Title: A Phase 1, Multi-center, Open-label, Dose De-escalation Study to Evaluate the Safety and Efficacy of Talimogene Laherparepvec in Pediatric Subjects With Advanced Non-central Nervous System Tumors That are Amenable to Direct Injection

Amgen Protocol Number (Talimogene Laherparepvec) 20110261

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Amendment 2 Date: 10 October 2018

Amendment 3 Date: 12 June 2020

Confidentiality Notice

Investigator's Agreement

I have read the attached protocol entitled A Phase 1, Multi-center, Open-label, Dose De-escalation Study to Evaluate the Safety and Efficacy of Talimogene Laherparepvec in Pediatric Subjects With Advanced Non-central Nervous System Tumors That are Amenable to Direct Injection, dated **12 June 2020**, and agree to abide by all provisions set forth therein.

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

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

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

at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

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

Signature

Name of Investigator

Date (DD Month YYYY)

Protocol Synopsis

Title: A Phase 1, Multi-center, Open-label, Dose De-escalation Study to Evaluate the Safety and Efficacy of Talimogene Laherparepvec in Pediatric Subjects With Advanced Non-central Nervous System Tumors That are Amenable to Direct Injection

Study Phase: Phase 1

Indication: Non-central nervous system (CNS) tumors

Primary Objective: To determine the safety and tolerability of talimogene laherparepvec, as assessed by incidence of dose-limiting toxicities (DLT), in pediatric subjects with advanced non-central nervous system tumors that are amenable to direct injection.

Secondary Objectives:

- To evaluate the anti-tumor activity of talimogene laherparepvec, as assessed by overall response rate (ORR), duration of response (DOR), time to response (TTR), time to progression (TTP), progression-free survival (PFS) using immune-related response criteria simulating Response Evaluation Criteria in Solid Tumor (RECIST 1.1) (modified immune-related response criteria simulating Response Evaluation Criteria in Solid Tumors [irRC-RECIST]), and overall survival (OS).

Safety Objective:

- To evaluate the safety and tolerability of talimogene laherparepvec.

Hypotheses: Talimogene laherparepvec injected in pediatric subjects with advanced non-CNS tumors that are amenable to direct injection will be safe as assessed by subject incidence of DLTs and the safety profile.

Primary Endpoint: Subject incidence of DLTs

Secondary Endpoints:

- ORR, DOR, TTR, TTP, and PFS using modified irRC-RECIST
- OS

Safety Endpoint:

- Subject incidence of adverse events and significant laboratory abnormalities

Study Design: This is a phase 1, multicenter, open-label study of talimogene laherparepvec in pediatric subjects with advanced non-CNS tumors that are amenable to direct injection in the clinical setting.

Approximately 18 to **24** pediatric subjects are expected to be enrolled **and treated with at least 1 dose of talimogene laherparepvec** into 2 cohorts stratified by age (permissible based on the incidence of DLTs, a minimum of 18 **dosed** subjects total **for the primary analysis**).

- Cohort A1 (12 to ≤ 21 years of age)
- Cohort B1 (2 to < 12 years of age)

Initially, 3 subjects 12 to ≤ 21 years of age are to be enrolled and treated at 100% of the recommended adult dose regimen of talimogene laherparepvec (cohort A1). The first dose administered will be up to 4.0 mL of 10^6 plaque-forming unit (PFU)/mL followed by a dose of up to 4.0 mL of 10^8 PFU/mL 21 days (+ 3 days) later. Subsequent doses of up to 4.0 mL of 10^8 PFU/mL will be administered approximately every 14 days (± 3 days) thereafter. The DLT evaluation period is 35 days from the initial administration of talimogene laherparepvec. The dose level review team (DLRT) will review the safety data of the first 3 subjects in the older age cohort A1 to decide if the younger age cohort B1 can be opened for enrollment. If none of the first 3 DLT-evaluable subjects in cohort A1 experiences a DLT, then cohort B1 will be opened for enrollment and treatment at the same dose level per the Study Design and Treatment Schema. If

a DLT occurs in the first 3 DLT-evaluable subjects in the older age cohort (A1 or A2), the younger age cohort will not open until a DLT rate < 33% is observed with at least 6 DLT-evaluable subjects in the older age cohort (A1 or A2).

Cohort A1 or B1 can enroll up to a maximum of **18** subjects **treated with at least 1 dose of talimogene laherparepvec with at least 9 DLT-evaluable subjects in cohort A1**. In the case of dose de-escalation, the minimum number of DLT-evaluable subjects at the de-escalated dose will be **6** (permissible based on the incidence of DLTs). After an age cohort is closed for further enrollment, if < 33% of all DLT-evaluable subjects in the cohort experiences a DLT at a dose level **(minimum of 6 DLT-evaluable subjects)**, the dose will be declared safe for the cohort.

If dose de-escalation is needed and if permissible based on the incidence of DLTs, a minimum of **6** DLT-evaluable subjects will be enrolled and treated at a lower dose level of talimogene laherparepvec (Dose Level -1). Dose de-escalation cohorts will obey the following naming convention, based on age at baseline, and the same DLT rules will be applied to the de-escalated cohorts:

- Cohort A2 (12 to ≤ 21 years of age)
- Cohort B2 (2 to < 12 years of age)

Sample Size: If permissible based on the incidence of DLTs, approximately 18 to **24 dosed** subjects will be enrolled into cohorts, stratified by age.

Summary of Subject Eligibility Criteria: Subjects must be 2 to ≤ 21 years of age at the time of informed consent/assent. Subjects must have local HSV-1 serostatus with measurable or non-measurable disease. Subject must have histologically or cytologically confirmed non-CNS solid tumor that recurred after standard/frontline therapy (or for which there is no standard/frontline therapy available). The subject must be a candidate for intralesional therapy and have Karnofsky performance status of ≥ 70% for subjects 12 to ≤ 21 years of age or Lansky play scale of ≥ 70% for children 2 to < 12 years of age. Subjects must have a life expectancy of > 4 months from date of enrollment 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 Section 4.2.

Investigational Product

Amgen Investigational Product Dosage and Administration: Talimogene laherparepvec will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures. Talimogene laherparepvec is supplied as a sterile frozen liquid in a single-use vial. 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.

The first dose of talimogene laherparepvec will be up to 4.0 mL of 10^6 PFU/mL administered on Day 1. The second injection, up to 4.0 mL of 10^8 PFU/mL, will be administered 21 days (+3 days) after the initial injection (ie, no sooner than day 22 but should not be delayed more than 3 days after the 21-day time point). All subsequent injections, up to 4.0 mL of 10^8 PFU/mL will be administered approximately every 14 days (± 3 days). The treatment cycle interval may be increased due to toxicity. See Section 6.2.1.2 for dose-cohort study de-escalation and stopping rules.

Procedures: Written informed consent/assent must be obtained from all subjects or legally acceptable representatives before any study specific screening procedures are performed. The following procedures will occur per the Table 3: review of eligibility criteria, demographics, medical, surgical and medication history, physical examination and vital signs, body weight, height, performance status, recording of concomitant medications, 12-lead electrocardiogram (ECG), review of adverse events, disease-related events and serious adverse events as well as reporting of potential or known unintended exposure to talimogene laherparepvec by a household member, caregiver, or healthcare provider, and survival assessment.

Blood will be collected for local laboratory testing including: hematology, serum chemistry, hepatitis B surface antigen and core antibody and hepatitis C virus antibody, prothrombin time (PT) or international normalization ratio (INR), and partial thromboplastin time (PTT) or activated PTT (aPTT), and blood for herpes simplex virus (HSV) serostatus at screening. In females of childbearing potential, urine pregnancy test will be performed locally. Central laboratory tests include: blood for HSV serostatus (with the exception of the screening test which will be done locally), [redacted]

Radiographic scans (as appropriate for tumor), clinical tumor assessments, and tumor marker assessments will also be performed. Talimogene laherparepvec will be administered at day 1 and 21 days (+3 days) after the initial injection. All subsequent injections will be administered approximately every 14 days (±3 days).

Subjects will have a safety follow-up visit approximately 30 (+ 7) days after the last dose of study treatment. Subjects will be followed for survival and use of subsequent anticancer therapies every 12 weeks (± 28 days) from the safety follow-up visit until death, subject or legally acceptable representative withdraws full consent/assent, or up to approximately 24 months after the last subject is enrolled in the study (whichever comes first).

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

Statistical Considerations:

Sample size consideration:

The sample size of **18 to 24 subjects will be enrolled and treated with at least 1 dose of talimogene laherparepvec with at least 9 DLT-evaluable subjects in cohort A1. For age cohort opening and dose de-escalation, criteria from** 3+3 phase 1 designs assuming a true DLT incidence rate < 33% **is used**. **Sample size for cohorts with age between 2 and 12 years are not required.**

A dose level will be considered safe for a cohort if < 33% of all DLT-evaluable subjects in a given cohort experiences a DLT **(minimum of 6 DLT-evaluable subjects)**. Table 5 and Figure 1 presents the probability of declaring a dose level safe (unsafe) for a range of true DLT rates for the protocol therapy **based on 6 DLT-evaluable subjects** (see triangle symbols). For example, the probability of declaring a dose level safe (unsafe) is 89% (11%), 42% (58%), and 11% (89%) if the true DLT rate is 10%, 30%, or 50%, respectively.

Interim Analyses

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

Planned methods of analysis:

The data will be analyzed by cohort and in the overall population. Descriptive statistics will be provided for demographic, safety, efficacy and exploratory endpoints.

The DLT analysis set will be used to summarize the subject incidence of DLTs for the study and the safety analysis set will be used for all other analyses of safety endpoints. The efficacy analysis will be conducted using the safety analysis set unless otherwise specified.

ORR, DOR, TTR, TTP, PFS, OS will be summarized in the overall population. ORR will be summarized with an associated exact 95% CI. DOR among responders, TTR, TTP, PFS and OS will be estimated using the Kaplan-Meier method.

Subject incidence of treatment-emergent and treatment-related adverse events will be summarized. Medical Dictionary for Regulatory Activities (MedDRA) will be used to code adverse events to a system organ class (SOC) and a preferred term within the SOC. The Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be used to grade severity of

adverse events. In addition, clinically significant laboratory changes and clinically significant changes in vital signs will be summarized with descriptive statistics. A summary of deaths after initiation of the study through 30 days since the last dose of talimogene laherparepvec will be provided.

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

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

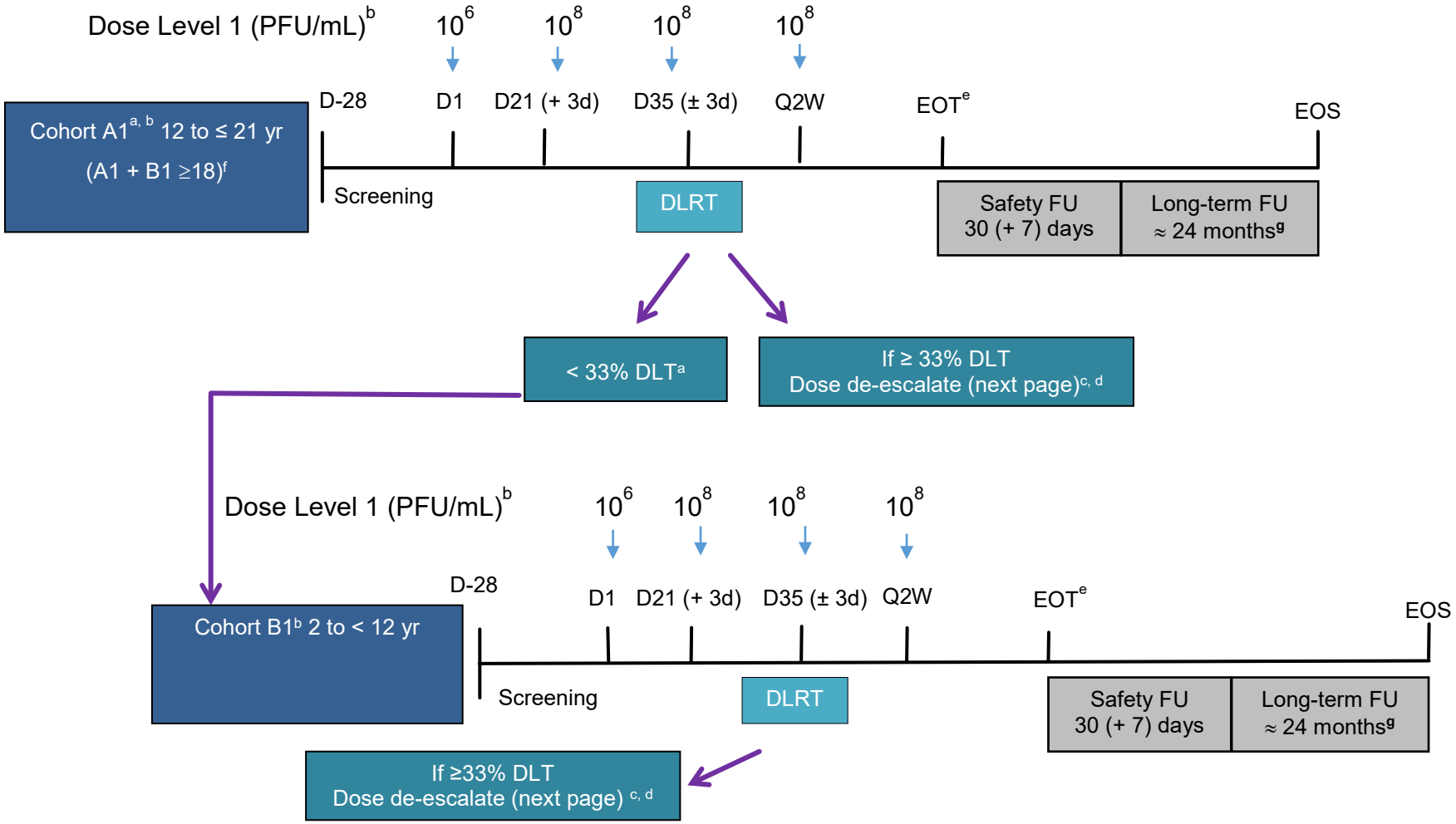
Summary statistics will be provided for vital signs, physical measurements and laboratory data. Details of the analysis will be provided in statistical analysis plan.

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

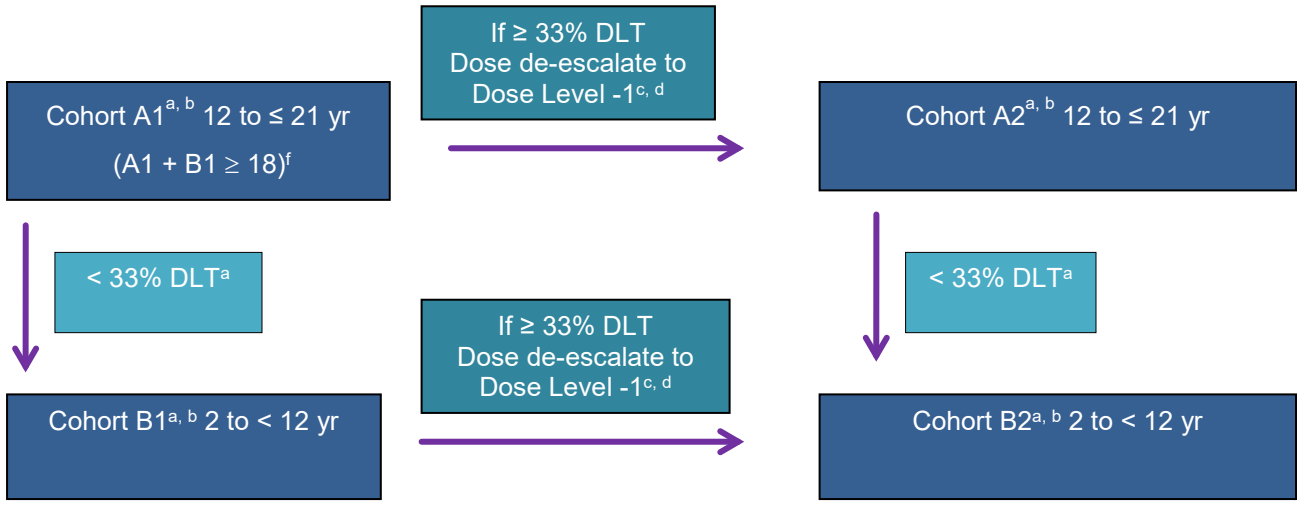
Sponsor: Amgen Inc.

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

Study Design and Treatment Schema



Dose De-escalation Rules



D = day; DLRT = dose level review team; DLT = dose-limiting toxicity; EOS = end of study; EOT = end of treatment; irRC-RECIST = immune-related response criteria simulating Response Evaluation Criteria in Solid Tumors; FU = follow-up; PFU = plaque-forming unit; yr = years of age

[a] Enrollment will begin with cohort A1. The DLT evaluation period is 35 days from the first dose of talimogene laherparepvec. The DLRT will review the safety data of the first 3 subjects in the older age cohort A1 to decide if the younger age cohort B1 can be opened for enrollment. If none of the first 3 DLT-evaluable subjects in cohort A1 experiences a DLT, then cohort B1 will be opened for enrollment and treatment at the same dose level. If a DLT occurs in the first 3 DLT-evaluable subjects in the older age cohort (A1 or A2), the younger age cohort will not open until a DLT rate < 33% is observed with at least 6 DLT-evaluable subjects in the older age cohort (A1 or A2).

[b] The initial dose administered (Dose Level 1) will be up to 4.0 mL of 10^6 PFU/mL followed by dose of up to 4.0 mL of 10^8 PFU/mL 21 (+ 3) days later. Subsequent doses of up to 4.0 mL of 10^8 PFU/mL will be administered every 14 (± 3) days thereafter. For additional details refer to Section 6.2.1.2.

[c] If the observed DLT rate is ≥ 33% in a cohort (eg, ≥ 33% DLT-evaluable subjects experience DLT after receiving either 10^6 or 10^8 PFU/mL dose) or if the DLRT deem the dose intolerable in a cohort in the DLT evaluation period, then dose de-escalation or discontinuation of treatment with subsequent enrollment stop for that cohort will occur.

[d] If dose de−escalation is needed and if permissible based on the incidence of DLTs, a minimum of **6** DLT-evaluable subjects will be enrolled and treated at a lower dose level of talimogene laherparepvec (Dose Level -1). The initial dose administered will be up to 4.0 mL of 10^6 PFU/mL followed by dose of up to 4.0 mL of 10^6 PFU/mL 21 days (+3 days) later. Subsequent doses of up to 4.0 mL of 10^6 PFU/mL will be administered 14 days (± 3 days) thereafter.

[e] Treatment visits continue until the subject has achieved a complete response, all injectable tumors have disappeared, confirmed progressive disease per modified irRC RECIST, intolerance of study treatment, 24 months from the date of the first dose of talimogene laherparepvec, or need for alternative anticancer therapy, whichever occurs first.

[f] If permissible based on the incidence of DLTs.

[g] **Subjects will be followed for survival and use of subsequent anticancer therapies every 12 weeks (± 28 days) from the safety follow-up visit until death, subject or legally acceptable representative withdraws full consent/assent, or up to approximately 24 months after the last subject is enrolled in the study, whichever occurs first.**

Study Glossary

Abbreviation or Term	Definition/Explanation
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANC	absolute neutrophil count
ASR	age-standardized incidence rates
AST	aspartate aminotransferase
[redacted]	
CI	confidence interval
CNS	central nervous system
CR	complete response
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug-induced liver injury
DLRT	Dose Level Review Team
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
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/assent from the study, completes the safety follow-up visit or long-term follow-up [whichever is later] or death).
End of Study (primary completion)	The primary completion date is defined as the date when the last subject is assessed or receive**d** an intervention for the final collection of data for the primary endpoint(s), whether the study concluded as planned in the protocol or was terminated early. The primary completion date is anticipated to occur **35 days after** the last subject has enrolled and **received at least 1 dose of talimogene laherparepvec**.
End of Study	The end of study date is defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, long-term follow-up), as applicable.
End of Treatment	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
EU	European Union
FCBP	female of childbearing potential
GCP	Good Clinical Practice

Abbreviation or Term	Definition/Explanation
GM-CSF	granulocyte macrophage colony-stimulating factor
HIV	human immunodeficiency virus
HSV, HSV-1	herpes simplex virus, herpes simplex virus type-1
ICH	International Council for Harmonisation
ICP	infected cell protein
INR	international normalization ratio
IPIM	Investigational Product Instruction Manual
IRB/IEC	institutional review board/independent ethics committee
irRC-RECIST	immune-related response criteria simulating Response Evaluation Criteria in Solid Tumors (RECIST)
IRT	**interactive response technology that is linked to a central computer in real time as an interface to collect and process information**
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PFU	plaque-forming unit
PR	partial response
PR Interval	PR interval is measured from the beginning of the P wave to the beginning of the QRS complex in the heart's electrical cycle as measured by ECG
PT	prothrombin time
PTT/aPTT	partial thromboplastin time/activated partial thromboplastin time
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
SCCHN	squamous cell cancer of the head and neck
SD	stable disease

Abbreviation or Term	Definition/Explanation
SOC	system organ class
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies) (ICH Guideline [E6]). Examples of source data include subject identification, randomization identification, and stratification value.
Study day 1	defined as the first day that protocol-specified investigational products are administered to the subject
[redacted]	
TTP	time to progression
TTR	time to response
ULN	upper limit of normal

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1. OBJECTIVES

1.1 Primary

To determine the safety and tolerability of talimogene laherparepvec, as assessed by incidence of dose-limiting toxicities (DLT), in pediatric subjects with advanced non-central nervous system (CNS) tumors that are amenable to direct injection.

1.2 Secondary

- To evaluate the anti-tumor activity of talimogene laherparepvec, as assessed by overall response rate (ORR), duration of response (DOR), time to response (TTR), time to progression (TTP), progression-free survival (PFS) using immune-related response criteria simulating Response Evaluation Criteria in Solid Tumor (RECIST 1.1) (modified immune-related response criteria simulating Response Evaluation Criteria in Solid Tumors [irRC-RECIST]), and overall survival (OS).

1.3 Safety

- To evaluate the safety and tolerability of talimogene laherparepvec.

1.4 Exploratory

[redacted]

2. BACKGROUND AND RATIONALE

2.1 Childhood Cancers

The incidence of childhood cancer is approximately 13 to 17 per 100 000 in both the United States (Siegel et al, 2014) and across Europe (Gatta et al, 2014). Across Europe, the incidence of childhood cancer varies widely, ranging from 9.1 to 17.8 per 100 000 (Gatta et al, 2014) and is generally higher in boys than in girls (Steliarova-Foucher et al, 2004). Among developing countries, limited data suggest a cancer incidence in the range of 8 to 10 per 100 000 (Magrath et al, 2013).

Most common cancer types in children are leukemia (age-standardized incidence rates [ASR], 44.8 per million), CNS tumors (ASR = 29.8 per million) and lymphomas

(ASR = 15.5 per million). According to age, the most common cancer type was neuroblastoma for infants (28%), leukemia for those aged 1 to 4 (41%), and CNS tumors for those aged 5 to 9. After age 10, lymphomas, carcinomas, germ-cell tumors, and bone tumors are more common, whereas embryonic tumors (ie, retinoblastoma, nephroblastoma [mainly renal tumors]) and hepatoblastoma (ie, mainly hepatic tumors) are rare. Childhood cancer represents 5% of all childhood deaths and 15% of all deaths amongst those age 5 to 14 (Steliarova-Foucher et al, 2004). Overall 1-year survival for all childhood cancers is 91%, 81% at 3-years, and 78% at 5-years (Gatta et al, 2014). Compared to the general population, children survivors are 8- to 11-times at greater risk of death, and their risk remains 3-times higher amongst those who survived 45 years after diagnosis (Steliarova-Foucher et al, 2004). Despite improvements in survival due to the implementation of multimodal therapy, survival for children with high risk solid tumors (comprising those with metastases, relapse or poor prognosis genomic features) is still poor and there is an unmet need to develop new drugs and therapies for this group of patients (Pui et al, 2011).

2.1.1 Oncolytic Virotherapy in Pediatric Oncology

Oncolytic viruses are attractive cancer therapies because of their potential to target and kill cancer cells and create an antitumor immune response while sparing normal cells with theoretically less toxicity than conventional therapies. Oncolytic viruses can be administered either via intratumoral injection or intravenously. Intratumoral injection of an oncolytic virus can be a difficult procedure to perform in children, particularly when targeting tumors that reside deep in the chest or abdomen. However, intratumoral injection has the advantage of delivering higher viral loads to the tumor, expediting delivery and potentially allowing to avoid rapid immune clearance.

Recently, Children's Oncology Group reported data from 2 oncolytic virus studies (Seneca Valley virus and reovirus). Both trials proved the feasibility and safety of this approach in children. The Seneca Valley virus (NTX-010) is a single-stranded RNA virus in the Picornaviridae family which showed efficacy in preclinical studies. The drug was safely administered intravenously at multiple dose levels, combined with oral and intravenous cyclophosphamide, and given in 2 doses (21 days apart) in 22 patients with recurrent refractory solid tumors. Diagnoses included neuroblastoma (n = 12), rhabdomyosarcoma (n = 3), carcinoid tumor (n = 4), and adrenocorticocarcinoma (n = 3). There was a single DLT (grade 3 pain) at the lowest dose level. All patients cleared the virus from blood and stool within 3 weeks and nearly all developed neutralizing

antibodies in spite of adding cyclophosphamide as immunomodulatory therapy, which appeared to limit efficacy as there were no objective responses. However, 10 of 16 patients had stable disease (SD) at the time of disease assessment (Burke et al, 2015). Reolysin is a double-stranded RNA virus in the Reoviridae family which selectively replicates in RAS-activated pediatric cancer cells in preclinical studies. Reovirus was safely administered intravenously alone for 5 consecutive days of a 28-day cycle or combined with oral cyclophosphamide in 24 patients with relapsed/refractory extracranial solid tumors, where the majority were rhabdomyosarcoma (n = 6), and osteosarcoma (n = 4). There were no DLTs; although grade 5 respiratory failure and a thromboembolic event were reported in the setting of disease progression. No virus was detected in the saliva or stool, and the average time of viremia clearance was 6.5 days with no virus noted in blood after 17 days. No objective responses were seen; although there were 3 patients with SD who received a second cycle. The authors concluded that the low incidence of tumor responses observed suggests that the utility of reovirus will likely require combination therapies which are currently being evaluated in adults (Kolb et al, 2015).

In addition to these trials, several other pediatric oncolytic virotherapy trials are being conducted. JX-594 (Pexa-Vec) is a double-stranded vaccinia virus in the Poxviridae family designed to destroy cancer cells through viral lysis and induce **granulocyte macrophage colony stimulating factor (**GM-CSF**)** driven tumor-specific immunity. Pexa-Vec was safely intratumorally injected into 6 pediatric patients; hepatocellular carcinoma (n = 3), neuroblastoma (n = 2), and Ewing's sarcoma (n = 1). All toxicities were ≤ grade 3. The most common side effects were fever, tachycardia and asymptomatic grade 1 treatment-related pustules that resolved within 3 to 4 weeks. No objective responses were noted; however, there was evidence of necrotic changes in 1 patient's necrotic injected tumor on magnetic resonance imaging (MRI) and a decrease in standard uptake value on positron emission testing 22 days following the first injection suggestive of a potential antitumor response (Cripe et al, 2015). Two trials of intratumoral oncolytic herpes simplex virus (HSV) (HSV 1716), a double-stranded DNA cytolytic virus with deletion of the virulence gene (ICP34.5) are ongoing in patients with recurrent non-CNS solid tumors (clinicaltrials.gov; NCT 00931931) and CNS tumors (clinicaltrials.gov; NCT02031965). An intravenous cohort has been added to the non-CNS trial for subjects not suitable for direct injections.

2.2 Amgen Investigational Product Background: Talimogene Laherparepvec

Talimogene laherparepvec is a virus-based oncolytic immunotherapy consisting of an immune-enhanced herpes simplex virus type-1 (HSV-1) that selectively replicates in solid tumors. In this genetically modified strain, the HSV-1 viral genes encoding ICP34.5 (a neurovirulence factor) and ICP47 (which blocks viral antigen presentation to major histocompatibility complex class 1 and 2 molecules) have been functionally deleted. The coding sequence for human 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. Talimogene laherparepvec enables both direct tumor lysis at the site of injection as well as enhancement of a systemic immune response by expression of GM-CSF in the tumor microenvironment to recruit and activate antigen presenting cells required for a T cell mediated antitumor response. In the pivotal study in which adult patients with injectable melanoma that was not surgically resectable were randomly assigned at a 2:1 ratio to intralesional talimogene laherparepvec or subcutaneous GM-CSF, systemic immune effects of talimogene laherparepvec were demonstrated with the finding that 15% of measureable visceral (uninjected) metastases reduced in size by > 50% among talimogene laherparepvec treated patients. Median duration of treatment in the talimogene laherparepvec and GM-CSF arms was 23.0 weeks (range, 0.1 to 78.9 weeks) and 10.0 weeks (range, 0.6 to 72.0 weeks), respectively. Median potential follow-up (time from random assignment to analysis) was 44.4 months (range, 32.4 to 58.7 months) at the primary analysis of OS. Additionally, development of vitiligo in talimogene laherparepvec treatment patients was seen in some patients indicating that an immune response to melanocyte antigens was induced (Andtbacka et al, 2015).

2.2.1 Preclinical Data

No dedicated juvenile toxicity studies have been conducted with talimogene laherparepvec in the clinical setting. A review of the literature, using the search terms “juvenile” or “adolescent”, “HSV-1”, and “infection” [PubMed (US National Library of Medicine, National Institutes of Health), 8 November 2016] does not identify a particular risk of juvenile HSV-1 infection compared to risks in adults. The toxicology program evaluated the safety of talimogene laherparepvec following repeated subcutaneous dosing for up to 13 weeks in the BALB/c mouse (Studies 4648-00027, 4648-00028, 4648-00029). Additional studies evaluated the safety of talimogene laherparepvec following a single intra-arterial dose in the rat (Study 4648-00031), a single intraprostatic dose in the dog (Study 4648-00032), and the repeated intravenous dosing in an

embryo-fetal developmental toxicity study in the BALB/c mouse (Study-117250). Supplemental studies evaluated neurovirulence with talimogene laherparepvec following direct intracerebral injection (Study 4648-00004) or intranasal instillation in the BALB/c mouse (Study 4648-00014). Additionally, the safety of a surrogate HSV-1 construct expressing murine GM-CSF administered as a repeated SC injection was evaluated in BALB/c mice (Studies 4648-00052 and 4648-00029). The mice used in toxicology studies were approximately 13- to 15-weeks old when studies commenced, whereas mice used in the pharmacology studies were generally 4- to 6-weeks old at study start. High and multiple doses of talimogene laherparepvec were well tolerated in immunocompetent mice following subcutaneous, intravenous, or intralesional injection across this age range, which spans adolescence in mice, with no noted difference in sensitivity by age, and with hematological and histological effects consistent with a normal response to viral infection (Amgen data on file).

The invitro therapeutic effect of talimogene laherparepvec was tested on a number of National Cancer Institute relevant cell lines. The solid tumors cell lines (rhabdomyosarcoma, rhabdoid tumors, Ewing's sarcoma, and neuroblastoma) were found to be sensitive, while leukemia and lymphoma cell lines showed resistance to talimogene laherparepvec. Talimogene laherparepvec was further tested in mouse xenograft models of Ewing's sarcoma (A-673), neuroblastoma (SK-N-AS), osteosarcoma (SJSA-1), rhabdoid tumor (G-401), and rhabdomyosarcoma (SJCRH30). Across these models, 65% to 100% of tumor growth inhibition was seen, and 10% to 30% of animals showed complete tumor regression (Amgen data on file). These data are consistent with reports in the literature of the efficacy of other HSV-1 oncolytic viruses (Waters et al, 2016).

2.2.2 Clinical Data

As of 26 October 2016, 15 clinical studies (including 2 extension studies) have been or are being conducted in several advanced tumor types (advanced solid tumors, melanoma, squamous cell cancer of the head and neck, and pancreatic cancer), with an estimate of 893 subjects treated with talimogene laherparepvec.

In the first-in-human study, 001/01, talimogene laherparepvec was administered in single ascending doses of 10^6, 10^7, or 10^8 plaque-forming unit (PFU)/mL (up to 4 mL). In the first 2 single-dose cohorts, subjects who were HSV-1 seronegative at study entry experienced more adverse events, including febrile influenza-like syndromes associated with symptoms of fatigue, rigors, erythematous skin rashes and small vesicles in the

skin. At the highest dose (10^8 PFU/mL), only HSV-1 seropositive subjects received talimogene laherparepvec and no rashes or rigors were observed. In the subsequent multidose part of the study, talimogene laherparepvec was well tolerated in HSV-1 seronegative as well as seropositive subjects who received a first dose of 10^6 PFU/mL, followed by 2 doses of 10^8PFU/mL. Febrile responses were minimal. Of the 17 subjects, 7 subjects were HSV-1 seronegative at baseline but within 21 days (3 weeks) after the initial dose of 10^6 PFU/mL was administered, 6 of the 7 subjects seroconverted. Based on these findings, to facilitate tolerance, enable seroconversion, and ensure consistency in dosing, the recommended dose in adults (both HSV-1 seropositive and seronegative groups) was established to be 10^6 PFU/mL followed by 10^8 PFU/mL 21 days (3 weeks) later. Subsequent dosing could safely be administered every 14 days (2 weeks).

The pivotal study (Study 005-05) was a phase 3, multinational, randomized, open-label study to assess the efficacy and safety of talimogene laherparepvec monotherapy versus GM-CSF in subjects with unresectable stage 3b, 3c or 4 melanoma. Among 436 patients randomized, the primary endpoint of durable response (objective response lasting continuously for ≥ 6 months) rate was significantly higher with talimogene laherparepvec than GM-CSF (16.3% vs 2.1% odds ratio = 8.9; $p < 0.0001$). ORR was also higher in the talimogene laherparepvec arm (26.4% vs 5.7%). Median OS was 23.3 months in the talimogene laherparepvec group versus 18.9 months in the GM-CSF group (hazard ratio 0.79, $p = 0.051$). The 3 most frequent adverse events observed in the talimogene laherparepvec group compared with the GM-CSF group, respectively, were fatigue (50.3%, 36.2%), chills (48.6%, 8.7%), and pyrexia (42.8%, 8.7%). Common (> 20%) treatment-emergent adverse events that occurred with a higher incidence (> 5%) in the talimogene laherparepvec group compared with the GM-CSF group, respectively, included chills (48.6% and 8.7%), pyrexia (42.8%, 8.7%), injection site pain (27.7%, 6.3%), nausea (35.6%, 19.7%), influenza like illness (30.5%, 15.0%), fatigue (50.3%, 36.2%), myalgia and vomiting (21.2%, 9.4%). The only grade 3 or 4 adverse events occurring in ≥ 2% of talimogene laherparepvec patients was cellulitis (2.1%). No fatal treatment-related adverse events occurred (Andtbacka et al, 2015).

In the earlier clinical studies, (001/01, 002/03 and 004/04), viral shedding was observed in only 11% of subjects across all 3 studies. The longest time that infectious virus was detected in the injection site swabs was 8 days post-injection. All swabs of the exterior of the dressing were negative for the infectious virus at all time points tested across all

studies. Thus, it appeared that the dressings were used effectively and prevented shedding of any virus from the tumors into the environment. Additional biodistribution and shedding data have been collected in study 20120324. Interim analysis of this ongoing study included 2447 samples from 30 subjects treated with talimogene laherparepvec. Talimogene laherparepvec DNA was detected with the greatest frequency in swabs of injected lesions, but the incidence of viral infectivity was low. No blood or urine samples have tested positive at 30 days after the last dose of talimogene laherparepvec. For additional information, refer to the talimogene laherparepvec Investigator's Brochure.

2.3 Pediatric Risk Assessment

The level of risk associated with talimogene laherparepvec in pediatric subjects with advanced solid tumors is expected to be similar to that experienced by the adult population; however, the incidence and severity of adverse events in the pediatric population is unknown. Based on data from preclinical studies, it seems unlikely that talimogene laherparepvec would have specific safety concerns in the juvenile patient population. The risk of viral therapy in neonates (0 to 3 months old) who have an immature immune system is not defined, but this population will not be included in the study due to the lack of eligible tumor types. This study is the first to use talimogene laherparepvec in pediatric subjects with non-CNS solid tumors and no/limited other therapeutic options. There is a possibility of no direct treatment benefit to the subjects. The results of this study are likely to define safe doses to be tested in a pediatric phase 2 study.

2.4 Rationale

Talimogene laherparepvec has demonstrated improved outcomes in advanced adult melanoma. Since there is no information to suggest that the mechanisms of action of talimogene laherparepvec (including virus replication in injected tumors and immune response against tumor antigens) would differ in children and adolescents compared to adults, it is expected that talimogene laherparepvec might have a similar beneficial effect on tumor response in children and adolescents as it had in adults. Preclinical experiments have demonstrated that talimogene laherparepvec is active in a number of pediatric tumors supporting further investigation of talimogene laherparepvec in refractory pediatric solid tumors such as rhabdomyosarcoma, Ewing's sarcoma and neuroblastoma (Amgen data on file). As talimogene laherparepvec has not been evaluated in a pediatric population, the first step to the evaluation is determination of

safety. Hence, a phase 1 dose de-escalation study is proposed starting with the recommended adult dose. Only pediatric subjects with advanced non-CNS tumors amenable to direct injection (excluding visceral organ injection) will be enrolled.

Enrollment will start with the oldest age cohort from 12 to ≤ 21 years of age. Because of the protocol-specified requirement for intratumoral injection of a nonvisceral lesion, the most likely eligible tumor types in this cohort will be Ewing's sarcoma, osteosarcoma, non-rhabdomyosarcomatous soft tissue sarcoma or rhabdomyosarcoma. This prediction is based on the relative incidence of the most common cancers in this age group (Bleyer et al, 2008). As the average age of diagnosis of these cancers is around 15 years old (Daw et al, 2015; Brasme et al, 2014; Spunt et al, 2002) and the time to tumor recurrence from diagnosis could vary from 1 to 5 years from the initial diagnosis (Daw et al, 2015; Chisholm et al, 2011; McTiernan et al, 2006; Spunt et al, 2002), the age when these patients might become eligible for this study could be up to 21 year old. Thus, the upper age limit for the oldest cohort was set at 21 years of age.

After review of the safety data in the oldest cohort, recruitment will open for the younger patients (2 to < 12 years of age). Subjects younger than 2 years of age are not included in this study due to the lack of eligible tumor types amendable for direct intratumoral injection and availability of effective treatment options.

The recommended adult talimogene laherparepvec dose of 10^6 PFU/mL followed by 10^8 PFU/mL 3 weeks later has been shown to be well tolerated in HSV-1 seropositive and seronegative adult subjects. Symptoms of pyrexia, chills and influenza-like illness occurred more frequently during the first 3 months of treatment, particularly in patients who were HSV-1 negative at baseline (Andtbacka et al, 2015). Given this finding, preemptive measures are strongly recommended prior to each talimogene laherparepvec dose to prevent the occurrence of the influenza-like symptoms in the pediatric subjects who might be more susceptible for developing these adverse events.

2.5 Clinical Hypotheses

Talimogene laherparepvec injected in pediatric subjects with advanced non-CNS tumors that are amenable to direct injection will be safe as assessed by subject incidence of DLTs and the safety profile.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a phase 1, multicenter, open-label study of talimogene laherparepvec in pediatric subjects with advanced non-CNS tumors that are amenable to direct injection in the clinical setting. The overall study design is described by the Study Design and Treatment Schema.

Approximately 18 to **24** pediatric subjects are expected to be enrolled **and treated with at least 1 dose of talimogene laherparepvec** into 2 cohorts stratified by age (permissible based on the incidence of DLTs, a minimum of 18 **dosed** subjects total **for the primary analysis**) as follows:

- Cohort A1 (12 to ≤ 21 years of age)
- Cohort B1 (2 to < 12 years of age)

Initially, 3 subjects 12 to ≤ 21 years of age are to be enrolled and treated at 100% of the recommended adult dose regimen of talimogene laherparepvec (cohort A1). The first dose administered will be up to 4.0 mL of 10^6 PFU/mL followed by a dose of up to 4.0 mL of 10^8 PFU/mL 21 days (+ 3 days) later. Subsequent doses of up to 4.0 mL of 10^8 PFU/mL will be administered approximately every 14 days (± 3 days) thereafter (see Section 6.2.1.1). The DLT evaluation period is 35 days from the initial administration of talimogene laherparepvec. Rules for DLT evaluation are described in Section 6.2.1.2.1. The dose level review team (DLRT) will review the safety data of the first 3 subjects in the older age cohort A1 to decide if the younger age cohort B1 can be opened for enrollment. If none of the first 3 DLT-evaluable subjects in cohort A1 experiences a DLT, then cohort B1 will be opened for enrollment and treatment at the same dose level per the Study Design and Treatment Schema. If a DLT occurs in the first 3 DLT-evaluable subjects in the older age cohort (A1 or A2), the younger age cohort will not open until a DLT rate < 33% is observed with at least 6 DLT-evaluable subjects in the older age cohort (A1 or A2). If any of the first 3 subjects in cohort A1 experiences a DLT, the DLRT will make a recommendation on whether an additional 3 subjects should be enrolled in cohort A1.

Cohort A1 or B1 can enroll up to a maximum of **18 dosed** subjects **with at least 9 DLT-evaluable subjects in cohort A1**. In the case of dose de-escalation, the minimum number of DLT-evaluable subjects at the de-escalated dose will be **6** (permissible based on the incidence of DLTs). After an age cohort is closed for further enrollment, if < 33% of all DLT-evaluable subjects in the cohort experiences a DLT at a

dose level **(minimum of 6 DLT-evaluable subjects)**, the dose will be declared safe for the cohort.

If dose de-escalation is needed and if permissible based on the incidence of DLTs, a minimum of **6** additional DLT-evaluable subjects will be enrolled and treated at a lower dose level of talimogene laherparepvec (Dose Level -1). The initial dose administered will be up to 4.0 mL of 10^6 PFU/mL followed by dose of up to 4.0 mL of 10^6 PFU/mL 21 days (+3 days) later. Subsequent doses of up to 4.0 mL of 10^6 PFU/mL will be administered approximately every 14 days (± 3 days) thereafter (see Table 1). Dose de-escalation cohorts will obey the following naming convention, based on age at baseline, and the same DLT rules will be applied to the de-escalated cohorts:

- Cohort A2 (12 to ≤ 21 years of age)
- Cohort B2 (2 to < 12 years of age)

Table 1. Dose De-escalation

Dose Level	Initial Dose	Subsequent Doses
1	10^6 PFU/mL	10^8 PFU/mL
-1	10^6 PFU/mL	10^6 PFU/mL

PFU = plaque-forming unit

3.1.1 Follow-Up

3.1.1.1 Safety Follow-up

Adverse events will be collected as described in Section 9.2. All subjects will complete a safety follow-up visit approximately 30 (+ 7) days after the last dose of study treatment. Adverse events and any concomitant medications associated with adverse events that occur 30 (+ 7) days following cessation of treatment will be reported, followed, and recorded in the case report form (CRF).

3.1.1.2 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 use of subsequent anticancer therapies every 12 weeks (± 28 days) from the safety follow-up until death, subject or legally acceptable representative withdraws full consent/assent, or up to approximately 24 months after the last subject is enrolled in the study. In addition, talimogene laherparepvec-related adverse events that occur through the end of the long term follow-up will be reported.

3.2 Number of Sites

The study will be conducted at approximately 22 sites in Europe and North America. Additional sites and countries may be added. Sites that do not enroll subjects within approximately 18 months of site initiation may be closed.

3.3 Number of Subjects

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

If permissible based on the incidence of DLTs, approximately 18 to **24** subjects will be enrolled into cohorts stratified by age (**a minimum of 18 dosed** subjects **for the primary analysis**).

Refer to Section 10.2 for sample size considerations.

3.4 Replacement of Subjects

Subjects enrolled may be replaced in a cohort 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). The decision to replace subjects will depend on the totality of reasons for subjects not completing the DLT evaluation.

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

The duration of screening for each subject will be approximately 28 days (1 month). The duration of treatment is anticipated to be 9 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 **and use of subsequent anticancer therapies every 12 weeks (± 28 days) from the safety follow-up visit until death, subject or legally acceptable representative withdraws full consent/assent, or up to** approximately 24 months after the last subject is enrolled in the study**, whichever occurs first**. The study duration for an individual subject is expected to be approximately 35 months.

3.5.2 End of Study

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

The primary completion date is anticipated to occur **35 days after** the last subject has enrolled and **received at least 1 dose of talimogene laherparepvec**.

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

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

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/assent must be obtained (see Section 11.1).

4.1 Inclusion Criteria

101 Subject's legally acceptable representative has provided informed consent/assent when the subject is legally too young to provide informed consent/assent and the subject has provided written assent based on local regulations and/or guidelines prior to any study-specific activities/procedures being initiated.

103 Should be willing to submit local HSV-1 serostatus within 28 days prior to enrollment.

106 Subject must be a candidate for intralesional injection, defined as one or more of the following:

- at least 1 injectable lesion ≥ 10 mm in longest diameter
- multiple injectable lesions that in aggregate have a longest diameter of ≥ 10 mm

NOTE: visceral lesions are not eligible for injection. Additionally, bone lesions are not eligible for injection unless there is a soft tissue component that is amenable to injection.

108 Life expectancy > 4 months from the date of enrollment.

111. Male or female subjects 2 to ≤ 21 years of age at the time of informed consent/assent.

112. Histologically or cytologically confirmed non-CNS solid tumor that recurred after standard/frontline therapy, or for which there is no standard/frontline therapy available.

113. Presence of measurable or non-measurable lesions as defined by irRC-RECIST

114. Performance status:
- Karnofsky ≥ 70% for 12 to ≤ 21 years of age.
- Lansky play scale ≥ 70% for children 2 to < 12 years of age.

116. Female subject of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to dosing. If urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. A female is considered of childbearing potential (FCBP), ie, fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

117.

118. Adequate organ function as defined as follows:
- Hematological (without need of hematopoietic growth factor and/or transfusion support within **7 days from screening assessment**)
  - absolute neutrophil count (ANC) ≥ 1.0 x 10^9/L
  - platelet count ≥ 75 x 10^9/L
  - hemoglobin ≥ 8 g/dL
- Renal
  - serum creatinine ≤ 1.5x upper limit of normal (ULN) for age, OR creatinine clearance ≥ 60 mL/min/1.73 m^2 for a subject with creatinine levels > 1.5x ULN for age. (Note: creatinine clearance need not be determined if the baseline serum creatinine is ≤ 1.5x ULN for age. Creatinine clearance should be determined per institutional standards).
- Hepatic
  - serum bilirubin ≤ 1.5× ULN for age **or ≤ 1.5× baseline value if baseline value was abnormal for a subject with Gilbert's syndrome** or direct bilirubin ≤ ULN for age for a subject with total bilirubin level > 1.5× ULN for age
  - aspartate aminotransferase (AST) ≤ 2.5x ULN for age or ≤ 5x ULN for age for subject with liver metastases
  - alanine aminotransferase (ALT) ≤ 2.5x ULN for age or ≤ 5x ULN for age for subject with liver metastases
- Coagulation
  - international normalization ratio (INR) or prothrombin time (PT) ≤ 1.5x ULN for age
  - partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT) ≤ 1.5x ULN for age

4.2 Exclusion Criteria

201. Diagnosis of leukemia, non-Hodgkin's lymphoma, Hodgkin's disease, or other hematologic malignancy.

202. Radiotherapy to the bone marrow within 6 weeks prior to enrollment OR within 3 months prior to enrollment if prior radiotherapy to the craniospinal axis or to at

least 60% of the pelvis was received; within 2 weeks prior to enrollment if local palliative radiotherapy was received.

203.

204. Primary ocular or mucosal melanoma.

206. History of other malignancy within the past 5 years with the following exception:

- malignancy treated with curative intent and with no known active disease present and has not received chemotherapy for > 5 years before enrollment and felt to be at low risk for recurrence by the treating physician.

207. History or evidence of active autoimmune disease that requires systemic treatment (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

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

210. Prior treatment with talimogene laherparepvec or any other oncolytic virus.

211. Prior treatment with a tumor vaccine.

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

214.

215.

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

217. 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, and entecavir), ribavirin, or interferon alpha within 12 weeks of initiation of study treatment.

218. Known or suspected human immunodeficiency virus (HIV) infection.

219. Received live vaccine within 28 days prior to enrollment.

220. No antiplatelet or anticoagulation medications allowed within 7 days prior to talimogene laherparepvec injection except low-dose heparin needed to maintain venous catheter patency.

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

222. Female subject of childbearing potential who is unwilling to use acceptable method(s) of effective contraception during study treatment and through 3 months after the last dose of talimogene laherparepvec. Note: Acceptable methods of effective contraception are defined in the informed consent/assent form. Where required by local laws and regulations, additional country-specific contraception requirements may be outlined in a country-specific protocol supplement at the end of the Appendix Section of protocol.

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

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 any psychiatric disorder, 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 Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.

227. Subject who is unwilling to minimize exposure with his/her blood or other body fluids to individuals who are at higher risks for HSV-1 induced complications (immunosuppressed individuals, HIV-positive individuals, pregnant women, or children under the age of 1 year) during talimogene laherparepvec treatment and through 28 days after the last dose of talimogene laherparepvec.

228. Evidence of clinically significant immunosuppression such as the following:
    - primary immunodeficiency state such as severe combined immunodeficiency disease
    - concurrent opportunistic infection
    - receiving systemic immunosuppressive therapy (> 2 weeks prior to enrollment), including oral steroid doses (with the exception of maintenance physiologic replacement). Subjects who require intermittent use of steroids for inhalation or local steroid injection will not be excluded from the study
    - less than 6 months from autologous bone marrow transplant or stem cell infusion
    - history of allogeneic bone marrow transplant

230. History or evidence of xeroderma pigmentosum.

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

232. Prior chemotherapy, treatment dose radiotherapy, or biological cancer therapy within 14 days prior to enrollment or has not recovered to Common Terminology Criteria for Adverse Events version 4.0 (CTCAE) grade 1 or better from adverse event due to cancer therapy administered more than 14 days prior to enrollment.

233. CNS tumor or clinically active brain metastases **(patient with a history of treated brain metastases are eligible if there is radiographic evidence of improvement upon the completion of CNS-directed therapy and no evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study).**

234. Currently receiving treatment in another investigational device or drug study, or less than **14** days since ending treatment on another investigational device or drug study(ies) **or has not recovered to CTCAE version 4.0 grade 1 or better from adverse event due to other investigational device or drug study administered more than 14 days prior to enrollment.** Other investigational procedures while participating in this study are excluded.

235. Major surgery ≤ **14** days prior to enrollment **or has not recovered to CTCAE version 4.0 grade 1 or better from adverse event due to surgery performed more than 14 days prior to enrollment.**

5. SUBJECT ENROLLMENT

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

Each subject who enters into the screening period for the study (defined when the subject or legally acceptable representative signs the informed consent/assent) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned by the interactive response **technology (IRT)**. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject. Subjects who are determined not eligible after screening must be screen-failed in the **IRT** system and the reason for the screen-failure provided. Subjects who do not meet all eligibility criteria may be rescreened 1 time at the discretion of the investigator. If a subject is being rescreened, he or she may need to reconsent to the study to ensure that the IRB/IEC approved main informed consent/assent form is signed within 28 days of enrollment. Subjects who are determined not eligible after rescreen must be screen-failed in the **IRT** system and the reason for the screen-failure provided. Subjects may only be enrolled once into this study.

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

5.1 Treatment Assignment

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

6. TREATMENT PROCEDURES

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

The Amgen Investigational Product used in this study includes: talimogene laherparepvec.

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

6.2 Investigational Product

6.2.1 Amgen Investigational Product (Talimogene Laherparepvec)

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

6.2.1.1 Dosage, Administration, and Schedule

Talimogene laherparepvec must be prepared and administered by a qualified healthcare professional. Subjects should be assessed clinically for adverse events/toxicity prior to each dose using the 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 3) and the results should be checked before each treatment. Dosing will occur only if these test values are acceptable per Section 6.2.1.2 and 6.2.1.3. Sedation can be used and the type and dose is up to the discretion of the investigator taking into consideration the subject's medical history, age, and site of disease. Additionally, use of pain medication (eg, acetaminophen/paracetamol/narcotic) or anti-anxiety medication (eg, benzodiazepine) as premedication to help decrease the pain or anxiety associated with the injection is acceptable and left to the discretion of the investigator. Because

flu-like symptoms are common adverse events experienced by HSV-seronegative subjects after talimogene laherparepvec treatment, premedication with the appropriate antipyretic and/or antiemetic medications prior to each talimogene laherparepvec treatment is strongly recommended to prevent the occurrence of these symptoms in the HSV-seronegative subjects. The type and dose will be up to the discretion of the investigator taking into consideration the subject's medical history and age.

Talimogene laherparepvec will be administered by intralesional injection only into injectable cutaneous, subcutaneous, nodal tumors, and other non-visceral tumors with or without image guidance. Talimogene laherparepvec must not be administered into tumor lesions in visceral organs.

The first dose of talimogene laherparepvec will be up to 4.0 mL of 10^6 PFU/mL administered on day 1. The second injection, up to 4.0 mL of 10^8 PFU/mL (or up to 4.0 mL of 10^6 PFU/mL for a dose de-escalated cohort), will be administered 21 (+ 3) days after the initial injection (ie, no sooner than day 22 but should not be delayed more than 3 days after the 21-day time point). All subsequent injections, up to 4.0 mL of 10^8 PFU/mL (or up to 4.0 mL of 10^6 PFU/mL for a dose de-escalated cohort), will be administered every 14 (± 3) days. The treatment cycle interval may be increased due to toxicity.

The maximum volume of talimogene laherparepvec administered at any dose is 4.0 mL for any individual lesion and in any treatment.

The recommended volume of talimogene laherparepvec to be injected into the tumor(s) is dependent on the size of the tumor(s) and should be determined according to the injection volume guideline in Table 2. It is recommended that each lesion should receive the maximum amount possible to inject due to tumor properties at each visit before moving on to the next lesion, using the prioritization model below and the injection volume guideline based on tumor size per Table 2. The lesion site injected will be recorded on the CRF.

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

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

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

1. any new injectable tumor that appeared since the last injection
2. by tumor size, beginning with the largest tumor
3. any tumor previously seen on tumor assessment that was too small to inject that has now become large enough to inject

Subjects will be treated with talimogene laherparepvec until subjects have achieved a complete response (CR), all injectable tumors have disappeared, confirmed progressive disease (PD) per modified irRC-RECIST, intolerance of study treatment, 24 months from the date of the first dose of talimogene laherparepvec, or need for alternative anti-cancer therapy, whichever occurs first. Due to the mechanism of action, subjects may experience growth in existing tumors or the appearance of new tumors prior to maximal clinical benefit of talimogene laherparepvec. Therefore, modified irRC-RECIST will be used instead of standard RECIST 1.1 (Nishino et al, 2014). Details can be found in Appendix D.

The dose (total volume and concentration), lesion site, treatment start date, and lot number of talimogene laherparepvec are to be recorded on the CRF.

6.2.1.2 Dose-cohort Study De-escalation and Stopping Rules

Unlike conventional treatments, talimogene laherparepvec is administered directly into tumors and the dose is dependent on tumor size rather than subject's age, weight or body surface area. As the adult doses were safe and well-tolerated, this phase 1 study is designed with a dose de-escalation schema, which is described in detail in Section 3.1 Study Design.

If the DLT is a serious herpetic event (eg, encephalitis, encephalomyelitis, or disseminated herpetic-like infection) caused by talimogene laherparepvec as

demonstrated by real-time polymerase chain reaction (qPCR) analysis, then the study will be terminated.

6.2.1.2.1 Rules for DLT Evaluation

The DLT evaluation period is 35 days from the initial administration of talimogene laherparepvec. For a subject to be considered DLT-evaluable, subjects must receive 2 doses of talimogene laherparepvec (one dose of up to 4.0 mL of 10^6 PFU/mL followed by a dose of up to 4.0 mL of 10^8 PFU/mL for Dose Level 1, or 2 doses of up to 4.0 mL of 10^6 PFU/mL for Dose Level -1) during the 35 day DLT evaluation period, with the exception when a DLT occurs after the first dose. Subjects may be replaced in a cohort if they are not evaluable for DLT (ie, a subject did not receive at least 2 treatments of talimogene laherparepvec, or ended the study treatment before completion of DLT evaluation period for a reason other than experiencing a DLT).

A DLRT will review the safety data to evaluate possible drug effects and DLT. The DLRT will review the safety data of the first 3 DLT-evaluable subjects in the older age cohort (A1 or A2) to decide if the younger age cohort can be opened for enrollment. The decision to open the younger age cohort for subject enrollment will be based on < 33% DLT rate of the first 3 DLT-evaluable subjects in the older age cohort (A1 or A2) during the DLT evaluation period.

If a DLT occurs in the first 3 DLT-evaluable subjects in the older age cohort (A1 or A2), the younger age cohort will not open until a DLT rate < 33% is observed with at least 6 DLT-evaluable subjects in the older age cohort (A1 or A2). The starting dose for the younger age cohort will be Dose Level 1 (if the DLT rate in the older age cohort at Dose Level 1 is < 33%) or Dose Level -1 (if Dose Level 1 is intolerable for the older age cohort). After both cohorts are open, the DLRT will review the safety data after the earlier of the following events: (a) the addition of 3 new DLT-evaluable subjects in a cohort **until there're 9 DLT-evaluable subjects in the cohort**; (b) a DLT rate ≥ 33% considering all DLT-evaluable subjects in a cohort**;** (c) at the occurrence of the first DLT in either cohort. **If deemed necessary, ad-hoc meetings to review the safety data can be convened anytime by the DLRT**.

After an age cohort is closed for further enrollment, the dose will be declared safe for the cohort if the DLT rate at the dose level is < 33% **(minimum of 6 DLT-evaluable subjects)**. If a DLT rate ≥ 33% is observed at any time in a cohort or if it is deemed **unsafe** by the DLRT to continue **enrollment** in the cohort, the dose will be declared intolerable for the cohort. If permissible based on the incidence of DLTs, **e**nrollment will

stop when 18 **dosed** subjects **evaluable for the primary analysis** have been confirmed across cohorts A1 and B1 except in the case of dose de-escalation when 6 additional DLT-evaluable subjects at Dose Level -1 will be needed (permissible based on the incidence of DLTs). Enrollment will not be halted while the DLT-evaluation period is still ongoing. During this time, investigators should contact the medical monitor to discuss the screening and enrollment of any potential subjects. However, enrollment may be halted for the following:

- if a DLT occurs in the older age cohort while both cohorts are enrolling subjects and before the younger age cohort reaches the first safety review, then further enrollment will be halted in the younger age cohort until a DLT rate < 33% is observed with at least 6 DLT-evaluable subjects in the older age cohort;
- if dose de-escalation occurs in any cohort while both cohorts are enrolling subjects.

The DLRT will consider the totality of available data across all cohorts in coming to any recommendation, including dose de-escalation, enrollment halt, opening or re-opening of cohort(s) for enrollment and/or the starting dose for the cohorts.

6.2.1.2.2 Rules for Dose De-escalation

- If the observed DLT rate is ≥ 33% in a cohort (eg, ≥ 33% DLT-evaluable subjects experience DLT after receiving either 10^6 or 10^8 PFU/mL dose) or if the DLRT deem the dose intolerable in a cohort in the DLT evaluation period, then dose de-escalation or discontinuation of treatment with subsequent enrollment stop for that cohort will occur.
- In the case that dose de-escalation is needed, a minimum of **6** additional DLT-evaluable subjects will be enrolled at Dose Level -1 (permissible based on the incidence of DLTs)
- If the younger age cohort starts at Dose Level -1, no dose re-escalation will be considered.

6.2.1.2.3 Definition of DLT

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

The occurrence of any of the following toxicities during the DLT evaluation period will be considered a DLT, if judged by the investigator to be related to the administration of talimogene laherparepvec:

- Grade 4 non-hematologic toxicity
- Grade 3 non-hematologic toxicity lasting > 3 days despite optimal supportive care
  - grade 3 fatigue will not be classified as DLT, irrespective of duration
- Any grade 3 or higher non-hematologic laboratory value if:
  - medical intervention is required, or
  - the abnormality leads to hospitalization, or

  - the abnormality persists for > 1 week unless deemed not clinically important per both investigator and sponsor.
- Febrile neutropenia grade 3 or grade 4
- Thrombocytopenia < 25 x 10^9/L associated with bleeding event requiring intervention
- Serious herpetic event:
  - herpetic encephalitis or disseminated herpetic infection
- Grade 5 toxicity (ie, death)
- Any other intolerable toxicity leading to permanent discontinuation of talimogene laherparepvec

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

Subjects who are in CR and no longer have injectable lesions will enter the 30-day safety follow-up and continue to have tumor assessments every 12 weeks for up to 24 months. Subjects who develop a new injectable lesion(s) within 12 months from the start date of treatment, but after all other injectable lesions have responded such that they are no longer injectable are eligible to restart treatment with talimogene laherparepvec under this protocol for up to a further 12 months. This includes subjects that achieve a CR and then develop a new injectable lesion.

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

Talimogene laherparepvec treatment should be continued based on the potential benefit/risk assessment of the subject.

Dose reduction within a cohort for an individual subject who experience adverse events is not allowed. If in the course of administration of talimogene laherparepvec the subject cannot tolerate the full dose due to an injection-related adverse event, the total volume given should be recorded, and the reason for intolerance should be documented as an adverse event.

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

If the subject requires corticosteroid dosing greater than that required for maintenance physiologic replacement therapy, talimogene laherparepvec dosing should be withheld.

If a subject demonstrates evidence of new or worsening CNS metastases, all study treatments should be withheld. Resumption of talimogene laherparepvec dosing should be left to the discretion of the investigator and discussed with the Amgen medical monitor.

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

If talimogene laherparepvec dosing is delayed by more than 6 weeks from the date of the planned dose due to the occurrence of an adverse event that is considered related to talimogene laherparepvec, the subject must be permanently withdrawn from talimogene laherparepvec treatment. If talimogene laherparepvec dosing is delayed by more than 6 weeks from the date of the planned dose for reasons other than treatment-related toxicity, the case must be reviewed by the Amgen medical monitor in conjunction with the investigator to determine if the subject can resume talimogene laherparepvec therapy. Reason for dose change of talimogene laherparepvec is to be recorded on CRF.

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

- Subject developed DLT during the DLT evaluation period.
- The subject, for any reason, requires treatment with another anticancer therapeutic agent for the study disease (other than the exceptions noted in Section 6.4). In this case, discontinuation from the study treatment occurs immediately upon introduction of the new agent.
- Confirmed PD occurs as defined per modified irRC-RECIST or clinical progression per the investigator.
- A grade 2 or greater immune-mediated adverse event (with the exception of vitiligo) or allergic reactions attributed to talimogene laherparepvec that would require a dose delay of greater than 6 weeks from the date of the planned dose.
  - NOTE: immune-mediated glomerulonephritis, vasculitis, and pneumonitis and exacerbation of psoriasis have been observed in subjects receiving talimogene laherparepvec in clinical trials. Most of these subjects had a history of other autoimmune disease and/or prior treatment with agents that offered plausible alternative etiologies; however, immune-mediated adverse events can potentially involve any organ system.
- Any other talimogene laherparepvec-related non-hematologic or hematologic toxicities grade 3 or greater that, in the opinion of the investigator, would require a dose delay of greater than 6 weeks from the date of the planned dose.
- The subject develops clinical evidence of any systemic herpetic infection (such as encephalitis or disseminated infection).

- An FCBP subject becomes pregnant or fails to use acceptable method(s) of effective contraception.
- A female subject breastfeeds while on study treatment.
- Concurrent medical illness that, in the judgment of the investigator, would make continued treatment with talimogene laherparepvec dangerous for the subject.
- Subject or legally acceptable representative withdraws consent/assent or wishes to stop the study treatment.

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

6.3 Other Protocol-required Therapies/Medications

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

6.4 Hepatotoxicity Stopping and Rechallenge Rules

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], AST, ALT, total bilirubin and/or 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 Amgen investigational product or other protocol-specified therapies 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 Amgen Investigational Product Due to Potential Hepatotoxicity

Amgen 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 for age following baseline total bilirubin < ULN or INR > 1.5
- AND current AST or ALT > 3x ULN for age 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, HSV, 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
  - 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 subject population and/or severity of the hepatotoxicity or event) if Amgen 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 Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

For subjects who do not meet the criteria for permanent discontinuation of Amgen 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 Amgen 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
≤ 3x ULN for age	> 5x ULN for ≥ 2 weeks
≤ 3x ULN for age	> 5x ULN and unable to adhere to enhanced monitoring schedule
≤ 5x ULN for age	> 8x ULN at any time

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

Amgen 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 Amgen Investigational Product After Potential Hepatotoxicity

The decision to rechallenge the subject should be discussed and agreed upon unanimously by the subject or legally acceptable representative, investigator, and Amgen medical monitor.

If signs or symptoms recur with rechallenge, then Amgen investigational product, 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 Amgen 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.

6.6 Other Treatment Procedures

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

If a subject demonstrates evidence of new or worsening CNS metastases, all study treatments should be withheld and the investigator or designee should notify the sponsor's medical monitor as soon as possible. Subjects may be allowed to remain on study after discussion between the sponsor's medical monitor and the investigator to determine the appropriateness of treatment resumption provided CNS lesions are adequately treated and corticosteroid dose does not exceed levels typically required for maintenance physiologic replacement. Re-exposure to talimogene laherparepvec may occur only if the investigator and sponsor agree that the subject safety will not be compromised.

6.7 Medical Devices

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

6.8 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, Medical Devices, and/or Procedures During Study Period

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

- other investigational agents or procedures
- concurrent experimental or approved anticancer therapies other than study drug and radiation therapy required for palliation.

In addition, the following are not permitted during the treatment period:

- Immunosuppressive agents with the exception of treatment for adverse events
- If the subject requires corticosteroid dosing for related toxicities, talimogene laherparepvec treatment must be withheld until the corticosteroid dose has decreased to doses acceptable for maintenance physiologic replacement
- Subjects who are receiving talimogene laherparepvec may not receive systemic antiherpetic drugs (eg, acyclovir, valacyclovir, famciclovir), but may receive a topically administered antiherpetic drug more than 20 cm from a talimogene laherparepvec injection site with the exception of treatment for adverse events.
- Childhood vaccinations that contain live attenuated virus

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. Re-exposure to talimogene laherparepvec may occur only if the investigator and sponsor agree that the subject safety will not be compromised.

Subjects in the safety follow-up period who have not demonstrated confirmed disease progression, rapid clinical deterioration, **clinical progression,** or intolerance to talimogene laherparepvec may not receive any experimental or approved antitumor therapies unless the sponsor's medical monitor is consulted and approved.

7. STUDY PROCEDURES

7.1 Schedule of Assessments

For Schedule of Assessments please refer to Table 3.

Table 3. Schedule of Assessments

Period	Screening (≤ 28 days)	Treatment[a, d]																				Safety Follow-up[b]	Long-term Follow-up[c]
Week		**1**		**2**	**4**		**5**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32[d]**		**Every 12 weeks**
Talimogene Laherparepvec Cycle		**1**	**1**	**1**	**2**	**2**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**		
Day		**1**	**2**	**8**	**22**	**23**	**29**	**36**	**50**	**64**	**78**	**92**	**106**	**120**	**134**	**148**	**162**	**176**	**190**	**204**	**218**		
General Assessments[d]																							
Informed consent/assent	X																						
Review of eligibility criteria	X																						
Demographics, medical, surgical and medication history	X																						
Physical exam		X							X				X				X				X	X	
Vital signs[e]		X			X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Body weight		X							X				X				X				X	X	
Height		X																					
Performance status[f]	X	X							X				X				X				X	X	
Recording of concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[g]
12-lead ECG	X																						
Review of adverse events, disease-related events and serious adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[h]
Survival assessment																							X

Footnotes defined on last page of the table.

Table 3. Schedule of Assessments

Period	Screening (≤ 28 days)	Treatment[a]																				Safety Follow-up[b]	Long-term Follow-up[c]
Week		**1**		**2**	**4**		**5**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32[d]**		**Every 12 weeks**
Treatment Cycle		**1**	**1**	**1**	**2**	**2**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**		
Day		**1**	**2**	**8**	**22**	**23**	**29**	**36**	**50**	**64**	**78**	**92**	**106**	**120**	**134**	**148**	**162**	**176**	**190**	**204**	**218**		
Local Laboratory Tests																							
Chemistry[d]	X	X			X			X		X		X		X		X		X		X		X	
Hematology[d]	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																						
PT or INR and PTT or aPTT	X																						
Urine pregnancy test[i]		X[j]																				X	
Central Laboratory Tests																							
Blood for HSV serostatus[k]	X							X														X	
[redacted]																							

Footnotes defined on last page of the table.

Table 3. Schedule of Assessments

Period	Screening (≤ 28 days)	Treatment[a]																				Safety Follow-up[b]	Long-term Follow-up[c]
Week		**1**		**2**	**4**		**5**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32[d]**		**Every 12 weeks**
Talimogene Laherparepvec Cycle		**1**	**1**	**1**	**2**	**2**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**		
Day		**1**	**2**	**8**	**22**	**23**	**29**	**36**	**50**	**64**	**78**	**92**	**106**	**120**	**134**	**148**	**162**	**176**	**190**	**204**	**218**		
Radiographic Tumor/Response Assessments[d]																							
Radiographic scans (± 7 days; appropriate to tumor)[s]	X								X				X						X			X	X[t]
Clinical tumor assessment[u]	X								X				X						X			X	X
Tumor markers (if clinically applicable)[v]	X	To be performed to confirm a suspected complete response, if elevated at baseline																				X	X
Treatment Administration																							
Talimogene laherparepvec administration		X			X			X	X	X	X	X	X	X	X	X	X	X	X	X	X[w]		
Reporting Exposure to Talimogene Laherparepvec																							
Exposure of subject's household member or caregiver[d]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Exposure of subject's healthcare provider[x, d]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Footnotes defined on next page.

ECG = electrocardiogram; HSV = herpes simplex virus; qPCR = real-time polymerase chain reaction; aPTT = activated partial thromboplastin time; CR = complete response; INR = international normalization ratio; irRC-RECIST = immune-related response criteria simulating Response Evaluation Criteria in Solid Tumors; PT = prothrombin time; PTT = partial thromboplastin time; [redacted]; ULN = upper limit of normal

[a] Treatment visits continue until the subject has achieved a complete response, all injectable tumors have disappeared, confirmed progressive disease per modified irRC-RECIST, intolerance of study treatment, 24 months from the date of the first dose of talimogene laherparepvec, or need for alternative anticancer therapy, whichever occurs first.

[b] Approximately 30 (+ 7) days after the last dose of study treatment.

[c] Subjects will be followed for survival and use of subsequent anticancer therapies every 12 weeks (± 28 days) from the safety follow-up visit until death, subject or legally acceptable representative withdraws full consent/assent, or up to approximately 24 months after the last subject is enrolled in the study, whichever occurs first.

[d] Subjects undergoing talimogene laherparepvec treatment beyond week 32 should continue general study assessments and local laboratory tests until the end of treatment (vital signs, recording of concomitant medications and review of adverse events, disease-related events and serious adverse events, [redacted], physical exam, body weight and performance status every fourth cycle and chemistry and hematology every second cycle). Exposure of subject's household member or caregiver and healthcare provider should continue to be checked at every cycle.

[e] Vital signs (blood pressure, heart rate, respiration rate, and temperature) to be collected predose.

[f] Karnofsky performance status will be used for subjects aged 12 to ≤ 21 years; Lansky play scale will be used for subjects aged 2 to < 12 years.

[g] Only anticancer therapies will be collected/recorded every 12 weeks during the long-term follow-up.

[h] Talimogene laherparepvec related adverse events.

[i] Female subjects of childbearing potential only. A female is considered of childbearing potential (ie, fertile), following menarche and until becoming post-menopausal unless permanently sterilized. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

[j] To be performed within 72 hours prior to dosing.

[k] Blood sample for HSV serostatus will be performed at a local laboratory at screening and at a central laboratory thereafter.

[redacted]

[m] Blood draw for real-time polymerase chain reaction (qPCR) testing of talimogene laherparepvec DNA will be performed at the following time points:

- day 1 (prior to and approximately 1 hour [± 15 minutes] and 4 hours [± 30 minutes] after talimogene laherparepvec administration), day 2 approximately 24 hours [± 30 minutes] after talimogene laherparepvec administration, day 8 (± 2 days), day 22 (prior to and approximately 1 hour [± 15 minutes] and 4 hours [± 30 minutes] after talimogene laherparepvec administration), day 23 approximately 24 hours [± 30 minutes] after talimogene laherparepvec administration, day 29 (± 2 days), day 36 (± 2 days) prior to dosing, and day 50 (± 2 days) prior to dosing.

[redacted]

[s] Radiologic imaging of all sites of disease must be performed (including imaging of the brain when clinically indicated). For subjects remaining on treatment with talimogene laherparepvec beyond week 32, radiologic imaging should continue every 12 weeks until confirmed progressive disease per modified irRC-RECIST or start of new anticancer treatment. All study imaging should be performed according to the calendar and not adjusted for any cycle initiation delays.
[t] Subjects who are in complete response and no longer have injectable lesions will enter the 30-day safety follow-up and continue to have tumor assessments every 12 weeks for up to 24 months.
[u] For subjects with metastatic melanoma, clinical tumor assessments, including clinical measurements of cutaneous, subcutaneous, or nodal measurement by caliper should be measured at baseline assessment, as well as subsequent scheduled tumor assessments. Measurements should continue every 12 weeks until confirmed progressive disease per modified irRC-RECIST or start of new anticancer treatment.
[v] Clinically applicable tumor markers appropriate for the tumor type include, but are not limited to, serum alpha fetoprotein, serum beta human chorionic gonadotropin and urine for homovanillic acid/vanillylmandelic acid. Tumor marker measurement is required to confirm CR if screening level of tumor marker was above the ULN and criteria for CR per modified irRC-RECIST guidelines are met.
[w] Treatment may continue for up to 24 months depending on response to and tolerance of talimogene laherparepvec.
[x] If applicable.

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

7.2 General Study Procedures

A signed and dated IRB/IEC-approved informed consent/assent must be obtained before any study-specific procedures are performed.

Procedures that are part of routine care are not considered study-specific procedures and may be used at screening to determine eligibility. All subjects will be screened for eligibility before enrollment. Only eligible subjects will be enrolled into the study. During treatment, assessments and procedures can be performed within 3 days of the planned visit unless specified in the study procedures. It is recommended that dosing occur on the same day of the week when possible (eg, if first dose is administered on Monday, all subsequent doses should be administered on a Monday).

7.2.1 Screening and Enrollment

Screening procedures are to be completed during the screening period within 28 days prior to enrollment. Subjects who do not meet all eligibility criteria may be rescreened once at the discretion of the investigator.

The time points for the procedures to be completed during the screening period are designated in the Schedule of Assessments (Table 3).

7.2.2 Treatment

Treatment begins when the first dose of protocol-required therapy is administered to a subject. Study treatment should begin as soon as possible after enrollment via the **IRT** system but no later than 5 days after enrollment.

Administration of protocol-required therapies is to be performed after all other required procedures are completed during each visit, unless otherwise stated. Upon permanent discontinuation from study treatment for any reason, a safety follow-up visit will be performed approximately 30 (+ 7) days after the last dose of talimogene laherparepvec. The time points for the procedures to be completed during the treatment period are designated in the Schedule of Assessments (Table 3).

7.2.3 Follow-Up

7.2.3.1 Safety Follow-up Visit

All subjects will complete a safety follow-up visit approximately 30 (+ 7) days after the last dose of study treatment. The time points for the procedures to be completed during the safety follow-up period are designated in the Schedule of Assessments (Table 3).

7.2.3.2 Long-term Follow-up

After the safety follow-up visit all subjects will enter the long-term follow-up. Subjects will be asked to come for a clinic visit or contacted by telephone to assess survival and initiation of additional anticancer therapy.

Contact for all subjects will be attempted every 12 weeks (± 28 days) following the safety follow-up visit until death, subject or legally acceptable representative withdraws full consent/assent, or up to approximately 24 months after the last subject is enrolled in the study, whichever comes first. During long-term follow-up concomitant medications recording is to be restricted to anticancer therapy and safety reporting will be limited to talimogene laherparepvec related adverse events.

For subjects who discontinued treatment for any reason other than confirmed PD, every effort should be made to perform radiographic scan for tumor assessments every 12 weeks until documentation of confirmed PD per modified irRC-RECIST, start of new anticancer therapy, or end of study, whichever occurs first.

7.3 Description of Study Procedures

7.3.1 Informed Consent/Assent

All subjects or legally acceptable representative must sign and personally date the IRB/IEC approved informed consent/assent and provide subject assent if appropriate 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's safety and treatment effectiveness.

7.3.3 Medical and Surgical History

Complete medical and surgical history will be collected. Medical history will include information on the subject's concurrent medical conditions. The current toxicity grade and severity will be collected for each condition that has not resolved. Record all findings on the medical history CRF.

7.3.4 Medication History

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

7.3.5 Physical Examination

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

7.3.6 Physical Measurement

Height in centimeters and weight in kilograms should be measured.

7.3.7 Electrocardiogram

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

7.3.8 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure, heart rate, respiratory rate, temperature. Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign CRF. Record all measurements on the vital signs CRF.

7.3.9 Performance Status

Karnofsky performance status will be used for subjects 12 to ≤ 21 years of age and Lansky play scale will be used for subjects 2 to < 12 years of age (Appendix E).

7.3.10 Adverse Events and Disease-related Events

Adverse events and disease-related events observed by the investigator or reported by the subject will be collected as per Section 9.

7.3.11 Concomitant Medications

Concomitant therapies are to be collected from informed consent to 30 (+7) days following cessation of treatment. For all concomitant therapies (including those being taken for the current malignancy) therapy name, indication, dose, unit, frequency and start and stop date will be collected (see Section 6.5). Only anticancer therapies will be collected/recorded every 12 weeks during the long term follow up.

[redacted]

7.3.13 Radiographic Assessment

Radiologic imaging of all sites of disease must be performed (including imaging of the brain when clinically indicated). The choice of imaging modality(ies) for tumor assessment should be tailored according to what is appropriate for the tumor type being assessed (eg, computed tomography [CT] or MRI of the primary tumor and CT of the chest may be sufficient for subjects with primary osteosarcoma whereas CT/MRI of the primary tumor as well as metastatic site[s], bone scan, and metaiodobenzylguanidine scan may be appropriate in subjects with neuroblastoma). All subsequent tumor assessments should include at least the same imaging modality(ies) and equipment as in baseline. Assessment of tumor response will be performed according to modified irRC-RECIST (Appendix D). Response (CR or partial response [PR]) or PD is to be confirmed by a second consecutive clinical and radiographic assessment no less than 4 weeks from the date of the first documented response or PD.

7.3.14 Clinical Tumor Assessment

For subjects with metastatic melanoma, clinical tumor assessments, including clinical measurements of cutaneous, subcutaneous, or nodal measurement by caliper should be measured at baseline assessment, as well as subsequent scheduled tumor assessments.

Clinically applicable tumor markers appropriate for the tumor type include, but are not limited to, serum alpha fetoprotein and serum beta human chorionic gonadotropin and urine for homovanillic acid/vanillylmandelic acid. Tumor marker measurement is required to confirm CR if screening level of tumor marker was above the ULN and criteria for CR per modified irRC-RECIST guidelines are met.

[redacted]

7.3.16 Reporting Potential or Known Unintended Exposure to Talimogene Laherparepvec

If a household member, caregiver, or healthcare provider who has had close contact with the subject is suspected to have been exposed to talimogene laherparepvec (eg, has signs or symptoms suspected to be herpetic in origin or is accidentally exposed to talimogene laherparepvec), report to Amgen the potential or known unintended exposure to talimogene laherparepvec, suspected related signs or symptoms, and detection of talimogene laherparepvec DNA by qPCR testing in a swab taken from a lesion, if any, in subject's household member, caregiver, or healthcare provider.

7.4 Laboratory Assessments

The following screening and on-study laboratory samples will be processed in local lab: hematology panel, chemistry panel, screening hepatitis B surface antigen and hepatitis B core antibody, screening hepatitis C virus antibody, screening coagulation tests, urine pregnancy test, clinically applicable tumor markers, and the screening HSV serostatus.

The central laboratory will be responsible for on-study testing of HSV serostatus (week 6 and safety follow-up), [redacted].

Specific analytes for serum chemistry, coagulation hematology, and other labs to be conducted on blood and urine samples are presented in Table 4.

Table 4. Laboratory Analytes

Chemistry	Coagulation	Hematology	Other Labs
Sodium	PT or INR	Red blood cell	Pregnancy test (urine)
Potassium	PTT or aPTT	Hemoglobin	qPCR for talimogene laherparepvec DNA
Chloride		Hematocrit	[redacted]
Bicarbonate		Platelets	Hepatitis C virus antibody
Calcium		White blood cell differential	Hepatitis B surface antigen and hepatitis B core antibody
Magnesium		Neutrophils	[redacted]
Phosphorus		Eosinophils	Blood for HSV serostatus
Total protein		Basophils	Applicable tumor markers[c]
Albumin		Lymphocytes	
Blood urea nitrogen or urea		Monocytes	
Creatinine[a]			
Total bilirubin[b]			
ALP			
AST			
ALT			
Glucose			

ALP = alkaline phosphatase; AST = aspartate aminotransferase; ALT = alanine aminotransferase; HSV = herpes simplex virus; INR = international normalization ratio; PT = prothrombin time; PTT/aPTT = partial thromboplastin time/activated partial thromboplastin time; qPCR = real time polymerase chain reaction; [redacted]; ULN = upper limit of normal

[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.

[b] Direct bilirubin should be measured at screening if total bilirubin is > 1.5x ULN for age.

[c] Clinically applicable tumor markers appropriate for the tumor type include, but are not limited to, serum alpha fetoprotein, serum beta human chorionic gonadotropin and urine for homovanillic acid/vanillylmandelic acid.

7.5 Sample Storage and Destruction

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

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

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

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

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

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

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw

Subjects (or a legally acceptable representative) 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 (or a legally acceptable representative) the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject (or a legally acceptable representative) the options for continuation of the Schedule of Assessments (Table 3) and collection of data, including endpoints and adverse events. The investigator must document the change to the Schedule of Assessments (Table 3) and the level of follow-up that is agreed to by the subject (eg, in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records).

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, 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 (or a legally acceptable representative) request
- safety concern (eg, due to an adverse event, ineligibility determined, protocol deviation, non-compliance, requirement for alternative therapy, pregnancy, other protocol-specified criteria)

- death
- lost to follow-up
- decision by sponsor (other than subject request, safety concern, lost to follow-up)
- disease progression (confirmed PD per modified irRC-RECIST or clinical progression)
- other protocol-specified criteria (Section 6.2.1.2.3)

8.3.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- decision by sponsor
- withdrawal of consent/assent 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 or if the investigator believes that the event is related to the investigational product(s), study treatment, or protocol required therapies. Further, any disease-related event which meets any of the seriousness criteria in Section 9.1.3 should be **recorded** as a Serious Disease-related Event **and reported to the sponsor or designee within 24 hours**.

Note: For situations where disease-related events are due to squamous cell cancer of the head and neck (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. For situations when an adverse event or serious adverse event is due to advanced non-CNS tumors, report all known signs and symptoms. Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (eg, metastatic sarcoma).

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

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

9.1.3 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 subject 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 nonserious) observed by the investigator or reported by the subject that occur after the first dose of talimogene laherparepvec through the safety follow-up visit (ie, 30 [+ 7] days after the last dose of talimogene laherparepvec), are **recorded** using the Event CRF as a Disease-related Event.

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

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

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

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

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

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

9.2.2 Adverse Events

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

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

The investigator must assign the following adverse event attributes:

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

The adverse event grading scale used will be the CTCAE version 4.0. The grading scale used in this study is described in Appendix A.

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

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

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

9.2.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent/assent through 30 (+7) days after the last dose of talimogene laherparepvec are recorded in the subject's medical record and are submitted to Amgen. All serious adverse events must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the Event CRF. Additionally, talimogene laherparepvec related serious adverse events that occur after the safety follow-up visit through the end of the long-term follow-up will be reported.

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

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

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

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

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

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

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

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

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after end of study. However, these serious adverse events can be reported to Amgen. In some countries (eg, European Union [EU] member states), investigators are required to report serious adverse events that they become aware of after end of study. If serious adverse events are reported, the investigator is to report them to Amgen 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 pregnancy occurs in a female subject, or female partner of a male subject, while the subject is taking protocol-required therapies, report the pregnancy to Amgen as specified below.

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

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

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

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

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

9.4 Reporting of Exposure to Talimogene Laherparepvec

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

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

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

10.1.1.1 Primary Endpoint

- Subject incidence of DLTs

10.1.1.2 Secondary Endpoints

- ORR, DOR, TTR, TTP, and PFS using modified irRC-RECIST
- OS

10.1.1.3 Safety Endpoint

- Subject incidence of adverse events and significant laboratory abnormalities

10.1.1.4 Exploratory Endpoints

[redacted]

10.1.2 Analysis Sets

10.1.2.1 DLT Analysis Set

The DLT analysis set will include DLT-evaluable subjects defined as subjects who had the opportunity to be followed for at least 35 days on treatment from the initial dosing and received at least 2 treatments of talimogene laherparepvec (except subjects who had a DLT after the first dose). Subjects may be replaced in a cohort 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).

10.1.2.2 Safety Analysis Set

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

10.1.3 Covariates

The following covariates may be used to examine clinical activity in subgroups or in multivariate analysis.

- Age at baseline (12 to ≤ 21 versus 2 to < 12 years of age)
- Sex (female versus male)
- HSV-1 baseline serostatus (positive versus negative)
- Baseline sum of largest diameter of target lesions
- Extent of disease (localized versus metastatic)
- Performance status (Karnofsky/Lansky play scale [70% versus > 70%])
- Prior lines of therapy in the recurrent/metastatic setting (0,1, 2, > 2)
- Prior surgery for current malignancy (yes versus no)
- Prior radiotherapy for current malignancy (yes versus no)

- Complete surgical resection of all gross diseases (yes versus no)
- Other covariates reported in the literature or from other Amgen studies maybe considered in the analysis as appropriate at the time of analysis.

10.2 Sample Size Considerations

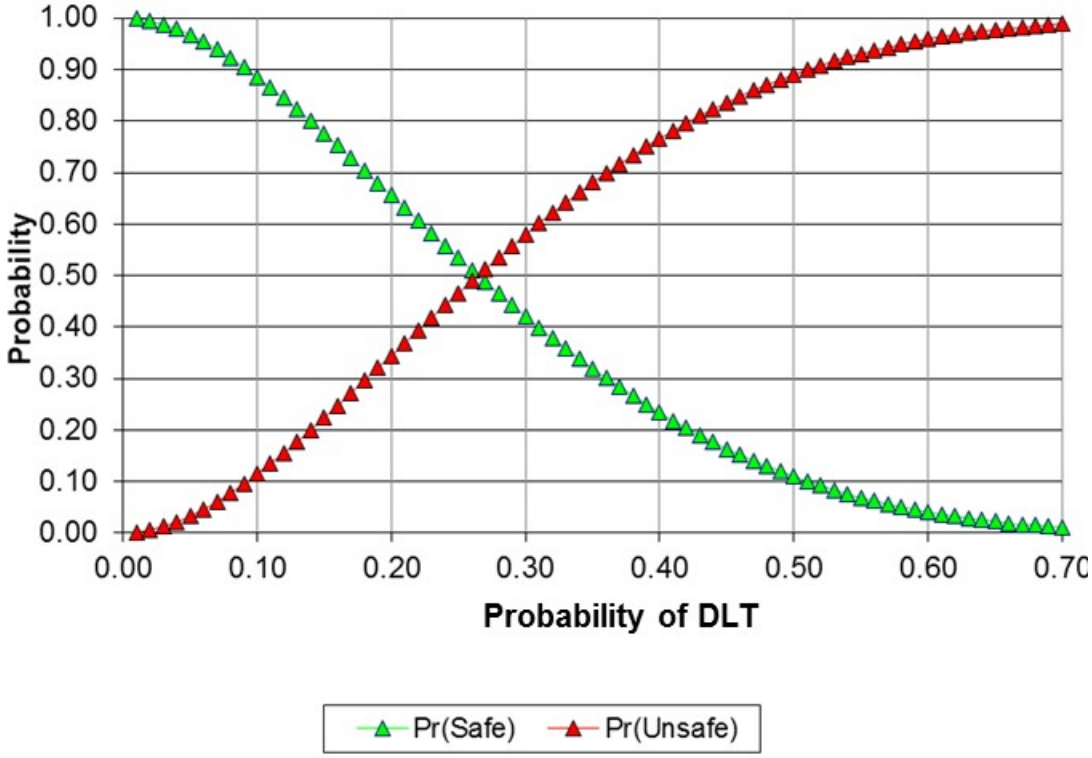
The sample size of **18 to 24 subjects will be enrolled and treated with at least 1 dose of talimogene laherparepvec including at least 9 DLT-evaluable subjects in cohort A1. For age cohort opening and dose de-escalation, criteria from** 3+3 phase 1 design assuming a true DLT incidence rate < 33% **is used**. **Sample size for cohorts with age between 2 and 12 years are not required.**

A dose level will be considered safe for a cohort if < 33% of all DLT-evaluable subjects in a given cohort experiences a DLT **(minimum 6 DLT-evaluable subjects**). Table 5 and Figure 1 presents the probability of declaring a dose level safe (unsafe) for a range of true DLT rates for the protocol therapy **based on 6 DLT-evaluable subject** (see triangle symbols in Figure 1). For example, the probability of declaring a dose level safe (unsafe) is 89% (11%), 42% (58%), and 11% (89%) if the true DLT rate is 10%, 30%, or 50%, respectively.

Table 5. Probability of Declaring a Cohort Safe or Unsafe

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

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



DLT = dose-limiting toxicity

10.3 Planned Analyses

10.3.1 Interim Analyses

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

10.3.2 Dose Level Review Team (DLRT)

An interim safety analysis is planned after the first 3 DLT-evaluable subjects for each cohort. A DLRT consisting of the Amgen study team, including at least 1 medical monitor, 1 safety representative, and 1 biostatistician, and at least 1 participating investigator who has recruited subjects into this study, will review the safety data to evaluate possible DLTs.

Based on the DLT evaluation rules in Section 6.2.1.2, the DLRT will recommend whether to continue the dose for 3 additional DLT-evaluable subjects in the cohort and if applicable, whether the younger age cohort can be opened for enrollment. Subsequent safety analyses are planned for: (a) every addition of 3 new DLT-evaluable subjects in a cohort **until there are 9 DLT-evaluable subjects in the cohort**; (b) if there have been

≥ 33% DLT rate in the cohort since the last safety analysis**;** (c) at the occurrence of the first DLT in either cohort. Based on the DLT evaluation rules and safety analyses, the DLRT will make recommendation on dose de-escalation, enrollment halt, the opening or re-opening of the cohort(s) for enrollment and/or the starting dose for the cohort(s). **If deemed necessary, ad-hoc meetings to review the safety data can be convened anytime by the DLRT**.

10.3.3 Primary Analysis

The clinical study report will be written based on the results of the primary analysis. The primary analysis will occur **35 days after** the last subject **has** enrolled and **received at least 1 dose of talimogene laherparepvec**.

10.3.4 Final Analysis

The final analysis will occur when all the subjects have discontinued the study treatment and have had the opportunity to complete the long-term follow-up visit. A separate clinical study report will be written with the updated results from the final analysis at the completion of the study.

10.4 Planned Methods of Analysis

The data will be analyzed by cohort and in the overall population. Descriptive statistics will be provided for demographic, safety, efficacy and exploratory endpoints.

10.4.1 Primary Endpoint

The DLT analysis set will be used to summarize the subject incidence of DLTs for the study and the safety analysis set will be used for all other analyses of safety endpoints. The efficacy analysis will be conducted using the safety analysis set unless otherwise specified.

10.4.2 Secondary Endpoints

Efficacy Endpoints:

ORR, DOR, TTR, TTP, PFS, and OS will be summarized in the overall population. ORR will be summarized with an associated exact 95% CI using the safety analysis set and excluding subjects without baseline measurable disease, if applicable. DOR among responders, TTR, TTP, PFS and OS will be estimated using the Kaplan-Meier method.

Safety Endpoints

Subject incidence of treatment-emergent and treatment-related adverse events will be summarized. **Treatment-emergent adverse events are defined as any adverse event occurring after first dose through 30 days after last dose of talimogene**

laherparepvec. Treatment-related adverse events are defined as treatment-emergent adverse events which are considered to be related to the treatment of talimogene laherparepvec, as determined by the investigator. Medical Dictionary for Regulatory Activities (MedDRA) will be used to code adverse events to a system organ class (SOC) and a preferred term within the SOC. The CTCAE version 4.0 will be used to grade severity of adverse events. In addition, clinically significant laboratory changes and clinically significant changes in vital signs will be summarized with descriptive statistics.

Subject incidence of all disease-related events, fatal disease-related events, serious disease-related events, and disease-related events leading to withdrawal from study drug will be provided.

A summary of deaths after initiation of the study through 30 days since the last dose of talimogene laherparepvec will be provided.

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

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

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

10.4.3 Exploratory Endpoints

[redacted]

[redacted]

10.5 Handling of Missing and Incomplete Data

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

11. REGULATORY OBLIGATIONS

11.1 Informed Consent/Assent

An initial sample informed consent/assent form is provided for the investigator to prepare the informed consent/assent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Amgen Clinical Study Manager to the investigator. The written informed consent/assent 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/assent from the subject or legally authorized representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational product(s) is/are administered.

The investigator is also responsible for asking the subject (or a legally acceptable representative) 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/assent and the subject's or legally acceptable representative 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/assent form is to be signed and personally dated by the subject or legally acceptable representative by the person who conducted the informed consent/assent discussion. The original signed informed consent/assent form is to be retained in accordance with institutional policy, and a copy of the signed consent/assent form is to be provided to the subject or legally acceptable representative.

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

11.2 Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed informed consent/assent 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/assent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

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

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

11.3 Subject Confidentiality

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

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.

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

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

11.4 Investigator Signatory Obligations

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

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

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

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

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

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

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

12.2 Study Documentation and Archive

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on 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 **IRT** system captures the following data points and these are considered source data: subject identification number.

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

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

Elements to include:

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

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

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

12.3 Study Monitoring and Data Collection

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

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

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

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

Data capture for this study is planned to be electronic:

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

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 3), the investigator can search publically available records [where permitted]) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

12.5 Language

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.

13. REFERENCES

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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 aspartate aminotransferase (AST) or alanine aminotransferase (ALT) and total bilirubin and/or international normalization ratio (INR) elevation according to the criteria specified in Section 6.4 require the following:

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

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 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 upper limit of normal (ULN) for age 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, alkaline phosphatase (ALP), bilirubin (total and direct), and INR within 24 hours
- In cases of total bilirubin > 2x ULN for age 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 creatine phosphokinase, haptoglobin, lactate dehydrogenase, 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 30 [+7] days (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. Electronic Adverse Event Contingency Report Form

A **Study 20110261** Talimogene Laherparepvec	**Electronic Adverse Event Contingency Report Form** **For Restricted Use**

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

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

Protocol specific reason(s):

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

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

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

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

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

3. ADVERSE EVENT

Provide the date the investigator became aware of this information: Day___ Month Year

Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP/drug under study	Is event serious?	If serious, enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the Event may have been caused by IP/drug under study or an Amgen device used to administer the IP/drug under study?								Outcome of Event -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
						Talimogene laherparepvec		<Pt/Init>		<Pt/Init>		<Pt/Init>			
						No✓	Yes✓	No✓	Yes✓	No✓	Yes✓	No✓	Yes✓		
				☐Yes ☐No											
				☐Yes ☐No											
				☐Yes ☐No											

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

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

Date Admitted Day Month Year	Date Discharged Day Month Year

	Site Number	Subject ID Number	

A **Study 20110261** Talimogene Laherparepvec	**Electronic Adverse Event Contingency Report Form** **For Restricted Use**

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

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

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

Medication Name(s)	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No✓	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											
	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

Site Number	Subject ID Number

A **Study 20110261** **Talimogene Laherparepvec**	**Electronic Adverse Event Contingency Report Form** **For Restricted Use**

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 APPROPRIATE FORM

1. Case Administrative Information

Protocol/Study Number: _____

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

2. Contact Information

Investigator Name _____ Site # _____

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

Institution _____

Address _____

3. Subject Information

Subject ID # _____ Subject Gender: ☐ Female ☐ Male Subject DOB: mm____/ dd____/ yyyy____

4. Amgen Product Exposure

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

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

If yes, provide product (or study drug) stop date: mm____/dd____/yyyy____

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

5. Pregnancy Information

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

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

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

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

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

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

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

_____

_____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

Effective Date: March 27, 2011 Page 1 of 1

Print Form

AMGEN Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX# enter fax number

1. Case Administrative Information

Protocol/Study Number: _____

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

2. Contact Information

Investigator Name _____ Site # _____

Phone (___) _____ Fax (___) _____ Email _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ Subject Date of Birth: mm____/ dd____/ yyyy____

4. Amgen Product Exposure

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

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

If yes, provide product (or study drug) stop date: mm____/dd____/yyyy____

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

5. Breast Feeding Information

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

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

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

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

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

_____

_____

Form Completed by:

Print Name: _____ Title: _____

Signature: _____ Date: _____

Effective Date: 05 April 2012 Version 2. Page 1 of 1

Appendix D. Modified irRC-RECIST Guidelines for Assessment of Disease Response

Note: Immune-related Response Criteria (irRC) simulating Response Evaluation Criteria in Solid Tumors version (RECIST) version 1.1 [irRC-RECIST] defined by Nishino et al, 2014, with modification will be employed to account for unique tumor response characteristics observed with immunotherapies to enable treatment beyond progression, if the subject is clinically stable.

Method of Measurement of Tumor Lesions:

Computed tomography scans (or magnetic resonance imaging [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). Measurability of lesions on CT scan is based on the assumption that CT slice thickness is 5 mm or less. Scan slices should ideally be 3 to 5 mm. MRI is acceptable to assess disease extent if used throughout the study.

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

Positron Emission Tomography (PET)/CT Scans:

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

Clinical lesion measurements:

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study

Ultrasound:

Ultrasound should not be used as a primary method to assess lesion measurements in response to treatment. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

At baseline, lesions are categorized as measurable or non-measurable according to the following definitions:

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
- ≥ 10 mm caliper measurement by clinical exam for superficial cutaneous or subcutaneous melanoma lesion as measured by caliper
- A lymph node must be ≥ 15 mm in short axis when assessed by CT scan or MRI.

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).

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 and characterized as non-target lesions. This will include any measurable lesions beyond the maximum number of 10 total or 5 per organ at each time point that were not chosen as target lesions. Only cancerous lesions should be selected as non-measurable lesions and not indeterminate lesions and lesions that could be cancer. Other examples of non-measurable lesions include some bone

lesions*, leptomeningeal disease, inflammatory breast disease, lymphangitic involvement of the skin or (lymphangitis cutis/pulmonis), and groups of lesions that are small and numerous.

Fluid Collections

Ascites, pleural effusion, or pericardial effusion should not be selected as non-measurable disease at baseline or, if new or increased, as evidence of progressive disease (PD). These collections may occur with both benign and malignant conditions, and their etiology is often not clear. These collections may be removed via interventional procedures, which can lead to a false interpretation of disease response. These fluid collections should not be used as a baseline non-target lesions or as evidence of disease response.

*** Bone Lesions:**

- Bone scans, PET scans or plain films are not considered adequate imaging techniques to measures bone lesions. However, these techniques can be used to confirm the presence or absence of bone lesions.
- Osteolytic (lytic) bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging technique such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Only the soft tissue component of the bone lesion should be measured.
- Many osteoblastic (blastic) bone abnormalities can be benign and should not be selected as baseline lesions. An isolated new small blastic lesion should not be selected as a new lesion unless there is demonstrated growth on subsequent scans. Multiple new blastic lesions that are clearly cancerous may be considered for new lesions.

Cystic Lesions:

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

Lesions with Prior Local Treatment:

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

Baseline Documentation of "Target" and "Non-Target" Lesions:

Baseline evaluations will be used to prospectively identify all sites of disease present as close as possible to the enrollment and never more than 4 weeks before the enrollment date. Sites of disease will be characterized as either target or non-target lesions.

Baseline Documentation of Target Lesions:

Up to 10 target lesions (a maximum of 5 per organ) 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.

The distribution of these target lesions should be representative of the subject's overall disease status. Target lesions should be selected on the basis of their size (lesions with longest diameter) and suitability for accurate repeated measurements by imaging techniques. 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.

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 of 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:

All other lesions (or sites of disease), including any measurable lesions that were not chosen as target lesions and pathological lymph node with short axis ≥ 10 mm but < 15 mm, should be identified as non-target lesions. Measurable non-target lesions (ie, lesions in an organ beyond the allowed maximum number of targets that would otherwise qualify as target lesions) should also be recorded and assessed qualitatively over the course of therapy. Non-measurable non-target disease measurements are not required, but these lesions are evaluated at each timepoint and will be evaluated as 'present', 'absent', or in rare cases 'unequivocal progression'.

Follow-up Assessment of Tumor Lesions:

At each subsequent tumor assessment, the sum of diameters of target lesions identified at baseline plus the sum of diameters of up to 10 (maximum 5 per organ) new measurable lesions per timepoint (for which the longest diameter is ≥ 10 mm for non-nodal lesions or the short axis is ≥ 15 mm for non-nodal lesions) are added together to provide the total tumor burden. If more than 10 new measurable lesions total (or 5 per organ) at a given timepoint are present, the new measurable lesions should be selected on the basis of their size and suitability for accurate repeated measurements by imaging techniques (CT or MRI). If there are lesions beyond the new measurable lesion limit during the course of the study for one subject, the additional lesions would be considered new non-measurable lesions.

Tumor Burden = sum of diameter of target lesions + sum of diameter of new measurable lesions.

Non-target disease measurements are not required and these lesions should be followed as “present”, “absent”, or “unequivocal progression”.

For non-nodal target lesions that become 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 an actual measurement is able to be provided, this should be recorded even if it is <5 mm. 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”. Nodal disease should always have the actual short axis measurement recorded even if the nodes regress to below 10 mm on study.

Response Evaluation:

Evaluation of Objective Response:

The subject response will be assessed based on tumor burden (the sum of diameters of target lesions plus the sum of up to 10 [maximum 5 per organ] new measurable lesions per timepoint), and, in the case of complete response (CR), the presence of any non-target and/or new non-measurable lesions. The overall response is derived from timepoint response assessments as described in Table 6 and Table 7.

Table 6. Definition of Measurable Tumor Response (Baseline Target and New, Measurable Lesions)

Complete Response (CR):	Disappearance of all lesions (whether measurable or not and whether baseline or new) and confirmation by a repeat, consecutive assessment no less than 4 weeks (28 days) from the date first documented. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial Response (PR):	Decrease in tumor burden[a] ≥ 30% relative to baseline confirmed by a consecutive assessment at least 4 weeks (28 days) after first documentation
Progressive Disease (PD):	Increase in tumor burden[a] ≥ 20% and at least 5 mm absolute increase relative to nadir (minimum recorded tumor burden) confirmation by a repeat, consecutive assessment no less than 4 weeks (28 days) from the date first documented PD.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD.
Unable to Evaluate (UE):	Any lesion present at baseline which was not assessed or was unable to be evaluated leading to an inability to determine the status of that particular tumor for that time point.
Not Applicable (NA)	No target lesions were identified at baseline
Not Done (ND)	Radiographic imaging was not performed at this time point to evaluate the response of measurable lesions

[a] Tumor Burden = sum of diameter of target lesions + sum of diameter of new measurable lesions.
Diameters used:

- For nodal disease, shortest axis
- For non-nodal disease, longest diameters

Table 7. Matrix for Determining the Overall Response at Each Assessment Point

Measurable Response	Non-measurable Response		Overall Response
Target and new, measurable lesions (tumor burden)[a], %	Non-target	New, nonmeasurable lesions	Using irRC-RECIST
↓100[b]	Absent/NA[c]	Absent	CR[d]
↓100	Present/ND/**UE**	Any	PR[d]
↓100	Unequivocal progression	Any	PR[d]
↓≥ 30	Absent/Present NA[c]/ND/**UE**	Any	PR[d]
↓≥ 30	Unequivocal progression	Any	PR[d]
↓< 30 to ↑< 20	Absent/Present/NA[c]/ND/**UE**	Any	SD
↓< 30 to ↑< 20	Unequivocal progression	Any	SD
↑≥ 20[e]	Any	Any	PD
UE[g]	Any	Any	UE
ND[g]	Any	Any	UE
NA[f]	Any	Any	UE

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; UE = unevaluable; ND = not done; NA = not applicable; irRC-RECIST = immune-related response criteria simulating Response Evaluation Criteria in Solid Tumors (RECIST)

[a] Disease relative to baseline, including new measurable lesions only (> 10 mm).

[b] Disappearance of all non-lymph node lesions and all lymph nodes < 10 mm in short axis would also be CR even if lymph node measurements prevent 100% tumor burden reduction.

[c] No non-target lesions identified at baseline.

[d] Assuming response (CR or PR) or progression are confirmed by a second, consecutive assessment at least 4 weeks (28 days) apart.

[e] In addition to relative increase of ≥ 20%, the tumor burden must also demonstrate an absolute increase of ≥ 5 mm from nadir for PD.

[f] No target lesions identified at baseline. When a subject has only nonmeasurable disease (ie, no target lesions identified at baseline) the response will be (UE) unevaluable.

[g] If one or more target/new measurable lesions are unevaluable or not measured but the sum of all evaluable target/new lesions measured show a ≥ 20% and at least 5 mm absolute increase relative to nadir, then the visit overall Target Response will be PD.

Determination of best overall response is based on changes in total tumor burden from the baseline (nadir, for PD) tumor assessment, regardless of any initial increase in baseline lesions or the appearance of new lesions.

Subjects are considered to have partial response (PR) or stable disease (SD) even if new lesions were present, as long as they met the respective thresholds of response as described in Table 7.

A best overall response of SD requires a visit response of SD or better no earlier than 49 days after the date of enrollment; otherwise the overall response will be UE.

Confirmation of Response (CR or PR):

To be assigned a status of CR or 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.

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

Confirmation of Disease Progression:

If a subject is classified as having PD at a post baseline tumor assessment, then confirmation of PD by a second assessment ≥ 4 weeks (28 days) later in the absence of rapid clinical deterioration (ie, rapid decline in performance status) or symptomatic disease requiring rapid initiation of alternative systemic anti-cancer therapy is required. The definition of confirmation of progression represents a ≥ 20% and at least 5 mm absolute increase in the total tumor burden (ie, the sum of diameters of target lesions plus new measurable lesions) compared to the nadir at 2 consecutive time-points at least 4 weeks (28 days) apart (with the date of progression considered to be the time of the initial evaluation showing PD).

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of PD at the time should have the reason for treatment discontinuation specified. Every effort should be made to document the objective progression even after discontinuation of treatment.

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

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

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.

Target lymph node previously present

For any target lymph node that is fully resected (and previously present ≥ 15 mm) and contained cancer or pathology results were unknown, 0 mm should not be recorded. In the event a measurement is not available, a 10 mm short axis should be reported.

For any target lymph node that is fully resected (and previously present ≥ 15 mm) and contained no cancer under pathology evaluation, 0 mm should not be recorded. In the event a measurement is not available, a 9 mm short axis should be reported.

Non-target lymph node previously present

For any non-target lymph node that is fully resected and contained cancer or pathology results were unknown, “present” should always be reported.

For any non-target lymph node that is fully resected and contained no cancer under pathology evaluation, “absent” should always be reported.

Lymph node not previously present

If a new lymph node was fully resected, measured and contained cancer or pathology results were unknown, it should be reported as a new non-measurable lymph node if its short axis was < 15 mm or, if it was ≥ 15 mm, it should be reported as a new measurable lymph node with a short axis of 10 mm.

If a new lymph node was fully resected, not measured and contained cancer or pathology results were unknown, it should be reported as a new non-measurable lymph node.

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

For any new lymph node that is fully resected and contained no cancer under pathology evaluation, it should not be recorded as either a target or non-target lesion. The full resection should only be reported on the Procedures eCRF.

Merging Lesions

When two or more target/new measurable lesions merge, the smaller lesion should have 0 (zero) 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/new non-measurable lesions merge, the smaller lesion should be recorded as "absent" for the current and all future assessments, and the larger lesion should be recorded as "present" for the current assessment and followed for future assessments.

If a target/new measurable lesion and a non-target/new non-measurable lesion merge, the non-target/new non-measurable lesion should be recorded as "absent" for the current and all future assessments while the target lesion/new measurable lesion should include both merged lesions for recording measurements.

Separating Lesions

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

When a non-target/new non-measurable lesions splits into 2 or more lesions, the largest part of the split lesion should be considered to be the previously recorded non-target/new non-measurable lesion and followed as "present" for the current assessment and followed for future assessments. Any new lesions that result from separating should be documented and followed for future assessments as new non-measurable lesions that were generated by separating and not truly new lesions.

Appendix E. Karnofsky Performance Status and Lansky Play Scale

Karnofsky Performance Status Scale	
Grade	**Descriptions**
100	Normal no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self; unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of his personal needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled; requires special care and assistance.
30	Severely disabled; hospital admission is indicated although death not imminent.
20	Very sick; hospital admission necessary; active supportive treatment necessary.
10	Moribund; fatal processes progressing rapidly.
0	Dead

Source: Schag, Heinrich, Ganz. 1984

Lansky Performance Status Scale	
Grade	**Descriptions**
100	Fully active, normal
90	Minor restrictions in strenuous physical activity
80	Active, but tired more quickly
70	Greater restriction of play *and* less time spent in play activity
60	Up and around, but active play minimal; keeps busy by being involved in quieter activities
50	Lying around much of the day, but gets dressed; no active playing, participates in all quiet play and activities
40	Mainly in bed; participates in quiet activities
30	Bedbound; needing assistance for even quiet play
20	Sleeping often; play entirely limited to very passive activities
10	Doesn't play; does not get out of the bed
0	Unresponsive

Source: Lansky, List, Lansky, Ritter-Sterr , Miller, 1987

Source: Schag et al, 1984; Lansky et al, 1987

Amendment 3

Protocol Title: A Phase 1, Multi-center, Open-label, Dose De-escalation Study to Evaluate the Safety and Efficacy of Talimogene Laherparepvec in Pediatric Subjects With Advanced Non-central Nervous System Tumors That are Amenable to Direct Injection

Amgen Protocol Number (Talimogene Laherparepvec) 20110261

EudraCT number 2015-003645-25

Amendment Date: 12 June 2020

Rationale:

This protocol is being amended to:

- Updated
  - (1) the number of pediatric subjects to be enrolled for the study from 18 to 27 to 18 to 24;
  - (2) the number of dose-limiting toxicities (DLT) evaluable subjects from 9 to 6 jn the event of a dose de-escalation; and
  - (3) the maximum of 18 subjects treated with at least 1 dose of talimogene laherparepvec with at least 9 DLT-evaluable subjects in cohort A1.

  Based on the current enrolment pattern of the study (a total of 11 subjects enrolled with 10 in cohort A1 and 1 in cohort B1), it's anticipated that the majority of the subjects enrolled going forward will be in cohort A1 (12 to ≤ 21 years). Thus, the sample size and the minimum number of DLT evaluable subjects for each cohort were adjusted for feasibility and evaluability for the primary endpoint.
- Update sample size considerations and DLT evaluation:
  - From 6 to 12 DLT-evaluable subjects to 18 to 24 subjects enrolled and treated with at least 1 dose of talimogene laherparepvec with at least 9 DLT-evaluable subjects in cohort A1
  - Clarify the 3+3 phase 1 design is for age cohort opening and dose de-escalation, assuming a true DLT incidence rate < 33% is used (with a minimum of 6 DLT-evaluable subjects)
  - Sample size for cohorts with age between 2 and 12 years are not required.
  - Clarified that after both cohorts are open, the Dose Level Review Team (DLRT) can review the safety data after the addition of 3 new DLT-evaluable subjects in a cohort until there're 9 DLT-evaluable subjects in the cohort. Additionally, ad-hoc meetings to review the safety data can be convened anytime, if deemed necessary. These changes were made to maximize the efficiency of the DLRT meeting based on safety need.

- Updated the definition for primary completion date to occur 35 days after the last subject has enrolled and received at least 1 dose of talimogene laherparepvec. The definition is modified based on the changes in the minimum number of DLT evaluable subjects for each cohort.
- Update objectives/endpoints:
  - [redacted]
  - Added exploratory objective and endpoint to assess [redacted]
- Inclusion criteria definition for adequate organ function is updated for
  - (1) hematological: no transfusion/growth factor support within 7 days from screening assessment instead of 4 weeks from screening blood count; and
  - (2) hepatic: serum bilirubin ≤ 1.5× baseline value if baseline value was abnormal for a subject with Gilbert's syndrome.

  These changes were made to ease restriction on the eligibility criteria since talimogene laherparepvec is not known to have serious adverse effects on bone marrow and liver function.
- Exclusion criteria updated:
  - for central nervous system (CNS) tumor or clinically active brain metastases updated with the clarification that subjects with a history of treated brain metastases shall be eligible if they fulfill the following criteria: radiographic evidence of improvement with CNS-directed therapy, and no interim progression is observed. This change was made to clarify the definition of clinically active brain metastases.
  - for receiving treatment in another investigational study device or study drug and major surgery updated to 14 days since ending treatment. These changes were made to align the wash out/waiting period from prior therapies with exclusion criteria 232, which was amended at the last protocol amendment.
  - Major surgery ≤ 14 days prior to enrollment or has not recovered to CTCAE version 4.0 grade 1 or better from adverse event due to surgery performed more than 14 days prior to enrollment.
- Updated language for reporting the serious disease-related events as all events to be reported to sponsor or designee within 24 hours.
- Make editorial and administrative changes throughout the document.

Amendment 2

Protocol Title: A Phase 1, Multi-center, Open-label, Dose De-escalation Study to Evaluate the Safety and Efficacy of Talimogene Laherparepvec in Pediatric Subjects With Advanced Non-central Nervous System Tumors That are Amenable to Direct Injection

Amgen Protocol Number 20110261

EudraCT number 2015-003645-25

NCT number NCT02756845

Amendment Date: 10 October 2018

Rationale:

This protocol is being amended to:

- Clarify that if [redacted]
- Update end of study language to align with the current protocol template language
- Update contraception language to align with the current risk and discomforts language
- Clarify transfusion timeframe in Inclusion Criterion 115 to ensure that adequate hematologic function is not confounded by a recent transfusion or growth factor support
- Clarify that subjects with history or evidence of giant congenital melanocytic nevi or dysplastic nevis syndrome are not excluded from the study (Exclusion Criterion 205) because such subjects are at risk of developing advanced melanoma with injectable disease and will therefore be eligible for the study
- Shorten the washout period for prior chemotherapy, treatment dose radiotherapy, or biological cancer therapy from 28 days to14 days prior to enrollment (Exclusion Criterion 229). The reason for this change is to ensure that subjects who are being considered for the study do not wait too long without treatment when they have already recovered from adverse event(s) due to prior therapy
- [redacted]
- Clarify that coagulation tests are only required at screening
- Update the number of sites participating in the study
- Update disease-related events language

- Remove ‘Reporting a Safety Endpoint as a Study Endpoint’ section as this section is not applicable to this study
- Update the matrix for determining the overall response to account for when nontarget lesion assessment was not done
- Remove self-evident corrections language
- Make editorial, typographical, and formatting changes throughout the document

Amendment 1

Protocol Title: A Phase 1, Multi-center, Open-label, Dose De-escalation Study to Evaluate the Safety and Efficacy of Talimogene Laherparepvec in Pediatric Subjects With Advanced Non-central Nervous System Tumors That are Amenable to Direct Injection

Amgen Protocol Number (Talimogene laherparepvec) 20110261

EudraCT number 2015-003645-25

Amendment 1 Date: 04 April 2017

Rationale:

The rationale for the major changes in the study design is provided below:

- The upper age limit of eligible subjects has been changed from 18 to 21 years of age to facilitate the enrollment of young adults with an advanced/recurrent/refractory pediatric tumor who might benefit from talimogene laherparepvec treatment.
- The lowest age cohort (0 to < 2 years of age) has been removed because of the following reasons:
  - the perceived toxicity risk of treating these pediatric patients, who have an immature immune system, with talimogene laherparepvec
  - the anticipated low benefit of talimogene laherparepvec treatment for this population for which standard of care and other proven salvage regimens are available for the type of advanced/recurrent/refractory pediatric tumor(s) seen in this age subset
- The requirement to enroll subjects according to herpes simplex virus type 1 (HSV-1) serostatus has been removed because of the following reasons:
  - low prevalence of HSV-1 positivity in the pediatric population
  - the addition of a recommendation to use premedication to mitigate the side effects of talimogene laherparepvec in HSV-1 negative subjects
- Maximum number of subjects enrolled was changed from 36 to 27 subjects because of the changes in the age cohorts.

Other changes to the protocol:

- Section 2 Background and Rationale was updated with background information that supports changes to the study design.
- Eligibility criteria were clarified and updated to reflect changes in the study design.
- Recommendation to use premedication with the appropriate antipyretic and/or antiemetic medications prior to each talimogene laherparepvec treatment was added to Section 6.2.1.1 Dosage, Administration, and Schedule.

- Rules for DLT evaluation were clarified and stopping rules were updated.
- Rules for opening younger age cohort were updated.
- Rules for dose de-escalation were updated.
- Childhood vaccinations that contain live attenuated virus were added to the list of excluded treatments.
- Schedule of Assessments table was updated to:
  - clarify the timing of procedures.
  - add an additional pregnancy test and performance status assessments
- Section 7.4 Laboratory Assessments was updated to clarify which tests will be done locally versus centrally.
- Text describing reporting procedures for serious adverse events was moved from Section 9.2.2.3 Reporting Serious Adverse Events After the Protocol-required Reporting Period to Section 9.2.2.2 Reporting Procedures for Serious Adverse Events.
- Exploratory endpoints were updated.
- Section 10 Statistical Considerations was updated to reflect changes in the study design.
- Appendix D was updated to clarify assessments for tumor response.
- Administration, typographical and formatting changes were made throughout the protocol.