by nivolumab approval on OS, we felt that PFS did not have a truly meaningful role in the assessment of the efficacy of TVEC+pembrolizumab in second line head and neck cancer as well as for regulatory purposes.
- Add the use of irRECIST investigator assessment for response assessments and remove RECIST 1.1 central review.
- Update QOL/PRO wording and elevation of QLQ C30-3L to secondary endpoint from exploratory.
- Update statistical methods to justify the endpoint changes and also to introduce OS IA and futility analyses.
- To add more detail around go no go decision from Phase 1b to 3.
- Add additional pembrolizumab background information.
- Add additional talimogene laherparepvec background information.
- Update IP discontinuation/withholding rules.
- Update radiographic tumor assessments (sites of disease, spiral CT).
- Add additional information for archival tumor tissue.
- Add additional information for HPV testing.
- Update safety reporting information.
- Administrative changes and editorial changes for clarification.

Amendment 1
Protocol Title: A Phase 1b/3 Multicenter, Randomized Trial of Talimogene Laherparepvec in combination with Pembrolizumab for the Treatment of Subjects With Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck

Amgen Protocol Number Talimogene Laherparepvec [AMG678] 20130232

EudraCT Number 2015-003011-38

Amendment Date:	07 June 2016
Superseding Amendment	28 June 2016

Rationale:

The protocol is amended primarily so that an injectable placebo may be added to pembrolizumab in the control arm and to convert the study from open-label to double-blind in phase 3. This is necessary in order to reduce the bias of having intralesional injections in only 1 arm of the study.

The following key changes have been incorporated into protocol amendment 1:

- Updated key contacts
- Changed phase 3 portion of study to be double-blind and added placebo to the pembrolizumab arm.
- Reordered sections to separate phase 1b and phase 3 in the synopsis, and general study procedures sections in order to more clearly delineate which sections are specific to each phase of the study. Additionally, to reduce the number of footnotes, reorganized Section 7 to provide more description to study procedures.
- Updated background information for talimogene laherparepvec and pembrolizumab to reflect recent publications or presentations and approvals.
- Updated biopsy requirements in inclusion criteria
- Removed biodistribution and shedding at select sites in phase 3 as we will have sufficient data from phase 1
- Removed PD-L1 status as a stratification factor
- Removed registry study option
- Updated contraception language for exclusion criterion and also sections related to pembrolizumab. This is to align with other pembrolizumab protocols.
- Added exclusion criteria for active tuberculosis in order to align with other pembrolizumab protocols.
- Updated text related to pembrolizumab, rescue medications, dose adjustment, overdose, and supportive care guidelines to align with other pembrolizumab protocols.
- Updated pregnancy and lactation reporting language to align with other talimogene laherparepvec and pembrolizumab protocols.

- Updated language to clarify the modified response criteria in the appendices (eg, how to evaluate separated lesions, criteria for confirmation of PD).
- Added optional photography substudy

Additional errors were identified and rectified in the superseding amendment, and administrative errors were corrected.

Amendment 1
Protocol Title: A Phase 1b/3 Multicenter, Randomized Trial of Talimogene Laherparepvec in combination with Pembrolizumab for the Treatment of Subjects With Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck

Amgen Protocol Number Talimogene Laherparepvec [AMG678] 20130232

EudraCT Number 2015-003011-38

Amendment Date: 07 June 2016

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