BACKGROUND INFORMATION

FOR

JOINT MEETING OF THE CELLULAR, TISSUE, AND GENE THERAPY, AND ONCOLOGIC DRUGS ADVISORY COMMITTEES

29 APRIL 2015

BIOLOGICAL LICENSE APPLICATION FOR TALIMOGENE LAHERPAREPVEC

Submitted: 27 March 2015

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List of Abbreviations

Abbreviation or Term	Definition/Explanation
BLA	Biologics License Application
BRAF	v-raf murine sarcoma viral oncogene homolog B
BSL-1	Biosafety Level-1
CI	confidence interval
cm	centimeter
CR	complete response
CRF	case report form
CRO	contract research organization
CT	computed tomography
DFS	disease-free survival
DRR	durable response rate
EAC	Endpoint Assessment Committee
ECOG	Eastern Cooperative Oncology Group
FACT-BRM	Functional Assessment of Cancer Therapy Biologic Response Modifier
FDA	Food and Drug Administration
GM-CSF	granulocyte macrophage colony-stimulating factor
HCP	health care provider(s)
HR	hazard ratio
HSV-1	herpes simplex virus, type 1
IFN-γ	interferon-gamma
IL-2	interleukin-2
IT	intratumoral(ly)
ITT	intent-to-treat
IV	intravenous
IVRS	interactive voice response system
LDH	lactate dehydrogenase
ORR	overall response rate
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFU	plaque-forming unit(s)
PR	partial response
(q)PCR	(quantitative) polymerase chain reaction
REMS	Risk Evaluation and Mitigation Strategy
SC	subcutaneous(ly)
SCID	severe combined immunodeficiency

List of Abbreviations

Abbreviation or Term	Definition/Explanation
SMQ	standard MedDRA query
SPA	Special Protocol Assessment
TCID50	median tissue culture infective dose
TOI	Trial Outcome Index
TNM	tumor-node-metastasis
US	United States
WHO	World Health Organization

1. EXECUTIVE SUMMARY

Introduction

Amgen is seeking approval of talimogene laherparepvec for the treatment of injectable regionally or distantly metastatic melanoma. This briefing document summarizes data included in the Biologics License Application (BLA) submitted to the US FDA in support of this indication. Statistically significant and clinically meaningful efficacy results are presented, along with evidence of a favorable safety profile, supporting talimogene laherparepvec's utility as a new treatment option for patients with injectable regionally or distantly metastatic melanoma.

Background on Melanoma and Current Therapies

Melanoma is the fifth most common cancer type and the most common cancer in young adults aged 25 to 49 years. With an estimated 76,100 people diagnosed with melanoma and an estimated 9,710 deaths in 2014, melanoma remains a significant public health problem in the US. Depending on the course of their disease, patients often undergo multiple treatment modalities (eg, radiation, surgical resection, systemic immunotherapy, targeted novel therapies, and/or cytotoxic therapy). For patients without visceral disease (stage IIIB/C and stage IVM1a), 5-year survival rates are ≤ 50%.

Until 2011, treatment options were limited to dacarbazine or high-dose interleukin-2. Since then, 6 new drugs have been approved in the US in 2 classes of agents: the BRAF targeted agents and the immune checkpoint inhibitors. Response rates are high for the targeted agents, but the duration of response can be limited by the emergence of resistance. Response rates are more modest with the immune checkpoint inhibitors, but can be durable. There are specific toxicities associated with these 2 classes of agents, and their overall benefit-risk profiles have been determined primarily in patients with the most advanced stages of melanoma. An unmet medical need exists for additional treatment options that can provide patients with regionally or distantly metastatic melanoma an opportunity to achieve durable responses with a favorable safety profile.

Background on Talimogene Laherparepvec

Talimogene laherparepvec is a first-in-class oncolytic immunotherapy based on a herpes virus type 1 (HSV-1) that has been genetically modified as follows:

- A principal HSV-1 protein involved in viral evasion from innate host defense, ICP34.5, has been removed. Elimination of ICP34.5 reduces neurovirulence by 10,000- to 1,000,000-fold as compared to wild-type HSV-1.

- Proper antigen processing (for virus and tumor antigens) has been restored via the removal of ICP47.
- The US11 gene has been moved under the immediate early promoter for ICP47. Immediate early expression of US11 enhances replication of ICP34.5-deficient HSV-1 strains in tumors (but not normal tissues), which would otherwise have less efficient replication compared to wild-type HSV-1.
- The gene encoding human granulocyte macrophage colony-stimulating factor (hGM-CSF) has been inserted in each of the two ICP34.5 regions in place of the deleted sequences.
- The susceptibility of talimogene laherparepvec towards anti-HSV-1 therapeutics (eg, acyclovir) has been maintained.

Talimogene laherparepvec is injected directly into cutaneous, subcutaneous, or nodal lesions, resulting in selective lysis of the injected tumor cells (and not normal tissue). This results in the release and presentation of tumor-derived antigens and local expression of GM-CSF to initiate a systemic anti-tumor immune response that also induces regression of noninjected and distant lesions.

Clinical Efficacy Data

The BLA is based primarily on a phase 3 study (Study 005/05) of talimogene laherparepvec vs GM-CSF. GM-CSF was selected as the comparator based on its biological activity as an immunostimulatory cytokine and preliminary evidence of effects in patients with melanoma. The predefined primary efficacy endpoint was durable response rate (DRR), defined as the percentage of subjects (ie, patients with melanoma participating in the clinical trial) with responses (complete response [CR] or partial response [PR]) maintained continuously for 6 or more months and beginning at any point within 12 months of initiating therapy. Compared with an endpoint of overall response rate without evidence of durability, DRR is more clinically relevant since it is expected to be more likely to lead to prolonged survival. Secondary efficacy endpoints included overall survival (OS), overall response rate (defined as the percentage of subjects with PR and/or CR), time to response, and duration of response. The key results are as follows:

- A total of 436 subjects with melanoma (stage IIIB/C or stage IV with limited visceral disease burden) were randomized in a 2:1 ratio to receive either intratumoral talimogene laherparepvec or subcutaneous GM-CSF. Fifty-three percent of subjects had received prior therapy for melanoma.
- Talimogene laherparepvec demonstrated efficacy based on the primary endpoint, significantly improving DRR compared with GM-CSF per a blinded independent Endpoint Assessment Committee (EAC; 16.3% vs 2.1% respectively; p <0.0001).

  - A significant association was observed between the achievement of a durable response and improved OS, with a 95% reduction in the risk of death for subjects with a durable response prior to 12 months.
  - Durable response was also associated with a longer treatment-free interval (67% reduction in the risk of subsequent therapy) and improvements in the Trial Outcome Index, a composite quality of life measurement (odds ratio 2.8; 95% CI: 1.1, 7.0).
  - Most subjects with a durable response (57%) had an improvement in the appearance of their lesions.
  - Analyses to assess potential bias (eg, due to differences in early discontinuations) indicated a robust treatment difference favoring talimogene laherparepvec.

- Talimogene laherparepvec improved the overall response rate (CR or PR) compared with GM-CSF per EAC (26.4% vs 5.7% respectively). In particular, the CR rate was higher in the talimogene laherparepvec arm (10.8%) than in the GM-CSF arm (0.7%).
  - Although unresectable at baseline, after treatment with talimogene laherparepvec, 9 subjects were able to undergo surgery that successfully resulted in no residual disease.
- At the time of the primary analysis, talimogene laherparepvec showed a positive trend in survival. The median OS was 4.4 months longer in the talimogene laherparepvec arm than in the GM-CSF arm (hazard ratio: 0.79; p = 0.051).
- Results of the preplanned final analysis of OS (3 years after randomization) were consistent with the primary analysis (hazard ratio: 0.79; descriptive p = 0.049). The emergence of a plateau in the Kaplan-Meier survival curves was apparent by 3 years, with more than one-third of subjects still alive in the talimogene laherparepvec arm. Separation in the survival curves by treatment arm persisted through 5 years.
- Clear evidence of a systemic effect of talimogene laherparepvec was demonstrated.
  - Among evaluable subjects, 34.2% had a ≥ 50% reduction in the total burden of non-injected non-visceral lesions, and 11.3% had a ≥ 50% reduction in the total burden of visceral lesions (predominantly in the lung and liver).
  - The time course was consistent with a delayed regional and systemic anti-tumor immune response.
  - The risk of developing visceral metastases was reduced in subjects receiving talimogene laherparepvec compared with those receiving GM-CSF.

In a supportive, single-arm phase 2 study (Study 002/03) enrolling 50 subjects with stage IIIC or stage IV melanoma, a 28% objective response rate (CR and PR in 14 of 50 subjects) per investigator assessment was observed.

Safety Data

The safety of talimogene laherparepvec was evaluated in 408 subjects exposed to talimogene laherparepvec across the clinical program (6 studies). Of these

408 subjects, 292 subjects were treated in the phase 3 study for a median duration of 23 weeks.

The safety experience with talimogene laherparepvec consisted primarily of nonserious adverse events and anticipated events such as flu-like symptoms and cellulitis.

- Most adverse events were mild or moderate (63.4% talimogene laherparepvec, 74.0% GM-CSF). The most frequently reported adverse events were flu-like symptoms such as pyrexia, chills, and influenza-like illness. The incidence of these adverse events was more frequent during the first 3 cycles of treatment.
- The most frequently reported serious adverse events (talimogene laherparepvec, GM-CSF) were disease progression (3.1%, 1.6%) and cellulitis (2.4%, 0.8%).
- The incidence of fatal adverse events was 3.4% in the talimogene laherparepvec arm and 1.6% in the GM-CSF arm. The most frequently reported fatal adverse event was disease progression, with the remaining events due to other underlying disease processes; no treatment-related fatal adverse events were reported in either treatment arm.
- Adverse events were the primary reason for discontinuing study treatment in 11 subjects (3.8%) in the talimogene laherparepvec arm and 3 subjects (2.4%) in the GM-CSF arm.
- Herpetic events, primarily oral herpes, were reported in 5.5% of subjects in the talimogene laherparepvec arm. No serious herpes complications were reported.
- Among 1217 Family Surveillance Questionnaires and 82 Health Care Staff Questionnaires completed during Study 005/05, no events of secondary transmission of talimogene laherparepvec were documented. In 4100 treatment visits, there were 5 accidental exposures in 4 individuals, which were asymptomatic or resolved with acyclovir.
- Thirty subjects (27 talimogene laherparepvec; 3 GM-CSF) continued into an extension study with a maximum total duration of treatment of 30.8 months. No new safety signals were identified.

Nonclinical and clinical biodistribution data indicated that talimogene laherparepvec DNA is generally cleared from blood and urine by 1 week after dosing, and was only sporadically detected in low copy numbers at later time points. Talimogene laherparepvec DNA was infrequently detected on the surface of injected lesions in clinical studies, and was not detected in any shedding tissues in nonclinical studies. In an ongoing clinical biodistribution and shedding study (20120324), talimogene laherparepvec DNA was detected via quantitative polymerase chain reaction (PCR) in blood and urine samples, as well as on the surface of injected lesions, the exterior of occlusive dressings, and in 1 oral mucosa swab. Testing for viral infectivity was positive for 3 samples (1.9%) from injected lesions; all other samples tested (including the exterior of the occlusive dressings) were negative for infectious virus.

Proposed Risk Management Plan

Herpetic infection, accidental exposure to talimogene laherparepvec, and secondary transmission to close contacts are risks associated with treatment. A comprehensive risk management plan is proposed that will include pharmacovigilance activities and risk minimization measures.

Routine pharmacovigilance will include monitoring of adverse events and reports of exposure during pregnancy and/or lactation, submission of periodic safety reports, and identification of new safety signals.

Targeted pharmacovigilance activities include the following:

- Follow-up questionnaires to collect detailed information on reported potential herpetic infection in patients (ie, people receiving the product in the postmarketing setting) treated with talimogene laherparepvec, and any events of suspected accidental transmission in close contacts and HCPs
- A PCR assay to detect talimogene laherparepvec DNA in patients treated with talimogene laherparepvec, HCPs, and close contacts who report signs or symptoms of suspected herpetic illness
- A postmarketing, prospective, observational, cohort study to evaluate the incidence of suspected herpetic infection, risk of secondary transmission, and risk of herpetic infections in immunosuppressed individuals
- An ongoing, multicenter, observational registry study to evaluate long-term safety of subjects who previously received talimogene laherparepvec in clinical trials
- An ongoing, single-arm, phase 2 study to evaluate clinical biodistribution and shedding in treated patients following the end of treatment

Proposed risk minimization measures include communication in product labeling to HCPs regarding the potential risk of disseminated herpetic infection in severely immunocompromised patients, accidental exposure, herpetic infection, cellulitis at the injection site, impaired healing at the injection site, immune-mediated adverse events, and the observed development of a plasmacytoma at the injection site. Beyond product labeling, a Risk Evaluation and Mitigation Strategy (REMS) with a communication plan is proposed. The goals of the REMS are to inform HCPs and patients about the risks of herpetic infections and accidental exposure associated with talimogene laherparepvec. The components of the REMS include the following:

- The Dear Healthcare Provider letter will provide information about disseminated herpetic infection in severely immunocompromised patients, accidental exposure of health care providers and close contacts to talimogene laherparepvec, and potential harm to the fetus or neonate in pregnancy.

- The patient safety brochure, designed in a patient-friendly format for patients and close contacts, will provide information on the important risks associated with talimogene laherparepvec noted above and safe use to prevent accidental exposure.

Overall Benefit and Risk Conclusions

The data support a favorable benefit-risk profile of talimogene laherparepvec in patients with injectable regionally or distantly metastatic melanoma.

- In a phase 3, randomized, controlled study, talimogene laherparepvec demonstrated consistent efficacy based on DRR and overall response rate, as well as a positive trend in OS, with a survival curve plateau emerging by 3 years, which is characteristic of immunotherapies. Efficacy was supported by a phase 2, single-arm study that also had a number of long-term survivors.
- The results and observations from the clinical program indicate an acceptable safety profile for talimogene laherparepvec, with a low rate of grade 3 or higher adverse events, and no documented cases of secondary transmission to close contacts of treated subjects.
- Important identified and potential risks will be managed through appropriate pharmacovigilance and risk minimization measures and risk communication.

Melanoma is a complex cancer that requires the use of multiple treatment modalities for patients over the evolution of their disease. Despite recent advances in therapy, not all patients currently benefit, and there is a need for additional treatment options in this population. Effective control of metastatic disease prior to the development of large visceral disease burden is particularly important, since the survival rate for patients with the most advanced disease stages is still unacceptably low. Based on talimogene laherparepvec's consistent anti-tumor efficacy, positive trend in survival, and minimal incidence of grade 3 adverse events observed in the phase 3 study, talimogene laherparepvec has a positive benefit-risk profile for the treatment of patients with injectable regionally or distantly metastatic melanoma and limited visceral disease that cannot be adequately addressed with surgery. The benefit-risk profile of talimogene laherparepvec is further improved in patients with regionally or distantly metastatic melanoma that has not yet metastasized beyond the skin or lymph nodes (ie, IIIB/IIIC and stage IVM1a), a patient population with unmet medical need that could particularly benefit from additional treatment options.

2. OVERVIEW OF MELANOMA

2.1 Disease Background and Pathology

Melanoma is a tumor of melanocytes and is the most deadly form of skin cancers. Melanoma represents approximately 5% of all new cancer cases, and is the fifth most common cancer type as well as the most common cancer type in young adults aged 25 to 49 years (SEER; 2014). With an estimated 76,100 people diagnosed with melanoma and an estimated 9,710 deaths in 2014, melanoma remains a significant public health problem in the US.

Because many melanomas originate on sun-exposed areas, ultraviolet radiation is considered to be the main environmental cause of most cutaneous melanomas (Welch et al, 2005). Other risk factors include geographical location and ethnicity; white populations have a 10-fold higher risk of developing melanoma than black, Asian, or Hispanic populations, presumably due to the degree of skin pigmentation (Stevens et al, 1990).

Melanoma in adults is categorized according to the American Joint Committee on Cancer melanoma tumor, node, metastasis (TNM) staging classification (Balch et al, 2001; Allen and Spitz, 1953; Balch et al, 2009). Stages are based on the thickness, ulceration, and mitotic rate of the primary tumor, degree of lymph node involvement, and presence and location of metastases (American Cancer Society, 2013). Disease is usually staged based on clinical presentation (ie physical exam, biopsy, imaging), and pathologic presentation (ie, clinical presentation, lymph node / organ biopsies); the latter is more commonly employed. Like other tumors, melanoma can spread by local extension (through lymphatics) or to distant sites (by hematologic routes) to any organ, most commonly lungs and liver (Markovic et al, 2007). Depending on the course of their disease, patients often undergo multiple treatment modalities (eg, radiation, surgical resection, systemic immunotherapy, targeted novel therapies, and/or cytotoxic therapy).

Melanoma that has not spread beyond the initial site of disease is highly curable by surgical intervention. Most of these cases are thin tumors that have not invaded beyond the papillary dermis (stage 1: thickness ≤ 1.0 mm or ≤ 2.0 mm in the absence of ulceration). Melanoma that has invaded deeper or has spread to regional lymph nodes (stage II to stage III) may be curable with wide (1 cm to 2 cm) excision of the primary tumor and removal of any involved lymph nodes (Karakousis et al, 2006; Balch et al 2009). However, even with extirpative resections, most patients with

clinically detectable metastases to lymph nodes and/or in-transit disease (ie, metastasis and growth > 2 cm from the primary tumor but not yet at the nearest lymph node) will experience recurrence (Balch et al, 2009). Recurrence was also observed within 1.5 years in at least 50% of stage III patients who underwent resection or complete lymph node dissection (Hofmann et al, 2002; White et al, 2002). Melanoma that has spread to multiple regional nodal sites or presents with in-transit / satellite lesions (stage IIIB/C) is infrequently curable with standard therapy. In such cases, 5-year survival rates range between 40% (for stage IIIC disease) and 59% (for stage IIIB disease) (American Cancer Society, 2013).

Melanoma that has spread to distant skin, nodes, or visceral organs (stage IV) is also infrequently curable with standard therapy, although long-term survival is occasionally achieved by resection of metastases (Howard et al, 2012).

For patients without visceral disease (stage IIIB/C and stage IVM1a), 5-year survival rates are ≤ 50% (Table 1). Median survival decreases from 59 months for stage IIIB/C to 6 months for stage IV M1c disease (SEER*Stat database, 2014).

Table 1. Overall Survival Rates by Melanoma Stage

Disease Stage	Metastatic Disease Location	OS Rate 1-Year	OS Rate 5-Year
IIIB/C[a]	skin or nodes only	89%	48%
M1a	distant skin or nodes only	70%	32%
M1b	lung only	48%	16%
M1c	other visceral organs[b]	26%	6%

[a] weighted average for IIIB and IIIC
[b] or isolated high lactate dehydrogenase
*Source: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 18 Regs Research Data, Nov 2013 Sub (1973-2011)*

2.2 Current Treatments

Currently approved therapies for melanoma are summarized in Table 2. Until 2011, only two treatments for unresectable or advanced melanoma were approved by the US Food and Drug Administration (FDA): dacarbazine and high-dose interleukin-2 (IL-2). Dacarbazine is associated with a response rate of < 10% (Anderson et al, 1995; Chapman et al, 1999; Wagner et al, 2000; Middleton et al, 2000). Interleukin-2 was approved based on durable CRs observed in up to 6% of 270 subjects treated across 8 clinical studies (Proleukin®, 2012).

In 2011, FDA approved an immune checkpoint inhibitor, ipilimumab (Yervoy®, 2013), and a v-raf murine sarcoma viral oncogene homolog B1 (BRAF) inhibitor, vemurafenib (Zelboraf®, 2014). These were the first agents to demonstrate a survival advantage in melanoma (versus a vaccine control in the case of ipilimumab and versus dacarbazine in the case of vemurafenib). Overall response rates were 10.9% and 48.4% for ipilimumab and vemurafenib respectively, and CR rates were < 2% for either treatment.

In 2013, dabrafenib, a BRAF inhibitor in the same class as vemurafenib (Tafinlar®, 2014), and trametinib, a MEK inhibitor indicated in $BRAF^{V600}$ mutant melanoma were approved (Mekinist®, 2014) based on improved progression-free survival (PFS) compared with chemotherapy. Objective response rates were 52% and 22% for dabrafenib and trametinib, respectively, and CR rates were ≤ 3% for either treatment. The combination of trametinib and dabrafenib is also approved based on durable response rate (Tafinlar®, 2014; Mekinist® 2014; Table 2). The complete response rate was 9%.

In 2014, the FDA approved 2 programmed death receptor-1 (PD-1) blocking antibodies: pembrolizumab and nivolumab for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if $BRAF^{V600}$ mutation positive, a BRAF inhibitor (Keytruda®, 2014; OPDIVO®, 2015; Table 2). Approval of these agents was based on response rates and duration of response; overall survival has not yet been reported.

Table 2. Current FDA-Approved Treatment for Melanoma

Therapy	Approved Indication	Endpoints Evaluated for Regulatory Approval (from USPI)	Approval Type (date)
Dacarbazine (DTIC)	Treatment of metastatic malignant melanoma (Dabarbazine for injection, 2015)	Not available	Full (27 May 1975)
Interleukin-2	Treatment of adults with metastatic melanoma (Proleukin®, 2012)	Objective response	Full (09 January 1998)
Ipilimumab	Treatment of unresectable or metastatic melanoma (Yervoy®, 2013)	OS	Full (25 March 2011)
Vemurafenib	Treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test (Zelboraf®, 2014).	Treatment-naïve: OS; investigator-assessed PFS and BORR Prior systemic therapy: IRC-assessed BORR	Full (17 August 2011)
Dabrafenib	Single agent: treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.	<u>Single Agent</u> Inv.-assessed PFS IRRC-assessed ORR and durable response rate	Single Agent: Full (29 May 2013)
	In combination with trametinib: treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test (Tafinlar®, 2014).	<u>In Combination</u> (Inv.- and IRRC-assessed ORR; Inv.-and IRRC-assessed duration of response	In Combination: Accelerated (09 January 2014)

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USPI = United States prescribing information; CR = complete response; PR= partial response; DOR = duration of response; OS = overall survival; FDA = Food and Drug Administration; PFS = progression-free survival; Inv. = investigator; IRC = independent review committee; BORR = best overall response rate; IRRC = independent radiological review committee; ORR = objective response rate

Table 2. Current FDA-Approved Treatment for Melanoma

Therapy	Approved Indication	Endpoints Evaluated for Regulatory Approval (from USPI)	Approval Type (date)
Trametinib	Single agent or in combination with dabrafenib: treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test (Mekinist®, 2014)	Single Agent PFS; ORR	Single Agent: Full (29 May 2013)
		In Combination (see data for dabrafenib)	In Combination: Accelerated (08 January 2014)
Pembrolizumab	Treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor (Keytruda®, 2014; OPDIVO®, 2015).	IRC-assessed ORR; duration of response	Accelerated (04 September 2014)
Nivolumab			Accelerated (22 December 2014)

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USPI = United States prescribing information; CR = complete response; PR= partial response; DOR = duration of response; OS = overall survival; FDA = Food and Drug Administration; PFS = progression-free survival; Inv. = investigator; IRC = independent review committee; BORR = best overall response rate; IRRC = independent radiological review committee; ORR = objective response rate

While the approval of these agents represents a clear milestone in the treatment of advanced melanoma, there are some inherent limitations. With the immunotherapies, the rate of complete response is still low. With the targeted agents (eg, vemurafenib, dabrafenib, trametinib), the duration of responses can be limited due to innate or acquired resistance (Wagle, et al, 2011). In addition, vemurafenib, dabrafenib, and trametinib are indicated only for patients with $BRAF^{V600}$ mutant tumors (40% to 50% of melanomas; Columbino et al, 2012). Each class of agent is associated with specific toxicities, which can limit or preclude treatment in some cases; the checkpoint inhibitors (eg, ipilimumab and the anti-PD-1 agents) are associated with serious and sometimes fatal immune-related adverse events, and the targeted agents can be associated with severe skin toxicity, secondary skin cancers, and serious febrile reactions. When assessing the benefit-risk of these new agents, it is important to note that approximately 80% or more of patients in the registrational studies had stage IVM1b or IVM1c disease. The benefit-risk profile is less well established in the small subsets of patients with stage III or IVM1a disease (Table 3). Finally, the most appropriate combination and sequencing of these new drugs are still not known.

Table 3. Disease Stages in Studies of Recently Approved Agents

	Subjects (N)	IIIB/C + IVM1a	IVM1b/M1c
Ipilimumab	540	11% (n=57)	89%
Pembrolizumab	173	17% (n=29)	83%
Nivolumab	107	22% (n=24)	78%
Vemurafenib	337	16% (n=54)	84%
Dabrafenib	187	15% (n=29)	85%
Trametinib	214	16% (n=34)	84%
Dabrafenib + Trametinib	211	11% (n=24)	89%

Source: Long et al, 2014; Robert et al, 2014; Topalian et al, 2014; Flaherty et al, 2012; Hauschild et al, 2012; Chapman et al, 2011; Hodi S et al, 2010

The incidence of melanoma continues to rise, and even with recent advances in treatment, there is an important medical need for additional treatment options. Therapeutic options that can provide long-term disease control by producing durable responses, while also offering a favorable safety profile, are still required. Based on its

demonstrated benefit-risk profile and unique mechanism of action, talimogene laherparepvec represents one such potential option.

3. BACKGROUND ON TALIMOGENE LAHERPAREPVEC

3.1 Use of Genetically Altered HSV-1 as an Oncolytic Virus

Genetically-modified herpes simplex virus type 1 (HSV-1) is one of several identified viruses that selectively destroy tumor cells while sparing normal cells. These viruses propagate efficiently in tumors and mediate tumor lysis by various means, often by exploiting defects in immune detection, cell death pathways, and translational controls that normally facilitate tumor growth (Russell et al, 2012). The discovery that a genetically modified HSV-1 demonstrated anti-tumor activity in a mouse tumor xenograft model led to the generation of various engineered viral strains designed to enhance anti-tumor potency, drive host immune anti-tumor responses, and reduce clinical risk (Martuza et al, 1991; Russell et al, 2012). The primary driver of HSV-1 neurovirulence is the gene encoding ICP34.5 (Chou et al, 1990; Bolovan et al, 1994). The discovery that infection of tumors by an ICP34.5-deficient HSV-1 results in lysis of many tumor types while sparing normal tissues has resulted in the investigation of various ICP34.5-deficient HSV-1 strains as potential oncology therapeutics (Campadelli-Fiume et al, 2011).

The interferon-protein kinase R (PKR) pathway is a critical host defense mechanism that has evolved to protect cells against viral infection. Cellular activation of the PKR response following HSV-1 infection normally shuts off protein synthesis, promotes apoptosis, and activates autophagy in an effort to contain viral replication and spread. In turn, HSV-1 relies on the viral protein ICP34.5 to circumvent the cellular PKR response and allow viral replication. The basis of preferential tumor cell killing by ICP34.5-deficient HSV-1 appears to derive from defects in the PKR pathway and autophagy that may arise in tumors, which allows ICP34.5-deficient HSV-1 to propagate efficiently in these cells. In contrast, non-tumor cells with an intact interferon-PKR response and autophagy are able to efficiently suppress viral replication and eliminate ICP34.5-deficient HSV-1 (Campadelli-Fiume et al, 2011). The basis for ICP34.5-mediated neurovirulence appears to be similarly linked to the effects of ICP34.5 on the PKR response, and the potential for induced autophagy, apoptosis and other anti-viral responses that protect against viral replication in the nervous system.

3.2 Talimogene Laherparepvec

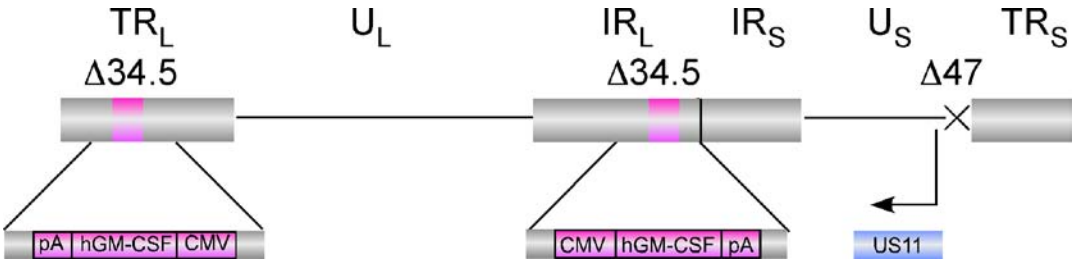
Talimogene laherparepvec is derived from a novel primary viral isolate (JS1, ECACC Accession Number 01010209), which demonstrates enhanced oncolytic activity towards

tumor cells as compared to the commonly used laboratory strains (eg, 17*syn*+) and other primary isolates (Liu et al. 2003).

The HSV-1 genome consists of linear, double-stranded DNA that is divided into two components, L (long) and S (short). Each component contains a unique region (U_L and U_S) flanked by inverted repeat regions, both internally (IR_L and IR_S) and at the termini (TR_L and TR_S). To facilitate the replication of talimogene laherparepvec in tumor cells but not in normal cells, and to maintain patient safety, the wild-type virus was genetically modified. These modifications are described below and shown in Figure 1.

- A principal HSV-1 protein involved in viral evasion from innate host defense, ICP34.5, has been removed. Deletion of ICP34.5 underlies preferential killing of tumor cells over normal cells. Selective viral replication in various tumors but not normal tissues is confirmed in nonclinical pharmacology and toxicology studies with talimogene laherparepvec. Elimination of ICP34.5 also reduces neurovirulence by 10,000- to 1,000,000-fold as compared to wild-type HSV-1 (Chou et al, 1990, Bolovan et al, 1994). Nonclinical studies with talimogene laherparepvec demonstrate markedly reduced neurovirulence following direct intracerebral injection or intranasal instillation as compared to that reported for wild-type HSV-1.
- In wild-type HSV-1, ICP47 impairs antigen processing and CD8+ T cell immunity (Hill et al, 1995, Ahn et al, 1996, Galocha et al, 1997, Goldsmith et al, 1998). Removal of ICP47 thus permits proper antigen processing (for both virus and tumor antigens) and is intended to aid the generation of a productive T cell adaptive immune response to facilitate development of an anti-tumor adaptive immune response. Enhanced MHC class I presentation is observed following elimination of ICP47 in the construction of talimogene laherparepvec.
- The US11 gene has been moved under the immediate early promoter for ICP47. Immediate early expression of US11 enhances replication of ICP34.5-deficient HSV-1 strains in tumors, which would otherwise have less efficient replication compared to wild-type HSV-1 (Taneja et al, 2001, Todo et al, 2001). When expressed as an immediate early gene, US11 rescues the growth defect associated with ICP34.5 deletion by inhibiting PKR before shutdown of protein synthesis, but does not restore neurovirulence in vivo (Mohr et al, 2001). Improved oncolysis is observed following immediate early expression of US11 in the construction of talimogene laherparepvec.
- The gene encoding hGM-CSF has been inserted in each of the two ICP34.5 regions in place of the deleted sequences. Local GM-CSF expression following intratumoral injection is intended to increase the influx and activation of antigen presenting cells, which process and present tumor-associated antigens derived from tumor cells as they die. These antigen presenting cells are intended to prime tumor-specific CD4+ and CD8+ T cells to stimulate and generate a systemic and specific anti-tumor immune response (Dranoff et al, 1993; Huang et al, 1994). Enhanced elimination of systemic (noninjected) tumors is observed following viral expression of GM-CSF.

Figure 1. Schematic of Talimogene Laherparepvec Genome



The talimogene laherparepvec genome is shown with the positions of the ICP34.5 and ICP47 deletions marked as Δ34.5 and Δ47, respectively; immediate early expression of US11 is driven by the ICP47 promoter. The site of the hGM-CSF cassette insertion is shown in pink and expanded to show the composition of the hGM-CSF expression cassette; the cytomegalovirus (CMV) promoter, hGM-CSF cDNA and a bovine growth hormone polyadenylation signal (pA) signal.

The susceptibility towards standard-of-care anti-HSV-1 therapeutics has been maintained via the viral thymidine kinase gene, which is responsible for phosphorylating common anti-herpes virus pro-drugs (eg, acyclovir, penciclovir, valacyclovir and famciclovir) to their active forms. In vitro studies demonstrated that talimogene laherparepvec remains susceptible to acyclovir.

None of the genetic modifications made to talimogene laherparepvec are considered to affect the capacity of HSV-1 to enter latency and subsequently reactivate. However, because talimogene laherparepvec is attenuated and replicates poorly in non-tumor tissue, the likelihood of developing a latent infection is reduced, and should a latent infection develop in nerve cells and the virus subsequently reactivate, clinical signs/symptoms may not develop.

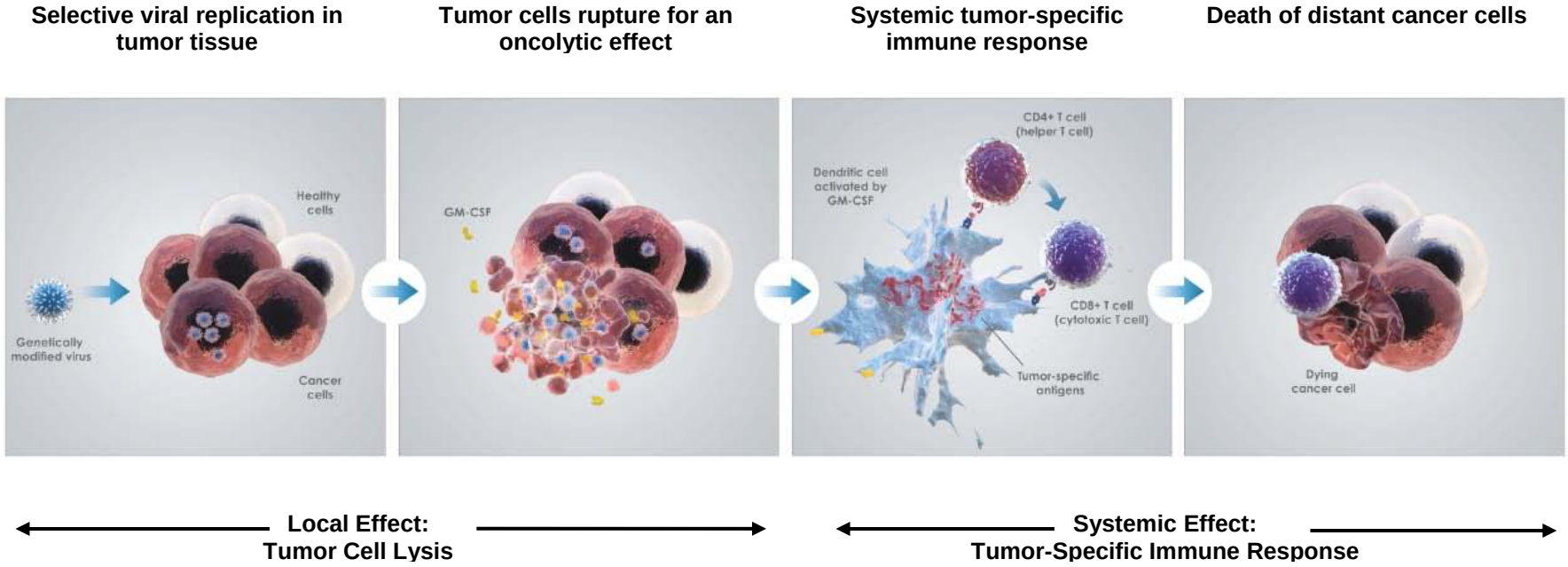
3.3 Mechanism of Action

The proposed mechanism of action of talimogene laherparepvec, depicted in Figure 2, is two-fold:

- to produce a direct oncolytic effect in injected lesions by replication of the virus in tumor cells, resulting in their lysis and the release of tumor-derived antigens while sparing normal tissues, and
- to produce a systemic anti-tumor immune response, which is enhanced by the local expression of GM-CSF.

Given this unique dual mechanism of action, talimogene laherparepvec is considered an oncolytic immunotherapy.

Figure 2. Dual Mechanism of Action for Talimogene Laherparepvec



3.4 Overview of Nonclinical Program

3.4.1 Nonclinical Pharmacology

The current model for the tumor-selective lysis of talimogene laherparepvec is based on the ability of normal cells to prevent replication of an ICP34.5-deficient HSV-1. In contrast, tumors may be impaired in anti-viral host defense pathways affecting host immunity or translational control, including the IFN/PKR response, thus allowing active viral replication and lysis (Meurs et al. 1993; Liang et al. 1999; Haus 2000; Farassati et al, 2001; Sarinella et al, 2006; Smith et al, 2006).

Specific mechanistic studies, designed to evaluate unique concerns related to the use of talimogene laherparepvec as an anti-cancer therapeutic, were conducted to evaluate direct lysis of a variety of tumor types in vitro. Studies were also conducted to evaluate selective tumor lysis and development of a systemic anti-tumor immune response following intratumoral (IT) injection in mice engrafted with a variety of human or syngeneic murine tumors. Because human GM-CSF does not bind to mouse GM-CSF receptor and has no activity in the mouse, certain nonclinical safety and pharmacology studies used a surrogate HSV-1 molecule encoding the murine version of GM-CSF (OncoVEX$^{mGM\text{-}CSF}$) to explore whether the expression of a pharmacologically active GM-CSF enhanced its activity or altered its safety.

The nonclinical pharmacology program demonstrated that:

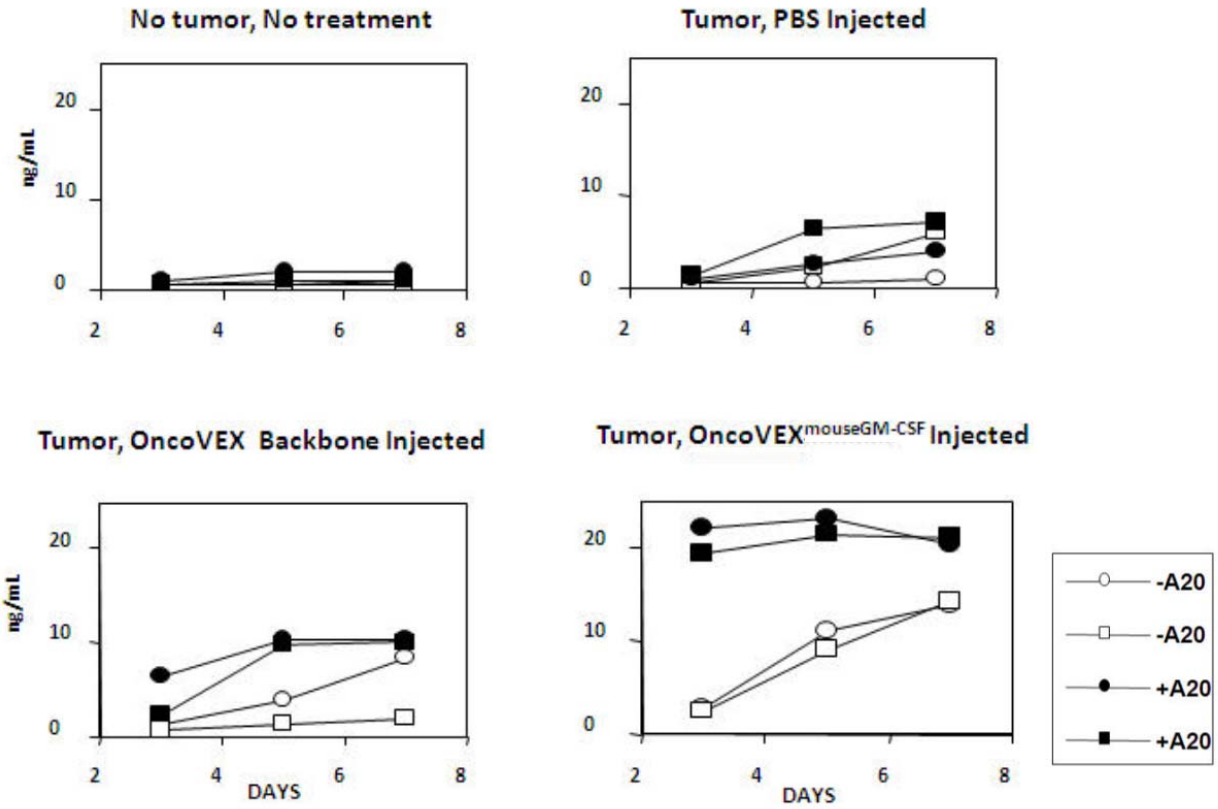
- Talimogene laherparepvec can kill a broad variety of tumor cells in vitro and in vivo. Expression of GM-CSF enhanced tumor cell killing in immune competent mice.
- Anti-tumor effects were observed in injected and noninjected (ie, contralateral) tumors in immune-competent mice. Whereas talimogene laherparepvec was detected in injected tumors, it was not detected in responding, noninjected tumors, indicating the development of a systemic anti-tumor immune response.
- Protection against tumor cell rechallenge was observed for up to 6 months in immune-competent mice following clearance of established tumors with talimogene laherparepvec and indicated the development of a durable anti-tumor immunity and immunological memory.
- Development of a tumor specific T cell-mediated immune response, as demonstrated by interferon-gamma (IFN-γ) production, is augmented by expression of GM-CSF as described below.

In this experiment, A20 tumors were implanted in 3 groups of immune-competent BALB/c mice; a fourth group of mice served as the control group (ie, no tumor) and were injected with phosphate buffered saline (PBS) only. Following the development of A20 tumors in the active groups, treatment was initiated by IT injection of either PBS,

OncoVEX backbone (JS1-/ICP34.5-/ICP47-), or OncoVEX$^{mouseGM\text{-}CSF}$; the no-tumor control group was left untreated. After two weeks, two mice were randomly selected from each group, splenocytes were prepared, and each suspension was incubated with either a) no cells added or b) mitomycin C-treated A20 cells [A20 cells were treated with mitomycin C before use to prevent their continued growth which could overwhelm the cultures and possibly distort the results]. The level of mouse IFN-ɣ in these supernatants was determined by capture ELISA following splenocyte T cell stimulation at 3, 5 and 7 days.

As shown in Figure 3 (presenting data from each of 2 mice per treatment group), a tumor-specific cell-mediated immune response was generated and enhanced by injection of A20 tumors with OncoVEX backbone or OncoVEX$^{mouseGM\text{-}CSF}$ compared with vehicle alone, and viral expression of GM-CSF (ie, OncoVEX$^{mouseGM\text{-}CSF}$) improved the immune response as compared to the virus that did not encode GM-CSF (ie, OncoVEX backbone).

Figure 3. IFN-gamma Release by Splenocytes From Individual Mice Treated as Indicated



3.4.2 Nonclinical Pharmacokinetics

Since talimogene laherparepvec is not administered systemically, traditional pharmacokinetic studies investigating absorption, distribution, metabolism, elimination, and drug-drug interactions are not relevant in evaluating oncolytic virus therapies such as talimogene laherparepvec. Nonclinical studies have therefore focused on the biodistribution and clearance, shedding, and replication of talimogene laherparepvec in normal and tumor-bearing mice.

- Clearance, biodistribution and shedding following intratumoral injection were characterized using a quantitative polymerase chain reaction (qPCR) assay to detect talimogene laherparepvec DNA. The qPCR assay detects a portion of amplified DNA, so is extremely sensitive, but does not indicate intact virus capable of infection.
  - Tumor: Talimogene laherparepvec DNA was present in tumor at 24 hours post last dose in 95% of samples tested, and persisted through 84 days post last dose in 20% of animals.
  - Shedding tissues: Talimogene laherparepvec DNA was not detected in testes, lachrymal glands, nasal mucosa or feces following IT dosing. Low levels of viral DNA were detected in urine after intravenous (IV) or subcutaneous (SC) administration in mice; urine samples after IT administration could not be analyzed for viral DNA due to assay inhibition. Viral DNA did not distribute to other shedding tissues, with the exception of a single salivary gland sample at Day 42.
  - Other tissues/organs: Talimogene laherparepvec DNA was not detected in bone marrow or eyes. Across all sample times (for tissues other than tumor), viral DNA was detected most frequently in blood (13%) and tissues associated with immune mediated viral clearance or tissues with high blood perfusion [spleen (16%), lymph nodes (8%), liver (8%), heart (5%), lungs (3%), and kidneys (3%)] following intratumoral administration. At 84 days postdose, low levels of viral DNA were detected in a few samples (1 to 2 specimens each, ≤ 2%) of spleen, liver, brain, and lymph node.
  - A total of five brain samples (approximately 3% in a total of 157 brain samples) had quantifiable talimogene laherparepvec DNA levels up to 84 days postdose across all mouse biodistribution studies. No adverse clinical signs were identified in any animal associated with a positive qPCR result in brain.

3.4.3 Nonclinical Toxicology

The toxicology program evaluated the safety of talimogene laherparepvec following repeated SC dosing for up to 12 weeks in the BALB/c mouse, and included studies evaluating repeated intratumoral injection. Evaluations for viral biodistribution in tissue, blood and excreta were conducted as a component of studies in both tumor-bearing and normal mice. In addition, a repeated IV dose study evaluated the embryo fetal developmental toxicity study of talimogene laherparepvec in the BALB/c mouse, including maternal-to-fetal viral transfer. Pivotal repeat-dose toxicology, biodistribution,

and embryo-fetal development studies were performed in accordance with Good Laboratory Practice regulations. Some studies evaluated the safety of repeated SC injection of OncoVEX$^{mGM\text{-}CSF}$ as a surrogate for talimogene laherparepvec, in which the human GM-CSF gene is replaced with the murine GM-CSF gene. Supplemental exploratory studies evaluated neurovirulence with talimogene laherparepvec following direct intra-cerebral injection or intranasal instillation in the BALB/c mouse, the in vitro susceptibility of talimogene laherparepvec to acyclovir as a standard-of-care anti-viral therapeutic, and tolerability or histopathology in tumor-bearing genetically immunodeficient mice (severe combined immunodeficiency (SCID) and nude strains).

- High and multiple doses (60-fold over the highest proposed clinical dose) of talimogene laherparepvec (up to 10^7 plaque-forming units [PFU]/animal) were well tolerated for up to 12 weeks in mice. In immune competent animals, the key histopathology findings were limited to reversible inflammatory responses at the injection site and immunological responses consistent with a normal response to viral infection.
- Data in severely immunocompromised (severe combined immunodeficiency [SCID] and nude mice) animals indicate a risk of disseminated herpetic infection, indicating a role for T-cells and B-cells in viral control; in particular, histopathological examination showed areas of necrosis and intranuclear inclusion bodies in the gastrointestinal tract, skin, brain, adrenal gland, pancreas and eyes of SCID mice. Higher doses of talimogene laherparepvec can be tolerated in athymic nude mice as compared to what is reported for wild-type HSV-1, indicating that talimogene laherparepvec may be attenuated for systemic viral infection in immune deficient mice.
- Published studies with ICP34.5-deficient HSV-1 viruses demonstrate 10,000- to 1,000,000-fold reduced neurovirulence as compared to wild type HSV-1 (Bolovan et al, 1994; Chou et al, 1990). Following direct intracerebral injection, talimogene laherparepvec demonstrated ~10,000-fold less neurovirulence as compared to that reported for wild-type HSV-1 (Study 4648-00004). Similarly, no mortality was seen in mice treated with talimogene laherparepvec by intranasal administration despite use of doses 100-fold greater than those doses associated with lethality in mice for wild-type HSV-1 (Study 4648-00014).
- Talimogene laherparepvec is equally sensitive to acyclovir as the unmodified parental strain of HSV-1.
- None of the genetic modifications made to talimogene laherparepvec are thought to affect the capacity of HSV-1 to enter latency and subsequently reactivate. The ICP34.5 deletion markedly reduces the ability of the virus to replicate in normal tissues and reduces neurovirulence; however, should talimogene laherparepvec enter latency in nerve cells and subsequently reactivate, clinical signs/symptoms may not develop.
- The risk of co-infection of the same cell by talimogene laherparepvec and wild type HSV-1 and successful recombination is considered low, since talimogene laherparepvec is directly injected into tumor cells and cannot spread effectively into normal tissue, while pre-existing or acquired HSV-1 would be in the mucosal tissues or neuronal ganglia of the patient.

3.5 Proposed Indication, Dosage and Regimen, Method of Administration, and Biosafety Level

Proposed Indication

The proposed indication for talimogene laherparepvec is the treatment of injectable regionally or distantly metastatic melanoma.

Dosage and Regimen

Talimogene laherparepvec is administered by intralesional injection into cutaneous, subcutaneous, and/or nodal lesions that are visible, palpable, or detectable by ultrasound guidance; visceral lesions are not injected.

The initial dose of talimogene laherparepvec is a concentration of 10^6 PFU/mL. Subsequent doses begin at least 3 weeks after the first dose and consist of talimogene laherparepvec at a concentration of 10^8 PFU/mL every 2 weeks. This dosing regimen was based on the results of phase 1 Study 001/01, in which subjects with HSV-1 seronegative status at baseline who received doses higher than 10^6 PFU/mL had more marked febrile reactions at higher doses following the first dose. Therefore, it was concluded that subjects who are HSV-1 seronegative at baseline should not receive > 10^6 PFU/mL of talimogene laherparepvec as the first dose. The administration of 10^6 PFU/mL as the first dose followed by multiple doses of 10^8 PFU/mL was well tolerated by all subjects. Additional details of the rationale for various aspects of the proposed dose and schedule are provided in Table 4.

Table 4. Rationale for Dose and Schedule of Talimogene Laherparepvec in Study 005/05

Initial dose of 10^6 PFU/mL	• In HSV seronegative patients, more pronounced local reactions and febrile influenza-like syndromes were observed with doses > 10^6 PFU/mL • This initial dose is sufficient for seroconversion without negatively impacting clinical response
3 week interval between 1st and 2nd dose	• Majority of HSV seronegative patients seroconvert within 3 weeks
Subsequent doses of 10^8 PFU/mL	• The 10^8 PFU/mL dose was well tolerated in seropositive patients and was the highest dose studied in clinical studies
2 week frequency after the 2nd dose	• Frequency based on timing of local reactions (~2 weeks) and indications of virus replication on tumor surfaces (~2 weeks)
Maximum volume of 4 mL	• Based on size of individual tumors expected to be injected, with recognition that after administration replication would occur • In animal studies, total doses up to 60-fold over the highest clinical dose have been evaluated without severe AEs; however, volumes above 4mL have not been evaluated in clinical studies

Talimogene laherparepvec is provided in single-use vials of 1 mL, each containing either 10^6 PFU / mL (for initial dosing), or 10^8 PFU / mL (for subsequent dosing). The maximum volume administered during each treatment is 4 mL, with precedence given to new, then larger, lesions; any single lesion can be injected at more than one treatment visit. The volume injected into each lesion is based on the longest lesion dimension. This ranges from ≤ 0.1 mL for a longest dimension ≤ 0.5 cm up to 4 mL for a longest dimension of > 5 cm (Table 5).

Table 5. Selection of Talimogene Laherparepvec Injection Volume Based on Lesion Size

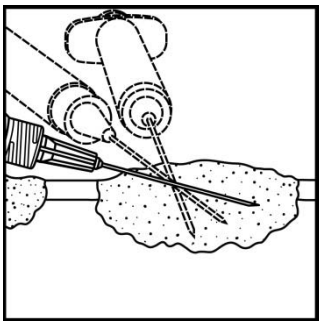
Lesion size (longest dimension)	Talimogene laherparepvec injection volume	Dose concentration: 10^6 (1 million) PFU/mL	Dose concentration: 10^8 (100 million) PFU/mL
> 5 cm	up to 4 mL	up to 4 million PFU	up to 400 million PFU
> 2.5 cm to 5 cm	up to 2 mL	up to 2 million PFU	up to 200 million PFU
> 1.5 cm to 2.5 cm	up to 1 mL	up to 1 million PFU	up to 100 million PFU
> 0.5 cm to 1.5 cm	up to 0.5 mL	up to 500,000 PFU	up to 50 million PFU
≤ 0.5 cm	up to 0.1 mL	up to 100,000 PFU	up to 10 million PFU

PFU = plaque-forming units

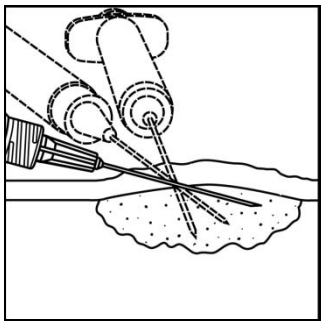
Method of Administration

Using a single insertion point, talimogene laherparepvec is injected along multiple tracks as far as the radial reach of the needle allows within the lesion (Figure 4); multiple insertion points can be used if the lesion is larger than the radial reach of the needle. To ensure even dispersion, the needle is pulled back without exiting, and redirected as often as necessary until the full dose is injected and dispersed. To maintain sterility, a separate needle is used to inject each lesion.

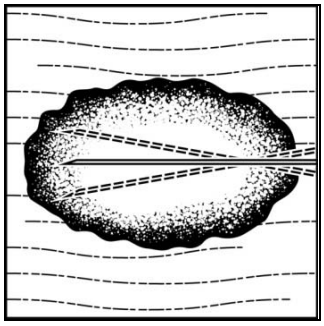
Figure 4. Method of Injection for Talimogene Laherparepvec



Injection administration for cutaneous lesions



Injection administration for subcutaneous lesions



Injection administration for nodal lesions

Biosafety Level

The deletions in the viral backbone render talimogene laherparepvec significantly less virulent than the parent organism, wild type HSV-1. The extensive characterization of talimogene laherparepvec and other ICP34.5 deleted versions of HSV-1 in animal models and humans, including the safe dosing of over 400 patients with talimogene laherparepvec, suggest that talimogene laherparepvec can be handled as a Biosafety Level -1 (BSL-1) at healthcare facilities. BSL-1 is defined as suitable for work involving well-characterized agents not known to consistently cause disease in immunocompetent adult humans, and that present minimal potential hazard to laboratory personnel and the environment (Biosafety in Microbiological and Biomedical Laboratories, 5th Edition, CDC, 2009).

Talimogene laherparepvec is not stable on occlusive dressings, with less than 1% input virus remaining after 24 hours (with a marked decrease in recoverable infectious virus observed between 4 and 8 hours). On plastic surfaces, an approximate 2-log reduction in virus infectivity was observed after 4 hours at room temperature. A variety of readily

available cleaning agents, including 2.5% bleach, 70% isopropyl alcohol, 0.8% Vesphene, or 0.8% LpH have been shown to reduce talimogene laherparepvec infectivity by more than 6 logs within 1 minute.

3.6 Overview of Clinical Program

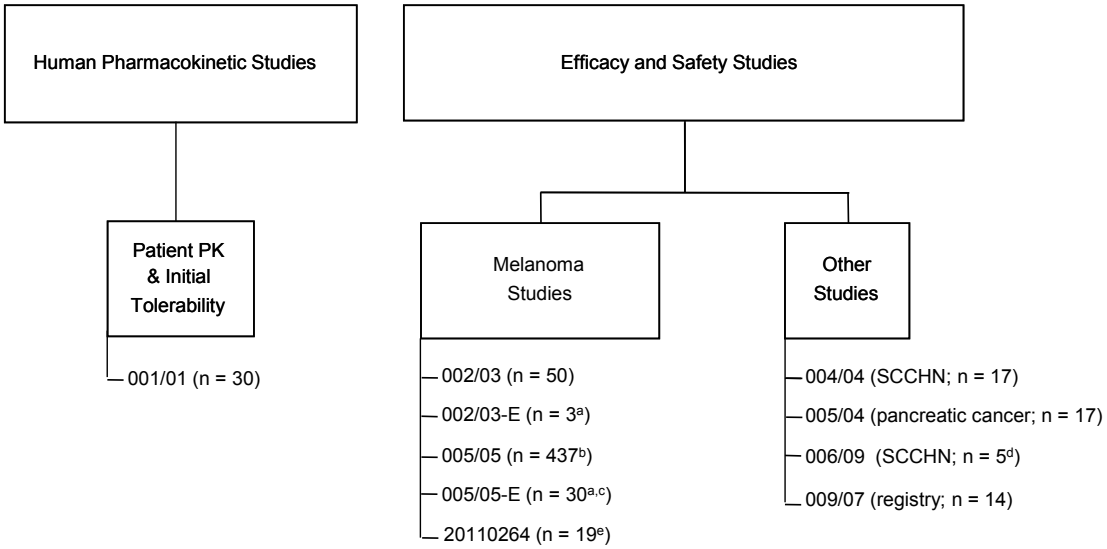
The safety and efficacy of talimogene laherparepvec in subjects with melanoma was evaluated in a pivotal, controlled, phase 3 study (Study 005/05) and a supportive, single-arm, phase 2 study (Study 002/03). The primary design aspects of each study are summarized in Table 6. Further studies in subjects with other tumor types included in the BLA are provided in Figure 5. These include a first-in-human study conducted in subjects with solid tumors (Study 001/01), efficacy/safety studies conducted in subjects with pancreatic cancer (Study 005/04) and squamous cell carcinoma of the head and neck (Studies 004/04 and 006/09), and an observational registry study for subjects previously treated with talimogene laherparepvec (Study 009/07). A study of talimogene laherparepvec in combination with ipilimumab in subjects with melanoma (Study 20110264) is also ongoing.

Table 6. Summary of Key Design Aspects in Melanoma Clinical Studies

	Study 002/03	Study 005/05
Study phase	2	3
Design	Open-label, single-arm	Randomized, open-label vs GM-CSF
Population Enrolled	Subjects with injectable stage IIIC or stage IV melanoma	Subjects with injectable stage IIIB/C or stage IV melanoma.
No. of Subjects Treated	50	436
Tumor Response Criteria	RECIST	Modified WHO
Dose and Schedule	Up to 4 mL x 10^6 PFU/mL (initial) Up to 4 mL x 10^8 PFU/mL (3 weeks after initial dose) Up to 4 mL x 10^8 PFU/mL (every 2 weeks thereafter)	
Treatment Duration	8 doses over 15 weeks; if biological activity was observed, dosing could continue for another 16 doses over 32 weeks	Minimum of 24 weeks unless subsequent therapy was required; maximum of 18 months depending on response
Status	Complete	Complete
Optional Extension	002/03-E	005/05-E

GM-CSF = granulocyte macrophage colony-stimulating factor; PFU = plaque-forming units; RECIST = Response Evaluation Criteria in Solid Tumors; WHO = World Health Organization

Figure 5. Organogram of Talimogene Laherparepvec Clinical Studies in This Marketing Application



PK = pharmacokinetics; SCCHN = squamous cell carcinoma of the head and neck
[a] Reflects a subset of subjects enrolled in the principal study
[b] Talimogene laherparepvec: n = 296; granulocyte macrophage colony-stimulating factor: n = 141. Includes one subject who was randomized 3 times (at 3 different sites). The subject ultimately received talimogene laherparepvec and was included in the safety analyses, but excluded from the intent-to-treat analyses.
[c] Talimogene laherparepvec: n = 27; granulocyte macrophage colony-stimulating factor: n = 3.
[d] Talimogene laherparepvec + chemoradiation: n = 2; chemoradiation only: n = 3
[e] Reflects enrollment at data cutoff. Data from nine subjects in Ph 1b portion are summarized separately.

3.7 Clinical Development History

Key interactions with the FDA leading up to the submission of the BLA are provided in Table 7.

Table 7. Key Regulatory Interactions for Talimogene Laherparepvec

Date	Activity
22 Apr 2005	Submitted IND; "Safe-to-Proceed" letter received May 2005
18 Jan 2008	Type B End-of-Phase 2 meeting to discuss the phase 3 clinical trial protocol
17 April 2008	FDA agreement achieved in the SPA for the phase 3 study (Study 005/05) protocol
08 Aug 2008	End-of-Phase 2 meeting to discuss CMC-specific issues
21 Jan 2011	Fast track designation granted
14 March 2011	Orphan drug designation granted
22 May 2013	Type B Meeting on the proposed post-marketing pharmacovigilance plan and risk minimization activities
04 Oct 2013	Type B Pre-BLA Meeting to discuss clinical, nonclinical and quality aspects of the talimogene laherparepvec program in advance of the submission of the BLA
25 July 2014	BLA submitted

IND = Investigational New Drug; SPA = Special Protocol Assessment; BLA = Biologics License Application

4. CLINICAL EFFICACY DATA

4.1 Study 005/05

4.1.1 Study Design and Endpoints

The primary evidence of efficacy in melanoma comes from a single phase 3, multicenter, open-label, randomized clinical study comparing talimogene laherparepvec and GM-CSF in 436 subjects with stage IIIB, stage IIIC and stage IV melanoma that was not surgically resectable. Subjects were to have at least one cutaneous, subcutaneous, or nodal lesion that was injectable either directly or via ultrasound guidance, and was measurable via calipers or computed tomography (CT) scan as having at least one diameter ≥ 10 mm; this could also include multiple injectable lesions with a total aggregate diameter ≥ 10 mm. Subjects were to have ≤ 3 visceral metastases (lung lesions excepted), and none of these visceral lesions could exceed 3 cm in diameter. The most advanced patients, who may not benefit from any delayed immune effects, were excluded. This included patients with advanced or rapidly progressing liver disease and patients with active brain or bone metastases. For similar reasons, subjects also were to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and lactate dehydrogenase levels (LDH) ≤ 1.5 times the upper limit of the normal range.

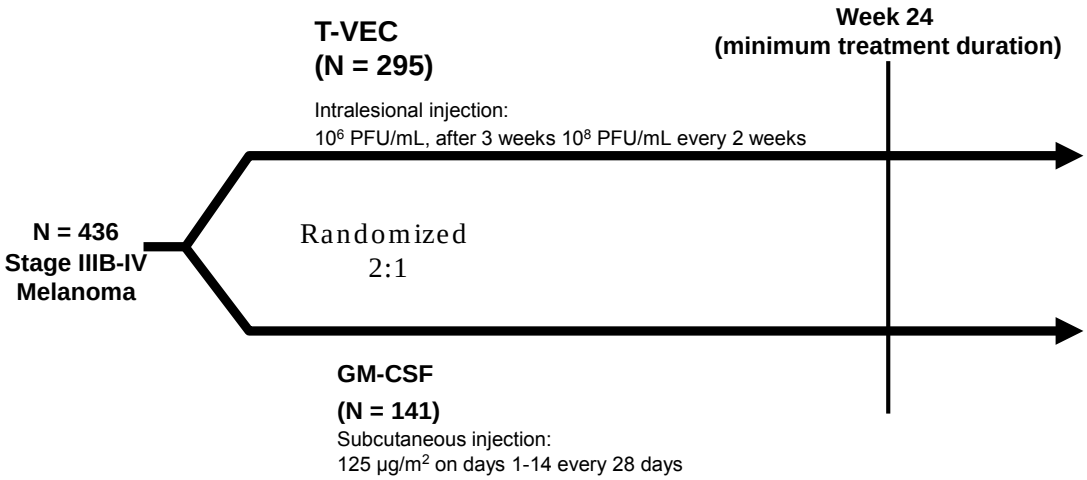
Subjects were randomized in a 2:1 ratio to receive either talimogene laherparepvec or GM-CSF (n = 295 and n = 141, respectively). Talimogene laherparepvec was administered as described in Section 3.5, and GM-CSF was administered at a dose of 125 $\mu g/m^2$/day SC for 14 days, followed by a 14-day rest period. To allow for the development of an adaptive immune response, subjects were treated for a minimum of 24 weeks or until no injectable lesions remained, and treatment was to continue during this period despite an increase in lesion size and/or development of any new lesion(s) unless other therapy for melanoma was required (per investigator discretion). Enrollment and treatment were conducted between 2009 and 2011. Subjects were followed for survival for 3 years after randomization (ie, through 2014).

The primary efficacy endpoint was DRR, defined as the rate of responses (CR or PR) maintained continuously for 6 or more months and beginning at any point within 12 months of initiating therapy. Compared with an endpoint of overall response without evidence of durability, an endpoint that describes durable response is more clinically relevant since it may be more likely to lead to prolonged survival.

Secondary efficacy endpoints included OS, overall response rate (ORR, defined as the percentage of subjects with PR and/or CR), time to response, and duration of response. Progression-free survival was not chosen as a secondary endpoint because an increase in lesion size and/or development of new lesion(s) prior to response was expected based on results from the phase 2 study (Study 002/03). Instead, time to treatment failure was chosen as another secondary endpoint. Time to treatment failure was defined as the time from randomization until the first episode of clinically relevant disease progression (ie, disease progression that was associated with a decline in performance status and/or, in the opinion of the investigator, required alternative therapy) where there was no subsequent response after the progression event, or until death.

Blinding was not possible in Study 005/05 due to the different modes of administration of the investigational products. Durable response and overall tumor response were confirmed by a blinded Endpoint Assessment Committee (EAC) (see Section 4.1.2.1). In addition, a number of sensitivity analyses were conducted to investigate potential biases as a result of the open-label nature of Study 005/05 (see Section 4.1.3.3).

Figure 6. Schema for Study 005/05



Dosing with Talimogene laherparepvec or GM-CSF continued until:

- Clinically relevant disease progression (eg, decrease in performance status) after 24 weeks on study; discontinuation due to disease progression was not mandated prior to 24 weeks
- Twelve months on therapy was reached without any response up to that time
- Intolerable toxicity
- The patient withdrew consent
- The investigator believed that it was in the best interest of the patient to stop investigational therapy or be given other therapy

Treatment with talimogene laherparepvec could not continue if there was no residual injectable disease

Rationale for Use of GM-CSF as Comparator

Granulocyte-macrophage colony-stimulating factor (GM-CSF) was chosen as an appropriate comparator for Study 005/05, as discussed and agreed upon with FDA as part of the SPA. A placebo control was rejected since subjects would derive no potential treatment benefit and its use would be a barrier to enrollment. Use of approved active controls would have been limited to dacarbazine and high dose interleukin-2 (IL-2), the only two therapies available when Study 005/05 was initiated, neither of which had demonstrated a survival benefit. As described in Section 2.2, response rates with these two treatments were low, and high-dose IL-2 is only indicated for patients with normal cardiac and pulmonary function due to its association with capillary leak syndrome (Proleukin®, 2012).

GM-CSF (sargramostim, Leukine®) is a cytokine approved in the US for use in myeloid reconstitution following myelosuppression. GM-CSF can also activate dendritic cells to increase antigen presentation and can potentiate both cell-mediated and humoral immune responses (Inaba et al, 1992; Fischer et al, 1988; Weisbart et al, 1985). This has led to its investigation as an anti-melanoma agent either in combination with other immunologic approaches (such as an immune adjuvant for cancer vaccines) or as monotherapy following surgery to prevent relapses (Kaufman et al, 2014).

At the time Study 005/05 was designed, results from a single-arm phase 2 study were available that suggested overall and disease-free survival (DFS) were significantly prolonged (compared with matched historical controls) in subjects who received post-surgical treatment with GM-CSF (125 $\mu g/m^2$ for 14 days followed by 14 days of rest) for 1 year after surgical resection, and that this treatment was well-tolerated (Spitler et al, 2000). These results were the basis for the design of a randomized, placebo-controlled, phase 3 cooperative group study (E4697) in which GM-CSF administered after surgery demonstrated a significant improvement in median DFS over placebo at the time of the initial analysis (11.8 months vs 8.8 months; hazard ratio [HR] = 0.827, p = 0.034). Significance was not achieved in a subsequent analysis (HR = 0.88, p = 0.14, 95% CI [0.73,1.04]); however, there were trends toward improvement in DFS and OS for the 40% of subjects in the study with most advanced stage of disease (resectable stage IV) disease (DFS: HR = 0.74; 95% CI [0.56, 0.99], p = 0.04; OS: HR = 0.72; 95% CI [0.5, 1.02]; p= 0.07) (Lawson et al, 2010).

Selection of GM-CSF, a potentially immunologically active and well tolerated agent, as the comparator in Study 005/05 could allow treatment to continue in both treatment arms long enough for the development of an anti-tumor immune response, as late responses were sometimes observed in the phase 2 study (Study 002/03). Finally, given that GM-CSF is the product of the transgene that is expressed by talimogene laherparepvec, it had potential biological relevance as a comparator.

Although the efficacy and safety of single-agent GM-CSF in melanoma has not been definitively established, its activity in unresectable, late-stage melanoma patients has recently been demonstrated. Results of a US cooperative group, randomized, phase 2 study in advanced melanoma (n = 245) showed that the addition of GM-CSF to ipilimumab significantly improved OS over ipilimumab alone (17.5 months vs 12.7 months), yielding a statistically significant 36% reduction in mortality risk (p = 0.014) (Hodi et al, 2013).

GM-CSF would be a valid comparator as long as it was no worse than a placebo. Based on the available evidence of its activity in melanoma, it is unlikely that GM-CSF treatment accelerated disease or shortened survival in Study 005/05. Moreover, any favorable effect of GM-CSF on response or survival in the current study would raise the threshold for demonstration of superiority relative to a placebo comparison.

4.1.2 Assessments and Analysis Methods

4.1.2.1 Prospectively Planned Analyses

Subjects underwent a formal documentation of treatment effect beginning on the first day of the second cycle of treatment. Skin lesions were measured by ruler and subcutaneous/nodal lesions by palpation with calipers to define lesion measurements; color digital photographs of all visible tumors were also obtained. Soft tissue nodal lesions were identified at baseline using whole body CT or PET scans and ultrasonograms, all of which were performed every 12 weeks after the start of treatment. Biopsies or residual pigmented areas or any areas no longer suspected to contain tumors could also be taken at any time per investigator discretion. Bi-directional measurements were documented by the investigator and compared to baseline measurements to determine response.

The endpoints of DRR and ORR were determined according to modified World Health Organization (WHO) criteria, based on the following response categories:

- CR: disappearance of all clinical evidence of tumor (both measurable and nonmeasurable but evaluable disease), including any new tumors which might have appeared. Any residual cutaneous or subcutaneous masses must be documented by representative biopsy to not contain viable tumor.
- PR: achieving a 50% or greater reduction in the sum of the products of the perpendicular diameters of all measurable tumors at the time of assessment as compared to the sum of the products of the perpendicular diameters of all measurable tumors at baseline. If any new tumors have appeared, the sum of the products of the perpendicular diameters of these must have reduced by 50% or more from when first documented.
- SD: neither sufficient overall tumor shrinkage to qualify for response (PR or CR) nor sufficient tumor increase to qualify for PD.
- PD: a >25% increase in the sum of the products of the perpendicular diameters of all measurable tumors since baseline, or the unequivocal appearance of a new tumor since the last response assessment time point.

As noted previously, a blinded EAC was used to confirm response data in the efficacy analyses. As described in the EAC Charter, the EAC consisted of a team of oncologists who hold a board certification in medical oncology and have experience treating subjects with melanoma. The EAC members were selected (with review by Amgen) by a contract research organization (CRO) that also entered into contracts with radiologists and dermatologists who reviewed data from this study.

The EAC confirmed subject response data when either of the following occurred:

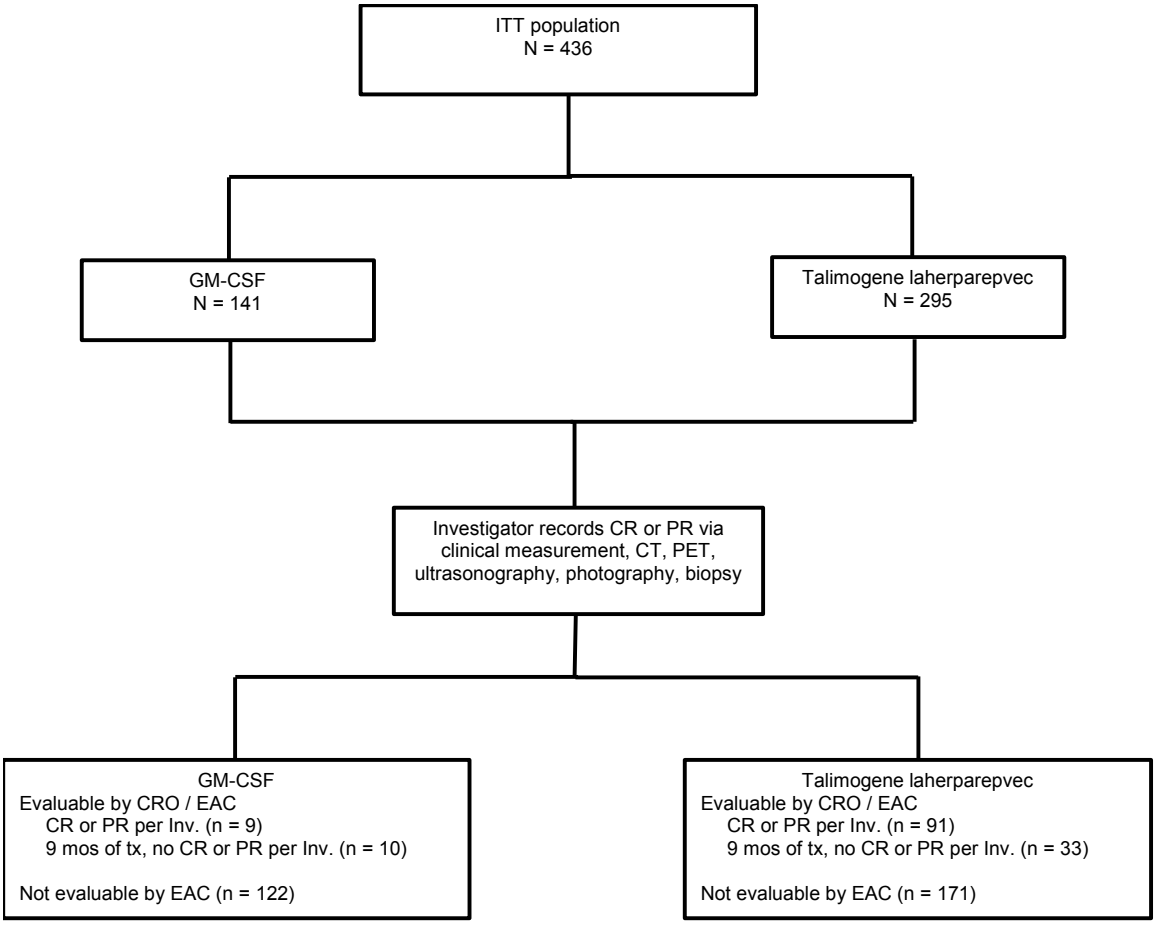
- The investigator recorded a CR or PR for a subject
- A subject reached 9 months of treatment without a response having been recorded. The 9-month timeframe was considered sufficient for a subject to have developed an adaptive response over 3 months (as observed via a scheduled radiological scan at 12 weeks after starting treatment) and for that response to have been sustained for 6 months to be considered a durable responder.

All relevant data (eg, clinical measurements, scans, photographs) were uploaded to a database at the CRO that was accessible for blinded evaluation by the CRO's radiologists and dermatologists. The results of these evaluations were forwarded to the EAC.

Two members of the EAC performed an independent assessment of response status at each visit for subjects triggered for EAC review. If there was disagreement between reviewers as to a subject's response status and/or the dates of response, a third independent EAC member, the adjudicator, provided a final determination of the results. Since evaluations are based on the presence of injectable and measurable cutaneous, subcutaneous, or nodal lesions, this level of review is more comprehensive than other

oncology studies in which only a select number of target lesions are considered for response assessment. In Study 005/05, data from 143 subjects were evaluated for response by the EAC (Figure 7).

Figure 7. Summary of Subjects Evaluated by Endpoint Assessment Committee



ITT = intent-to-treat; GM-CSF = granulocyte macrophage colony-stimulating factor; CR = complete response; PR = partial response; CT = computed tomography; PET = positron emission tomography; CRO = contract research organization; EAC = Endpoint Assessment Committee; Inv. = investigator; tx = treatment

The primary analysis of DRR was conducted when no further subjects had the possibility of meeting the criteria for durable response in Study 005/05 (data cutoff date: 21 December 2012). The primary analysis of DRR was performed using a two-sided unadjusted Fisher Exact test to determine whether talimogene laherparepvec improved DRR relative to GM-CSF. The Fisher Exact test was applied to the intent-to-treat (ITT) population. Multivariate statistical analyses (secondary analyses including a logistic regression model corresponding to the Fisher Exact test) tested for treatment effect while controlling for the potentially important prognostic factors.

The primary analysis of OS (defined as the time from the date of randomization to the date of death from any cause) was conducted as of 31 March 2014 when 290 deaths (as specified in the study's statistical analysis plan) occurred. Overall survival time was censored at the last date the patient was known to be alive when the confirmation of death was absent or unknown. Subjects were censored at the date of randomization if no additional follow-up data were obtained. The primary method for the OS analysis was an unadjusted log-rank test. Statistical significance was to be declared at a 2-sided 0.05 level. The Cox proportional hazard model was used to estimate the hazard ratio for the treatment effect. In addition, the Cox model was used to adjust for the same prognostic factors used in the analysis of DRR. Kaplan-Meier medians were derived along with 95% confidence intervals. A final analysis of OS was conducted at 3 years after randomization using the same analysis method. However, this analysis was considered descriptive.

To evaluate the efficacy of talimogene laherparepvec in subgroups defined by the stratification factors and key covariates, the treatment effect on durable response, overall response, and OS was investigated using Gail and Simon quantitative and qualitative interaction tests.

Secondary endpoints of response onset, time to treatment failure, duration of response, and response interval were analyzed using a log-rank test for the ITT population.

Two types of exploratory analyses were performed on the data from the primary analysis of OS to explore the association between durable response and OS among subjects randomized to each separate treatment arm. The first was a landmark analysis to compare DR and survival at fixed times through 18 months. In addition, a more formal time-dependent proportional hazard model was evaluated where onset of DR was analyzed as a time-dependent covariate.

4.1.2.2 Post-hoc Analyses

The following post-hoc analyses were conducted:

- Duration of response in responding subjects:

  Since duration of response is based on achieving a CR or PR, duration of response was defined to be zero if no PR or CR was ever achieved. An analysis including only responding subjects in each arm was conducted. An analysis evaluating the duration of CR was also conducted.
- Progression prior to response:

To evaluate the proportion of subjects who may have progressed before ultimately responding to treatment, an analysis was conducted to evaluate the percentage of subjects who had an increase in tumor burden of ≥ 25% and/or appearance of new lesions before ultimately achieving a durable response per EAC. Increases in tumor burden and/or appearances of new lesions have also been observed with other immunotherapies (ie, pseudoprogression).

- Association between durable response and treatment-free interval:

  A landmark analysis was conducted to evaluate the association between durable response and treatment-free Interval (the interval from the last dose of study therapy received to the first dose of subsequent systemic therapy).

- Association between durable response and Trial Outcome Index:

  A landmark analysis was conducted to evaluate the association between durable response and the Trial Outcome Index, a quality of life measure based on the validated Functional Assessment of Cancer Therapy Biologic Response Modifier (FACT-BRM).

- Analyses of potential sources of bias:

  An analysis was conducted to evaluate the potential effect of bias on DRR per EAC due to imbalances in early discontinuations between treatment arms. In this analysis, the number of durable responses for subjects who discontinued early was imputed (in the GM-CSF arm only) based on the DRR for those GM-CSF subjects who did not discontinue early.

  An analysis also was conducted to evaluate potential differences in the incidence and timing of subsequent anticancer therapy between treatment arms.

  A sensitivity analysis for OS was conducted based on updated survival status for subjects lost to follow-up, based on publicly available information.

Systemic Effects

At FDA's request, a post-hoc analysis of systemic activity (ie, beyond local effects in injected lesions) in the talimogene laherparepvec arm was conducted.

As described in Section 3.5, precedence for injection is given to new, and then to larger lesions. In addition, the maximum volume per dose is 4 mL. Therefore, not all measurable lesions were recorded as injected; such lesions were considered "noninjected" for purposes of this analysis.

The following endpoints were evaluated to assess responses in various lesion types (injected, noninjected nonvisceral lesions, and noninjected visceral lesions):

- Incidence of lesion response among all lesions
- Subject incidence of lesion response
- Subject incidence of overall response

- Maximum decrease in tumor burden (individual lesions and overall)
- Time to individual lesion response

Analyses of systemic effects were based on measurable lesions from subjects in the Systemic Effect Analysis Set (subjects who received at least 1 dose of talimogene laherparepvec, administered intralesionally).

Lesion Response

The maximum decrease in tumor size (based on bidimensional measurements per modified WHO criteria) for evaluable lesions was categorized (> 0%, ≥ 50%, 100%) and presented by lesion type. The incidence of lesion response was reported as the proportion of lesions in the "≥ 50%" category.

Overall Lesion-Type Response

Overall tumor burden was calculated as the sum of tumor sizes (based on bidimensional measurements per modified WHO criteria) of all lesions of the same type at a visit. The incidence of overall lesion-type response (ie, an overall lesion-type burden with a ≥ 50% decrease from baseline) was summarized by lesion type. The incidence of subjects with lesion-type response was summarized for each lesion type. Graphical presentations of the distribution of the maximum decrease in overall lesion-type burden were produced using waterfall plots.

Time to Lesion Response

Time to lesion response by lesion type was analyzed using the Kaplan-Meier method for evaluable lesions of the same lesion type. For new lesions, the time to lesion response was assessed from the time the lesion was first detected. Kaplan-Meier estimates of event quartiles and the corresponding 95% CIs, when estimable, were based on a sign test (Brookmeyer and Crowley, 1982). In the case where the median could not be estimated by the Kaplan-Meier method, the median was estimated from an exponential model.

Time to response for lesions that responded was summarized as a continuous variable.

Risk of Developing Visceral Metastases

In addition, the risk of developing visceral metastases was evaluated using the Kaplan-Meier method and Cox proportional hazards models. Visceral/bone metastasis-free survival was calculated from date of randomization to date of appearance of first

visceral or bone melanoma lesion(s). Subjects who did not develop visceral or bone lesions were censored at the date of their last tumor response assessment. Tumor assessments were not required after treatment discontinuation due to disease progression, including in the absence of first visceral or bone melanoma lesions.

Clinical Benefit

At FDA's request, outcomes describing clinical benefits such as a decrease in pain, an improvement in Quality of Life, and prolonged survival were tabulated for the subjects with a durable response per EAC.

4.1.3 Results

4.1.3.1 Disposition, Demographics and Baseline Disease Characteristics

The ITT population consisted of 436 randomized subjects (295 talimogene laherparepvec; 141 GM-CSF; Table 8). A total of 418 subjects received ≥ 1 dose of investigational product (291 talimogene laherparepvec, 127 GM-CSF). As of the primary analysis cutoff date, all subjects in the talimogene laherparepvec and GM-CSF arms had discontinued treatment. The most common reason for treatment discontinuation was progressive disease (65.6% talimogene laherparepvec, 74.8% GM-CSF).

As of the primary analysis cutoff date, 56.9% of subjects in the talimogene laherparepvec arm and 70.2% of subjects in the GM-GSF arm had discontinued study treatment and long-term survival follow-up. The most common reason for study discontinuation was death (97.6% talimogene laherparepvec, 86.9% GM-CSF).

Table 8. Subject Disposition With Discontinuation Reason (Study 005/05; Intent to Treat Population)

	GM-CSF (N = 141)	Talimogene Laherparepvec (N = 295)	Total (N = 436)
Investigational product accounting			
Subjects who never received study treatment	14 (9.9)	4 (1.4)	18 (4.1)
Subjects who received study treatment	127 (90.1)	291 (98.6)	418 (95.9)
Subjects continuing study treatment[a]	0 (0.0)	0 (0.0)	0 (0.0)
Subjects who discontinued study treatment[a]	127 (90.1)	291 (98.6)	418 (95.9)
Maximum allowed dose without PR/CR	9 (7.1)	26 (8.9)	35 (8.4)
PR or CR for at least 6 continuous months	0 (0.0)	42 (14.4)	42 (10.0)
Progressive disease	95 (74.8)	191 (65.6)	286 (68.4)
Adverse event	3 (2.4)	11 (3.8)	14 (3.3)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)
Deaths	3 (2.4)	5 (1.7)	8 (1.9)
Consent withdrawn	12 (9.4)	10 (3.4)	22 (5.3)
Physician decision	5 (3.9)	6 (2.1)	11 (2.6)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)
Study completion accounting			
Subjects continuing study treatment and long-term survival follow-up	42 (29.8)	127 (43.1)	169 (38.8)
Subjects who discontinued study	99 (70.2)	168 (56.9)	267 (61.2)
Lost to follow-up	1 (1.0)	0 (0.0)	1 (0.4)
Deaths	86 (86.9)	164 (97.6)	250 (93.6)
Consent withdrawn	11 (11.1)	3 (1.8)	14 (5.2)
Physician decision	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (1.0)	1 (0.6)	2 (0.7)

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[a] Treatment in Study 005/05
N = Number of subjects in the analysis set.
Number of subjects screened: 684
First subject randomized: 11MAY2009.
Intent to treatment population includes all subjects that have been randomized. Subjects will be analyzed using the randomized treatment.
Source: Study 005/05 Primary CSR Table 14-1.1

The mean age of subjects enrolled in this study was 63 (range: 22 to 94) years (Table 9). Most subjects were men (57%) and were white (98%). With regard to baseline disease characteristics, most subjects had an ECOG score of 0. Of the enrolled subjects, approximately 57% had disease limited to the skin or lymph nodes (stage IIIB/C, stage IV M1a) while the remainder had Stage IV M1b and M1c disease, including 4 subjects (all randomized to talimogene laherparepvec) with prior brain metastases. In addition, 53% of subjects had received prior therapy for melanoma

(other than or in addition to surgery, adjuvant therapy, or radiation). The 3 most common prior therapies were biologic therapy (33%), chemotherapy (29.1%), and radiation therapy (23%). Overall, 58% of subjects were seropositive for wild-type HSV-1 at baseline.

Table 9. Key Baseline Demographics (ITT Population; Study 005/05)

	GM-CSF (N = 141)	Talimogene Laherparepvec (N = 295)	Total (N = 436)
Sex - n (%)			
Male	77 (54.6)	173 (58.6)	250 (57.3)
Female	64 (45.4)	122 (41.4)	186 (42.7)
Race - n (%)			
White	138 (97.9)	289 (98.0)	427 (97.9)
Black	2 (1.4)	1 (0.3)	3 (0.7)
Asian	0 (0.0)	1 (0.3)	1 (0.2)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (0.3)	1 (0.2)
Other	1 (0.7)	3 (1.0)	4 (0.9)
Age (years)			
n	141	295	436
Mean	62.92	63.14	63.07
SD	14.13	13.67	13.80
Median	64.00	63.00	63.00
Q1, Q3	54.00, 74.00	54.00, 74.00	54.00, 74.00
Min, Max	26.0, 91.0	22.0, 94.0	22.0, 94.0
ECOG performance status - n(%)			
0	97 (68.8)	209 (70.8)	306 (70.2)
1	32 (22.7)	82 (27.8)	114 (26.1)
Missing	12 (8.5)	4 (1.4)	16 (3.7)
Disease stage from CRF - n(%)			
Stage IIIB	12 (8.5)	22 (7.5)	34 (7.8)
Stage IIIC	31 (22.0)	66 (22.4)	97 (22.2)
Stage IV M1a	43 (30.5)	75 (25.4)	118 (27.1)
Stage IV M1b	26 (18.4)	64 (21.7)	90 (20.6)
Stage IV M1c	29 (20.6)	67 (22.7)	96 (22.0)
Missing	0 (0.0)	1 (0.3)	1 (0.2)
Line of therapy per IVRS			
First line	65 (46.1)	138 (46.8)	203 (46.6)
≥ Second line	76 (53.9)	157 (53.2)	233 (53.4)
HSV-1 status			
Negative	45 (31.9)	97 (32.9)	142 (32.6)
Positive	78 (55.3)	175 (59.3)	253 (58.0)
Unknown	18 (12.8)	23 (7.8)	41 (9.4)

N = Number of subjects in the analysis set; SD = sample standard deviation; Q1 = first quartile; Q3 = third quartile . ECOG = Eastern Cooperative Oncology Group; IVRS = interactive voice response system
Intent to treatment population includes all subjects that have been randomized. Subjects were analyzed using the randomized treatment.
Source: Study 005/05 Primary CSR Table 14-2.2.1

4.1.3.2 Primary and Secondary Efficacy Endpoints

Treatment with talimogene laherparepvec statistically significantly improved DRR compared with GM-CSF (16.3% vs 2.1%, $p < 0.0001$; Table 10). Similar results were observed based on investigator assessment of DRR (19.0% vs 1.4%; $p < 0.0001$). A high degree of correlation was observed between the EAC and investigator assessments (kappa statistic 0.78; 95% CI: 0.69, 0.87).

Treatment with talimogene laherparepvec also improved ORR per EAC (26.4% talimogene laherparepvec, 5.7% GM-CSF), particularly with regard to the proportion of subjects with a CR (10.8% talimogene laherparepvec, 0.7% GM-CSF).

Among the 86 responders (78 talimogene laherparepvec, 8 GM-CSF) included in a post-hoc analysis, the duration of response (CR or PR) was longer in the talimogene laherparepvec arm. In the talimogene laherparepvec arm, 56 responses were still ongoing at the end of treatment; the median duration of response had not been reached and was not estimable. Based on Kaplan-Meier estimates, the probability of talimogene laherparepvec-treated subjects still being in response at 12 months was 65%. The probability of talimogene laherparepvec-treated subjects still being in complete response was 84% at 12 months, 75% at 24 months, and 72% at 36 months (extending beyond 4 years).

Of the responders in the talimogene laherparepvec arm, 42 (54%) experienced an increase in overall lesion size of ≥ 25% and/or developed at least one new lesion prior to ultimately achieving a response, consistent with a delayed immune response.

The median time to treatment failure was 8.2 months in the talimogene laherparepvec arm and 2.9 months for the GM-CSF arm (hazard ratio 0.42; 95% CI: 0.32, 0.54).

Table 10. Summary of Tumor Response Results per EAC From Study 005/05

Study Endpoint	GM-CSF (N=141)	Talimogene laherparepvec (N=295)
Durable Response Rate	2.1% (95% CI: 0.0, 4.5)	16.3% (95% CI: 12.1, 20.5)
	Unadjusted odds ratio 8.9; (95% CI: 2.7, 29.2); p < 0.0001	
Overall Response Rate	5.7% (95% CI: 1.9%, 9.5%)	26.4% (95% CI: 21.4%, 31.5%)
CR - n (%)	1 (0.7%)	32 (10.8%)
PR - n (%)	7 (5.0%)	46 (15.6%)
Duration of response (median)	2.8 months	Not reached
	HR: 0.40; (95% CI: 0.14, 1.18)	
Time to Response (median)	3.7 months (95% CI: 1.9, 5.6)	4.1 months (95% CI: 3.8, 5.4)
Time to Treatment Failure[a] (median)	2.9 months (95% CI: 2.8, 4.0)	8.2 months (95% CI: 6.5, 9.9)
	HR: 0.42; (95% CI: 0.32, 0.54)	

[a] Time from randomization until the first episode of clinically relevant disease progression where there is no subsequent response after the progression event, or until death. These data reflect the investigator's assessment because the EAC assessment does not provide sufficient information for this endpoint.

Source: Study 005/05 Primary CSR Table 10-3, Table 14-4.2.1, and Table 14-4.11.3

In the primary analysis of OS, at a median follow-up time of 44.4 months, median OS for the ITT population was 4.4 months longer in the talimogene laherparepvec arm relative to GM-CSF (hazard ratio = 0.79; 95% CI: 0.62, 1.00; p = 0.051; Table 11 and Figure 8). The median OS was 23.3 months for talimogene laherparepvec and 18.9 months for GM-CSF. Kaplan-Meier survival rates over 4 years ranged from 73.7% at 1 year to 32.6% at 4 years in the talimogene laherparepvec arm and 69.1% to 21.3%, respectively, in the GM-CSF arm.

Based on results of a post-hoc analysis, the median OS for subjects who met the criteria for durable response and overall objective response were not estimable due to an insufficient number of events in either treatment arm. For subjects who met the criteria for durable response, the 3-year Kaplan-Meier survival rate was 96% (95% CI: 84%, 99%) for talimogene laherparepvec and not estimable for GM-CSF due to a lack of events (Table 11). For subjects who met the criteria for overall objective response, the 3-year Kaplan-Meier survival rates (95% CI) were 88% (79%, 94%) for talimogene laherparepvec and 75% (32%, 93%) for GM-CSF. The 4-year Kaplan-Meier survival rates were lower, but were still above 75%, for both durable and objective responders.

As per the Statistical Analysis Plan, a final, descriptive analysis of OS was conducted when all subjects had been followed for at least 3 years after randomization. After an

additional 4 months of follow-up (relative to the primary analysis of OS), median OS was 4.4 months longer in the talimogene laherparepvec arm compared to the GM-CSF arm [23.3 months and 18.9 months respectively (Table 11 and Figure 9)]. The unstratified hazard ratio was 0.79 (95% CI: 0.62, 1.00), with a descriptive p-value of 0.049. These results reflect one additional death event and are consistent with the results observed in the primary analysis of OS.

Table 11. Overall Survival Results

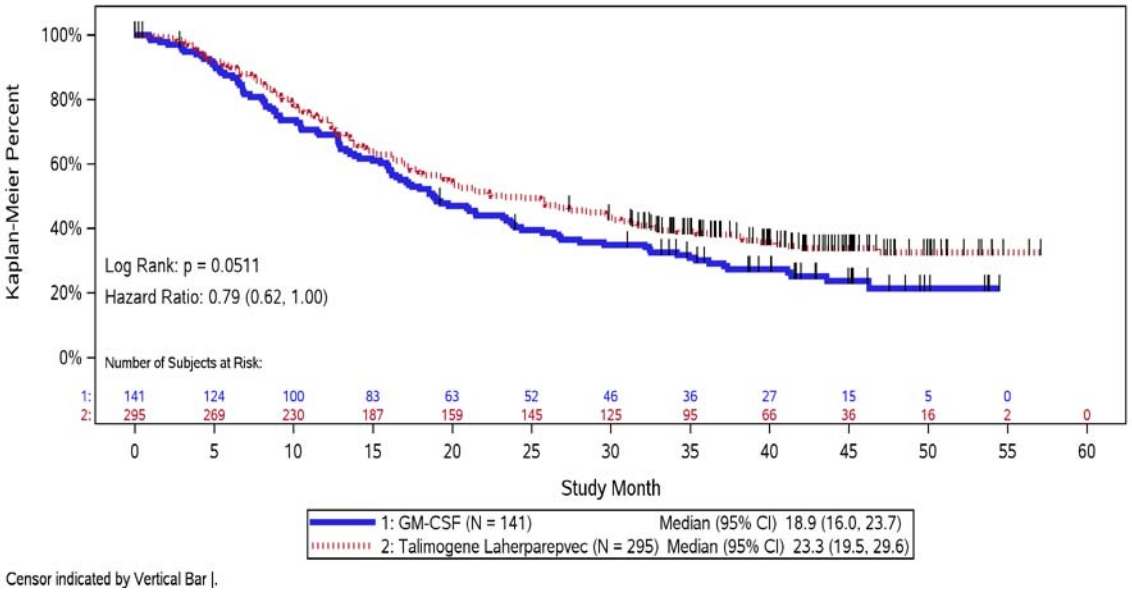
Overall Survival	GM-CSF	Talimogene laherparepvec
Primary Analysis (290 events)		
Deaths – n (%)	101 (71.6)	189 (64.1)
Median OS, Months (95% CI)	18.9 (16.0, 23.7)	23.3 (19.5, 29.6)
HR (95% CI), p-value	0.79 (0.62, 1.00), 0.051	
KM OS estimates - %		
ITT Population (n)		295
At Month 12	69.1	73.7
(95% CI)	(60.6, 76.2)	(68.3, 78.4)
At Month 24	40.3	49.8
(95% CI)	(32.0, 48.4)	(44.0, 55.4)
At Month 36	30.1	38.6
(95% CI)	(22.5, 38.0)	(33.0, 44.2)
At Month 48	21.3	32.6
(95% CI)	(13.7, 30.0)	(26.6, 38.7)
Durable Responders per EAC (n)		48
At Month 36	100	95.8
(95% CI)	(-,-)	(84.4, 98.9)
At Month 48	100	89.0
(95% CI)	(-,-)	(72.2, 95.9)
Objective Responders per EAC (n)		78
At Month 36	75.0	88.2
(95% CI)	(31.5, 93.1)	(78.5, 93.7)
At Month 48	62.5	77.7
(95% CI)	(22.9, 86.1)	(64.5, 86.5)
Final Analysis (291 events)		
Deaths – n (%)	101 (71.6)	190 (64.4)
Median OS, Months (95% CI)	18.9 (16.0, 23.7)	23.3 (19.5, 29.6)
HR (95% CI), p-value[a]	0.79 (0.62, 1.00), 0.049	
KM estimate - %		
At Month 36	30.4	38.9
(95% CI)	(22.9, 38.3)	(33.3, 44.4)
At Month 48	23.9	34.5
(95% CI)	(16.8, 31.7)	(28.9, 40.1)
At Month 60	--	33.4
(95% CI)	--	(27.7, 39.2)

-- = not applicable; GM-CSF = granulocyte macrophage colony-stimulating factor; OS = overall survival; HR = hazard ratio; CI = confidence interval

[a] P-value is descriptive.

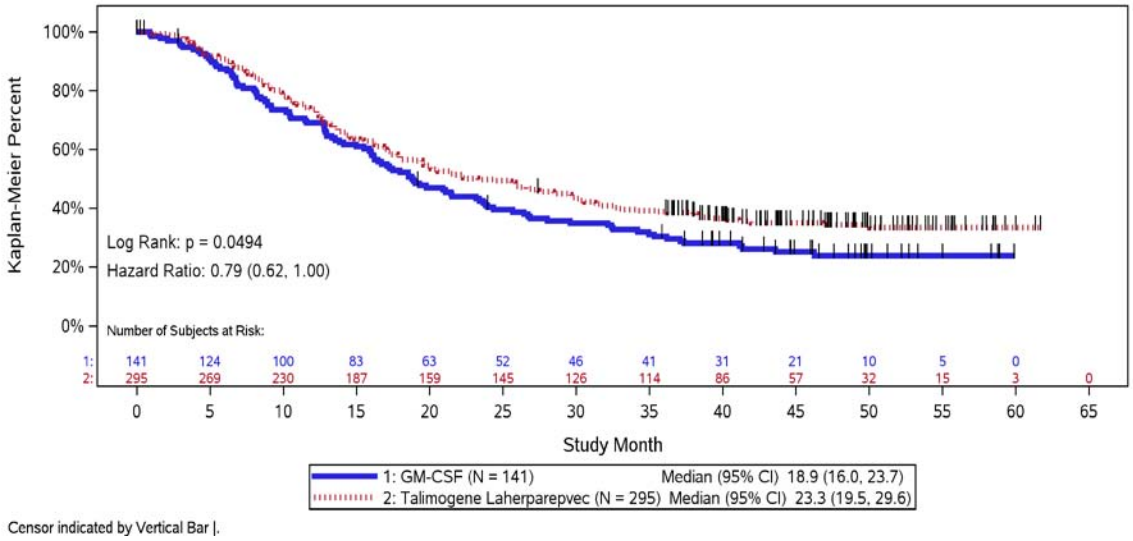
Source: Study 005/05 Supplemental CSR Table 14-4.3.1, Table 14-4.3.19, Table 14-4.3.20; Final analysis Table 14-4.3.1

Figure 8. Kaplan-Meier Curve: Primary Analysis of Overall Survival (Intent-to-Treat Population, Study 005/05)



Source: Study 005/05 Supplemental CSR Figure 14-4.1.1

Figure 9. Kaplan-Meier Curve : Final Analysis of Overall Survival (Intent to Treat Population, Study 005/05)



Source: Study 005/05 Final Analysis Figure 14-4.1.1

4.1.3.3 Additional Analyses

Subgroup Analyses of Durable Response and Overall Survival

At the time of their respective primary analyses, DRR and OS were analyzed for the ITT population within subgroups defined by randomization stratification factors and / or key covariates. These analyses were considered exploratory because the study was not

sufficiently powered to prospectively detect treatment differences within these subgroups.

The treatment effect of talimogene laherparepvec on durable response rate (Figure 10) was heterogeneous across subgroups based on the stratification factors and / or key covariates. The magnitude of the estimated treatment effect on durable response and OS was statistically significantly greater (ie, nominal $p \leq 0.05$, not adjusted for multiplicity) in certain subgroups, particularly subjects with stage IIIB/C and IV M1a disease and subjects who received talimogene laherparepvec as first-line therapy (Figure 11).

Baseline HSV serostatus (positive, negative) was a covariate considered to be clinically meaningful in the analysis of efficacy. As shown in Table 12, talimogene laherparepvec statistically significantly improved durable and overall response rates (per EAC) compared with GM-CSF regardless of baseline HSV serostatus.

Figure 10. Forest Plot (Absolute Difference) for Durable Response Rate per EAC: Key Covariates Based on CRF Collection (Study 005/05; Intent to Treat Population)

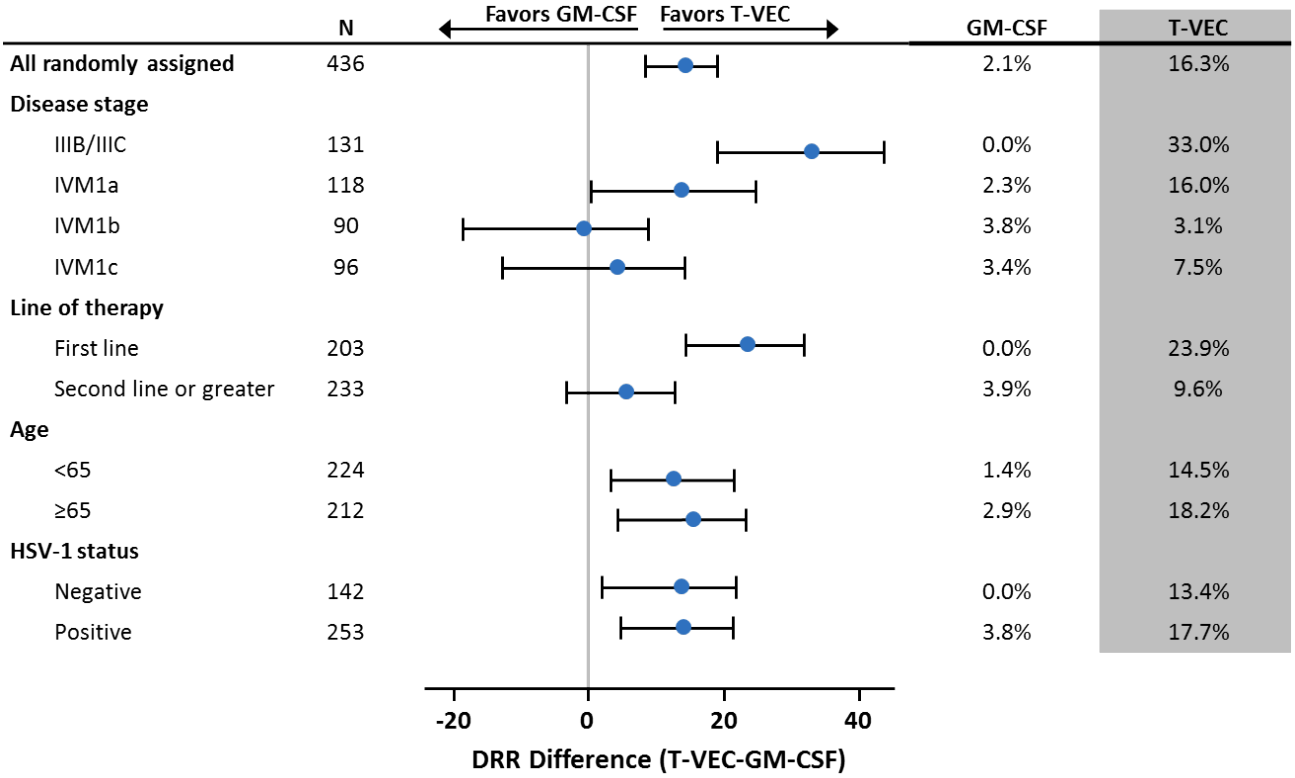


Figure 11. Forest Plot (Hazard Ratio) for Overall Survival: Key Stratification Factors and Covariates (Study 005/05, Intent to Treat Population)

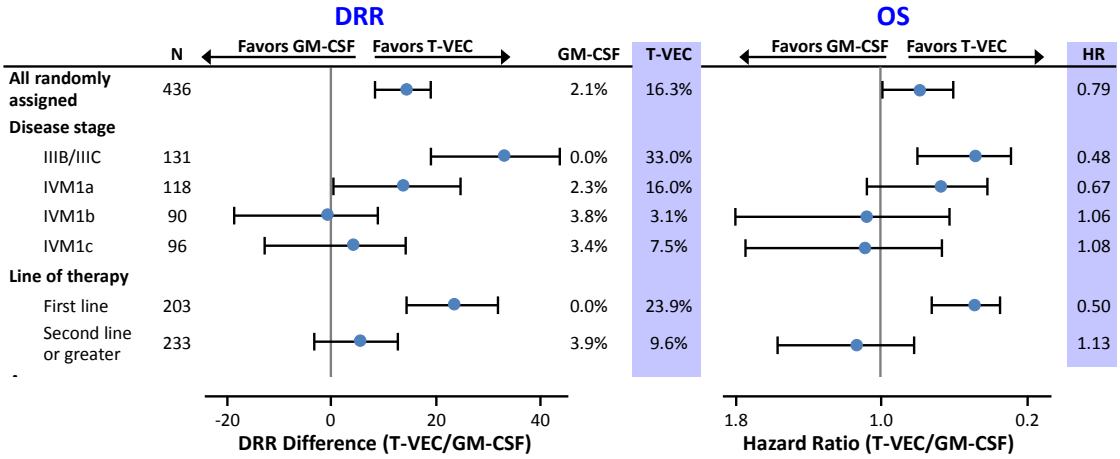


Table 12. Durable and Overall Response per EAC by Baseline HSV Serostatus (Study 005/05; ITT Population)

	Baseline Seronegative Subjects		Baseline Seropositive Subjects	
	GM-CSF (N = 141)	Talimogene laherparepvec (N = 295)	GM-CSF (n = 141)	Talimogene laherparepvec (n = 295)
Durable Response Rate				
n/N' (%)	0/45 (0.0)	13/97 (13.4)	3/78 (3.8)	31/175 (17.7)
p-value		0.0095		0.0023
Overall Response Rate				
n/N' (%)	2/45 (4.4)	23/97 (23.7)	6/78 (7.7)	50/175 (28.6)
p-value		0.0042		0.0001

GM-CSF = granulocyte macrophage colony-stimulating factor, ITT = intent-to-treat; EAC = Endpoint Assessment Committee, HSV = herpes simplex virus

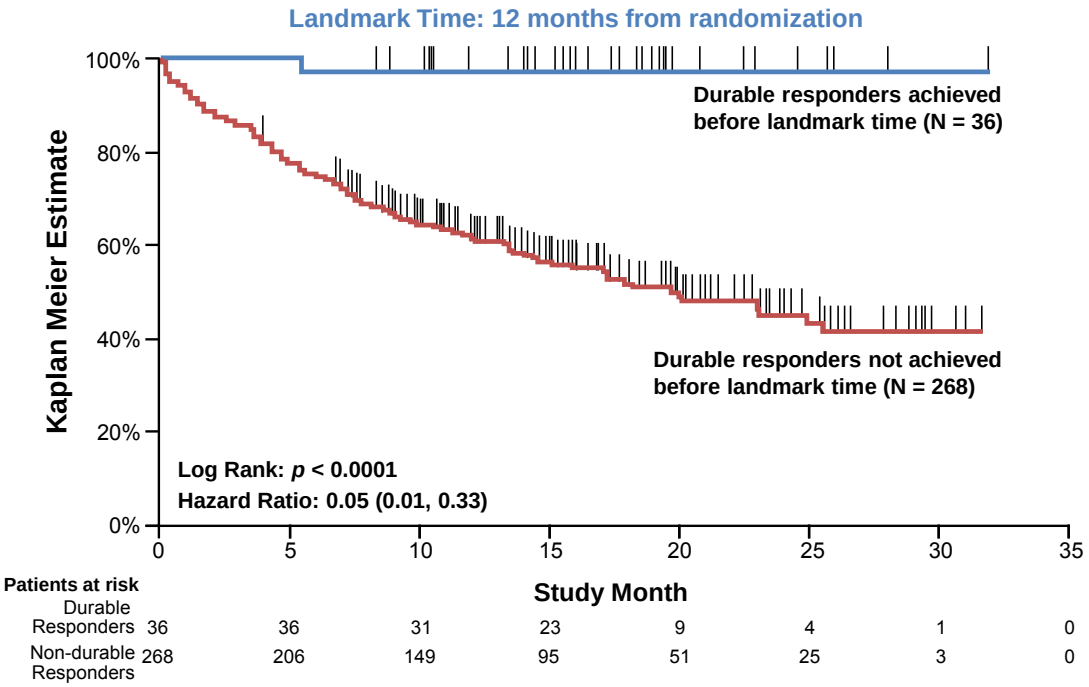
N' = number of subjects with given baseline serostatus. For durable and overall response, n refers to the number of subjects demonstrating a response.

Source: 005/05 Primary CSR Table 14-4.3.1 and Table 14-4.18

Association Between Durable Response and Overall Survival

In a prespecified exploratory analysis, a strong association was noted between durable response and OS. Among subjects still alive at 12 months in the ITT population, durable response was associated with a 95% decrease in the risk of death, if the durable response was achieved prior to 12 months (Figure 12).

Figure 12. Association Between Durable Response and Overall Survival at 12 Months (Study 005/05: ITT Population)



Similar results were seen in landmark analyses at 9 and 18 months. When onset of durable response was analyzed as a time-dependent covariate, results were consistent with a decreased risk of death of 92%.

Association Between Durable Response and Treatment-free Interval

A post-hoc landmark analysis was conducted in subjects with tumor assessments for ≥ 9 months. In this analysis, durable response at 9 months, as assessed by the EAC, was associated with a longer treatment-free interval (p = 0.0007), with an approximate 67% reduction in the risk of initiating subsequent systemic therapy (hazard ratio 0.33). In addition, using the same landmark definition, subjects who had a durable response had a 28% higher probability of not initiating new systemic therapy at 36 months from their last dose of study therapy than those who did not achieve a durable response (95% CI: 11, 44).

Association Between Durable Response and Trial Outcome Index

In a post-hoc landmark analysis, a significant association between the achievement of a durable response and improvement in TOI (a measure of quality of life) was observed (p = 0.025), with an odds ratio of 2.8 (95% CI: 1.1, 7.0). A greater proportion of subjects

who achieved a durable response per the EAC reported improvements in TOI (58.1%) when compared with those who did not achieve a durable response (30.0%).

Clinical Benefit

Of the 51 subjects with a durable response, all had a CR or PR per EAC ongoing at the time of the primary analysis (Table 13). In addition, most subjects were still alive at the time of the most recent contact date (49 subjects were still alive after 3 years) and did not require subsequent systemic anti-cancer therapy during the follow-up period. Among subjects with visible tumor metastases, many had appreciable improvement in the appearance of their disease.

Table 13. Clinical Outcomes for Subjects With Durable Responses per EAC

	Durable responders (N = 51)
Cosmetic Benefit[a]	
Yes	29 (57%)
No	22 (43%)
Survival > 3 years[b]	
Yes	49 (96%)
No	2 (4%)
Subsequent anti-cancer therapy[b]	
Yes	16 (31%)
No	35 (69%)
Best overall response per EAC at the time of primary analysis	
CR	24 (47%)
PR	27 (53%)

[a] Improvement in the appearance of disfiguring lesion(s) on the body and extremities or improvement in the appearance of any lesions in face, scalp and neck
[b] Final OS analysis data

Analyses of Potential Sources of Bias

Early Discontinuation of Treatment

In the all-randomized population, a total of 131 subjects (30%) were identified as having discontinued treatment early, with a higher proportion in the GM-CSF arm (58 of 141, 41%) compared to the talimogene laherparepvec arm (73 of 295, 25%). A post-hoc sensitivity analysis was conducted to explore the potential impact of this difference. When the number of durable responses per EAC for subjects who discontinued early

was imputed (in the GM-CSF arm only) based on the DRR for those subjects receiving GM-CSF who did not discontinue early, the DRR was 16% in the talimogene laherparepvec arm and 4% in the GM-CSF arm (descriptive p = 0.0003). These results suggest that early discontinuations in the GM-CSF arm did not strongly affect the treatment difference.

Use of Subsequent Anticancer Therapy

In a post-hoc analysis to evaluate potential differences between treatment arms in the use of subsequent anticancer therapy, the overall incidence of subsequent chemotherapy, immunotherapy, targeted agents, radiotherapy, surgery, or other therapy was 65% in the talimogene laherparepvec arm and 77% in the GM-CSF arm (Table 14). The median time to subsequent anti-cancer therapy was shorter in the GM-CSF arm (4.8 months vs 11.3 months). A similar trend was observed when the analysis was limited to more recently approved agents (ipilimumab, vemurafenib, dabrafenib, or trametinib) or ipilimumab only. The difference between treatment arms in subsequent therapy may have biased the OS effect in favor of GM-CSF.

Table 14. Time to Subsequent Anticancer Therapy (All Randomized Subjects, Study 005/05)

	KM Median (m) (Incidence [%])		
	GM-CSF	Talimogene laherparepvec	HR (95% CI)
All subsequent anticancer therapy	4.8 (77%)	11.3 (65%)	0.47 (0.37, 0.60)
Subsequent ipilimumab, vemurafenib, dabrafenib, or trametinib	21.4 (43%)	52.7 (39%)	0.77 (0.57, 1.06)
Subsequent ipilimumab	30.9 (35%)	52.7 (36%)	0.90 (0.64, 1.26)

Sensitivity Analysis of OS Based on Updated Survival Status

A post-hoc sensitivity analysis of the primary OS analysis was conducted to update survival status (based on publicly available information) and censoring times for 10 subjects in Study 005/05 who were lost to follow-up or had withdrawn consent. At the time of this analysis, survival status had been confirmed for 3 of the 10 subjects (1 death, 2 subjects still alive). In this analysis, the hazard ratio was 0.804, with 95% CI: 0.631, 1.023.

Systemic Effects

Subject Populations

These analyses were conducted on the Systemic Effect Analysis Set (ie, subjects in the ITT population of Study 005/05 who received at least one dose of talimogene laherparepvec). Subjects were evaluable for lesion-level responses if they had a lesion with at least two assessments of bidimensional measurements; subjects were evaluable for overall lesion-type burden analyses if they had at least two visits with nonmissing values for overall lesion-type burden.

Injected and noninjected non-visceral lesions were predominantly located in the skin, soft tissue, and lymph nodes; however, the location of half of the noninjected lesions was specified as “other.” Visceral lesions were primarily located in the lung and liver.

Incidence of Lesion Response

Among 2116 evaluable lesions directly injected with talimogene laherparepvec, 1361 (64.3%) decreased in size by ≥ 50%, including 995 that completely resolved (ie, decreased in size by 100%; Figure 13). Of 981 noninjected non-visceral lesions, 331 (33.7%) decreased in size by ≥ 50%, including 212 lesions that completely resolved. Of 177 visceral lesions, 27 (15.3%) decreased in size by ≥ 50%, including 16 lesions that completely resolved (Figure 14).

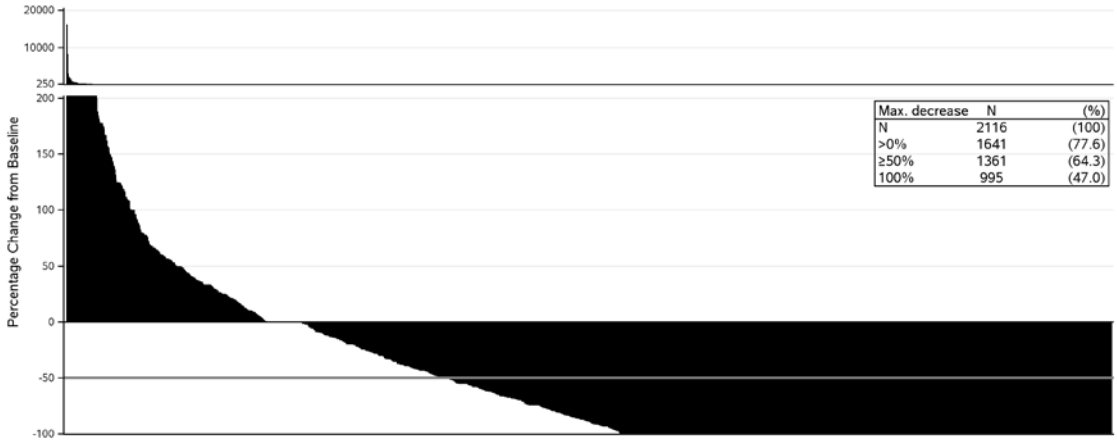
Subject Incidence of Overall Lesion-Type Response

A total of 78 of 220 evaluable subjects (35.5%) had a ≥ 50% reduction in the total burden of all lesions. Twenty-seven of 79 subjects (34.2%) had a ≥ 50% reduction in the total burden of noninjected non-visceral lesions. Eight of 71 subjects (11.3%) had a ≥ 50% reduction in the total burden of visceral lesions.

Time to Lesion Response

The Kaplan-Meier median time to lesion response (baseline or new lesions) was shortest for lesions that were directly injected (21.1 weeks), followed by noninjected non-visceral lesions (44.1 weeks) and noninjected visceral lesions (110.4 weeks); this is consistent with initiation of a delayed regional and systemic anti-tumor immune response to talimogene laherparepvec.

Figure 13. Maximum Percent Change in Evaluable Injected Lesions (Study 005/05 Systemic Effect Analysis Set – Talimogene Laherparepvec Arm)

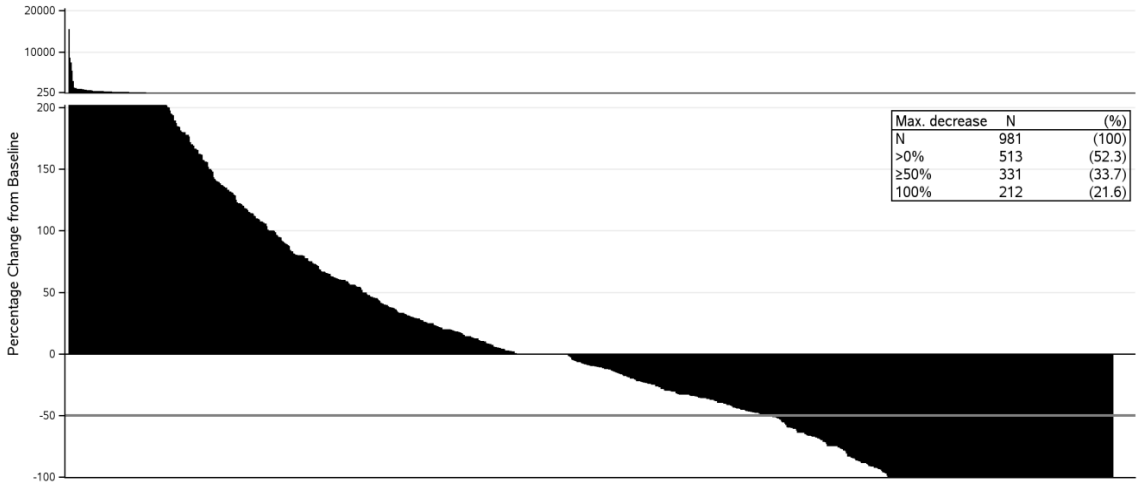


Lesion measurements per investigator.
Evaluable indicates at least 2 assessments with bi-dimensional measurements.
Injected lesion indicates baseline or new lesion ever injected.
There is one subject with an injected lesion with an errata noted in the CSR for the lesion location (thyroid) which is shown as an injected lesion.
Systemic Effect Analysis Set: subjects in ITT population who had received at least one dose of study therapy.

Program: /userdata/stat/amg678/onc/00505/analysis/primary_201303_systemic/figures/f-eff-watrfal-cg-pt-sys.sas
Output: f14-04-014-001-eff-watrfal-chg-pct-inj-les-sys-tvec-se-l.rtf (Date Generated: 14MAR14 08:04) Source Data: adlmsys

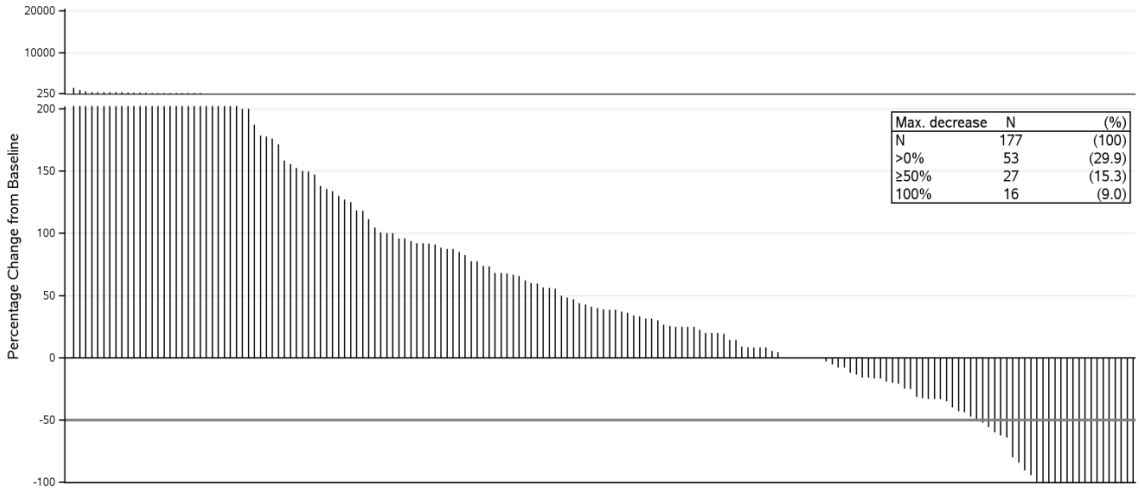
Figure 14. Maximum Percent Change in Evaluable Noninjected Lesions (Study 005/05 Systemic Effect Analysis Set, Talimogene Laherparepvec Arm)

Noninjected Non-Visceral Lesions



Lesion measurements per investigator.
Evaluable indicates at least 2 assessments with bi-dimensional measurements.
Non-injected lesion indicates baseline or new lesions never known to be injected.
Systemic Effect Analysis Set: subjects in ITT population who had received at least one dose of study therapy.

Noninjected Visceral Lesions



Lesion measurements per investigator.
Evaluable indicates at least 2 assessments with bi-dimensional measurements.
Non-injected lesion indicates baseline or new lesions never known to be injected.
Systemic Effect Analysis Set: subjects in ITT population who had received at least one dose of study therapy.

Risk of Developing Visceral Metastases

A post-hoc analysis was conducted to evaluate the effect of talimogene laherparepvec vs GM-CSF on the risk of developing visceral metastases in subjects with no visceral disease at baseline. In an analysis adjusted for baseline total tumor area, although 86% of subjects were censored, the risk of developing visceral metastases was lower

with talimogene laherparepvec treatment than with GM-CSF (hazard ratio = 0.41, 95% CI: 0.19, 0.89; descriptive p = 0.024).

Effects of Post-Treatment Resection

Study 005/05 was not designed to prospectively collect data on subjects who underwent surgical resections for their disease. However, information regarding resections during the study was provided to Amgen for medical review. Based on medical review, a total of 33 melanoma-related resections were performed in subjects receiving talimogene laherparepvec, of which 61% were palliative in intent or did not successfully render the subject disease free (Table 15). Thirteen subjects had melanoma-related surgeries that were considered to be non-palliative. In 4 subjects, there was no evidence of residual tumor in the surgical specimen, and in 9 subjects, there was no evidence of disease after surgery.

Table 15. Melanoma-related Resections in Study 005/05

	Number of Subjects (%)
Melanoma-related resections[a]	33 (100%)
Palliative	20 (61%)
Non Palliative	13 (39%)
Pathological CR at time of surgery	4 (12%)
No evidence of disease after surgery	9 (27%)

[a]Based on medical review

Long-Term Efficacy

An open-label extension study evaluated the safety and efficacy of extended treatment with talimogene laherparepvec for subjects who could potentially benefit from continued treatment beyond that allowed in Study 005/05. The maximum treatment duration during this extension study was 61.3 weeks (approximately 14 months). Among subjects treated with talimogene laherparepvec in the extension study (n = 27), 2 subjects whose best response was “stable disease” and 3 subjects whose best response was PR during Study 005/05 achieved a best response of CR during the extension study. All but 1 of these subjects were still CRs at the time of their last assessment.

4.2 Study 002/03

4.2.1 Study Design and Endpoints

Study 002/03 was a single-arm, open-label, phase 2 study evaluating talimogene laherparepvec in subjects with stage IIIC or stage IV melanoma. Subjects had to have

histologically proven Stage IIIC (including at least 2 palpable lymph nodes, extracapsular or in-transit metastases) or Stage IV melanoma that was not eligible for curative surgery. Measureable disease requirements were the presence of one or more tumors 0.5 to 10 cm in the longest diameter that were accessible and suitable for injection (ie, not bleeding or weeping). Subjects also had to have an ECOG Performance status of 0 or 1.

Up to 10 cutaneous and subcutaneous tumors that were measurable (≥ 20 mm with conventional techniques or ≥ 10 mm with spiral CT scan) and suitable for injection were identified, measured, photographed, scored for injection site reaction using Common Toxicity Criteria for Adverse Events (CTCAE) Version 3, and documented on a body map. At least 1 tumor was left uninjected to assess uninjected response. Uninjected tumors were evaluated in the same manner as injected tumors. Uninjected tumors were required to be at least 5 cm from the nearest injected tumor and could not be treated with talimogene laherparepvec at any time unless permission was obtained from Amgen.

Talimogene laherparepvec was administered as described in Section 3.5.

Efficacy endpoints were tumor response rate, time to response, duration of response, time to progression, and overall survival.

4.2.2 Assessments and Analysis Methods

4.2.2.1 Prospectively Planned Analyses

Tumor size was evaluated by the investigator at each visit by measurement of tumors using calipers. Photographs of injected tumors were obtained at each visit, and photographs of uninjected tumors and CT scans were obtained every 12 weeks. All responses were determined objectively (ie, CT scan, clinical measurements, biopsy) at 2 visits at least 4 weeks apart.

Tumor burden for a visit was calculated as the sum of the longest diameters of all tumors identified and measured up to that visit. Tumor response at each visit was derived from tumor burden based on modified RECIST, as follows:

- CR: zero tumor burden
- Partial response (PR): a 30% or greater decrease in tumor burden
- PD: a 20% or greater increase in tumor burden
- SD: none of the above (a < 30% decrease and < 20% increase in tumor burden)

All data were reported descriptively, without formal comparisons.

4.2.2.2 Post-hoc Analyses

Systemic Effects

At FDA's request, a post-hoc analysis of systemic activity (ie, beyond local effects in injected lesions) in talimogene laherparepvec-treated subjects was conducted. This analysis was conducted in a manner similar to that for Study 005/05, except that lesion response was considered to be a ≥ 30% maximum decrease instead of ≥ 50% as in Study 005/05.

4.2.3 Results

Of the 50 subjects enrolled, 14 (28%) achieved a response; 8 (16%) of which were CR. Seven of the 8 subjects with a CR had either stage IIIC or stage IVM1a disease, while subjects with PR were balanced across stages IIIC, IVM1a, and IVM1c (Table 16).

Of the 14 subjects with objective responses, 7 had ongoing responses at 1 year after the first dose and 2 had ongoing responses at 18 months after the first dose. Median overall survival was 448.0 days (approximately 14.7 months).

Table 16. Best Objective Tumor Response by Disease Stage (Intent-to-Treat Population) (Study 002/03)

Subgroup	No. of Subjects	Complete Response	Partial Response	Objective Response
Overall	50	8	6	28%
Stage				
IIIC	13	4	2	46%
IVM1a	13	3	2	38%
IVM1b	5	0	0	0%
IVM1c	19	1	2	16%

Source: Study 002/03 CSR Table 14.5.1 and Table 14.5.2

Results from analyses of systemic effects were as follows:

- Of the 50 subjects who received talimogene laherparepvec in Study 002/03, 49 subjects (98.0%) had at least 1 noninjected lesion: 26 subjects (52.0%) with only noninjected non-visceral lesions and 23 subjects (46.0%) with at least 1 visceral lesion. Twenty-four subjects with noninjected non-visceral lesions and 12 subjects with visceral lesions were evaluable for overall lesion-type burden.
- In an analysis of overall noninjected lesion-type burden, 12 of 24 subjects (50.0%) had a ≥ 30% reduction in the total burden of noninjected non-visceral lesions, and 2 of 12 subjects (16.7%) had a ≥ 30% reduction in the total burden of visceral lesions.

- Among 128 evaluable lesions directly injected with talimogene laherparepvec, 86 (67.2%) decreased in size by ≥ 30% and 59 (46.1%) completely resolved. Of 146 noninjected non-visceral lesions, 60 (41.1%) decreased in size by ≥ 30%, the majority of which (44 [30.1%]) completely resolved. Of 32 visceral lesions, 4 (12.5%) decreased in size by ≥ 30%, and 3 (9.4%) completely resolved.
- The median time to lesion response (baseline or new lesions) was shortest for lesions that were directly injected (18.4 weeks), followed by noninjected non-visceral lesions (23.1 weeks) and visceral lesions (51.3 weeks), consistent with initiation of a delayed, systemic anti-tumor immune response to talimogene laherparepvec.

Three subjects received additional treatment during an extension study. One additional response (CR) was observed during the extension study for a combined overall response rate of 30%. Of these 15 responses, 8 were still ongoing after 1 year, and 2 were ongoing after 2 years.

Twenty-three of the 50 subjects enrolled in the Study 002/03 were alive at the end of the study. In an analysis of OS data from 14 of these subjects who entered a long-term registry study (Study 009/07) after completing Study 002/03, 8 subjects survived for longer than 5 years after initiating treatment. Long-term survival data was not available from the remaining 9 subjects who did not enter into the registry study.

5. SAFETY DATA

5.1 Safety Assessment

Throughout the clinical development program, safety was evaluated through the collection of treatment-emergent adverse events and assessment by the investigator of their severity, relationship to treatment, onset and duration, and outcome. Other assessments were changes in laboratory values, minimum critical toxicities, vital signs, and physical examination findings.

The primary analysis of safety, particularly adverse events, was based on Study 005/05 (Primary Melanoma Analysis Set). A second dataset that includes adverse event data from Studies 002/03 and 005/05 (and their respective extensions) was also analyzed (Supportive Melanoma Analysis Set), and supported the conclusions from the phase 3 study. The Program-Wide Analysis Set included data from the Supportive Melanoma Analysis Set and from several smaller studies in various tumor types, including melanoma.

5.2 Safety Overview

5.2.1 Exposure

Across the clinical program, 408 subjects were exposed to ≥ 1 dose of talimogene laherparepvec; 269 subjects were exposed to talimogene laherparepvec for < 6 months, 96 subjects were exposed for 6 to < 12 months, 23 subjects were exposed for 12 to < 18 months, and 20 subjects were exposed for ≥ 18 months.

In Study 005/05, the safety population consisted of 419 subjects (292 talimogene laherparepvec; 127 GM-CSF). The median duration of treatment was 23 weeks (range: 0.1 to 78.9) in the talimogene laherparepvec arm and 10 weeks (range: 0.6 to 72) in the GM-CSF arm. For subjects who continued into the extension study, the maximum duration of treatment with talimogene laherparepvec was 30.8 months.

In the talimogene laherparepvec arm, the median (Q1, Q3) number of talimogene laherparepvec injections was 12 (6, 19). The median (Q1, Q3) volume of talimogene laherparepvec administered was 3.0 (2.0, 4.0) mL at cycle 1 and 3.3 (1.8, 4.0) mL at subsequent cycles.

In the GM-CSF arm, the median (Q1, Q3) number of GM-CSF doses was 42 (28, 70), which is consistent with a more frequent dosing schedule relative to talimogene laherparepvec (14 days of every 28-day treatment cycle as opposed to 2 days in each 28-day cycle).

Unless otherwise noted, all results are from Study 005/05 (Primary Melanoma Analysis Set).

5.2.2 All Adverse Events

At least one adverse event was reported for most subjects in Study 005/05 in both treatment arms (99.3% in the talimogene laherparepvec arm and 95.3% in the GM-CSF arm; Table 17). Most adverse events were mild or moderate in severity (63.4% talimogene laherparepvec, 74.0% GM-CSF). The most common adverse events were flu-like symptoms consistent with the administration of a virus. Chills, pyrexia, and influenza-like illness were most frequent during the first 3 cycles of treatment and resolved within 3 days of onset. No new safety findings were observed with longer-term exposure to talimogene laherparepvec during Study 005/05-E.

Table 17. Adverse Events by Preferred Term Occurring in ≥ 20% of Subjects in Either Treatment Arm (Safety Population; Study 005/05)

Preferred Term	GM-CSF (N = 127) n (%)	Talimogene Laherparepvec (N = 292) n (%)	Total (N = 419) n (%)
Number of subjects reporting treatment-emergent adverse events	121 (95.3)	290 (99.3)	411 (98.1)
Fatigue	46 (36.2)	147 (50.3)	193 (46.1)
Chills	11 (8.7)	142 (48.6)	153 (36.5)
Pyrexia	11 (8.7)	125 (42.8)	136 (32.5)
Nausea	25 (19.7)	104 (35.6)	129 (30.8)
Influenza like illness	19 (15.0)	89 (30.5)	108 (25.8)
Injection site pain	8 (6.3)	81 (27.7)	89 (21.2)
Vomiting	12 (9.4)	62 (21.2)	74 (17.7)

GM-CSF = granulocyte macrophage colony-stimulating factor
Treatment-emergent adverse events include all adverse events that began between the first administration of study treatment and 30 days after the last administration of study treatment.
N = Number of subjects in the analysis set.
Safety population includes all randomized and treated subjects. Randomized subjects who do not receive at least one dose of study treatment are excluded. Subjects are analyzed using the treatment received.
The order of the frequency is based on the column of "Talimogene Laherparepvec".
Coded using MedDRA version 15.1

Source: Study 005/05 Primary CSR Table 14-6.2.9

No clinically relevant trends in blood pressure/respiratory measurements or hematology and chemistry laboratory parameters were observed during Study 005/05.

5.2.3 Serious Adverse Events

The incidence of serious adverse events was 25.7% in the talimogene laherparepvec arm and 13.4% in the GM-CSF arm (Table 18). Imbalances were noted in the events of cerebral hemorrhage, gastrointestinal hemorrhage, deep vein thrombosis, and pleural effusion (each occurring in 3 subjects in the talimogene laherparepvec arm and no subject in the GM-CSF arm). For the events of cerebral hemorrhage and pleural effusion, Amgen medical review of the cases did not identify a new safety signal, as the events were reported in the setting of disease progression (including metastases to the brain and malignant pleural effusions). The events of gastrointestinal hemorrhage were reported in a subject who started Coumadin (due to atrial fibrillation) 9 days before the event; a subject with hemorrhoids who underwent an EGD that showed possible gastritis and colonoscopy that showed a polyp; and a remaining subject who had an endoscopy that was suspicious for a gastrointestinal melanoma lesion. With regard to the deep vein thrombosis events, other than the underlying cancer, no other risk factors for the development of deep vein thrombosis were evident.

Given the longer median duration of treatment in the talimogene laherparepvec arm, an exposure-adjusted analysis was conducted to mitigate potential bias; the exposure-adjusted subject incidence of serious adverse events was 47.5 and 38.3 per 100 subject years in the talimogene laherparepvec and GM-CSF arms, respectively. Disease progression was the most frequently reported serious adverse event in both arms (3.1% in the talimogene laherparepvec arm; 1.6% in the GM-CSF arm), followed by cellulitis (2.4% and 0.8%, respectively), pyrexia (1.7% and 0% respectively), and tumor pain (1.4% and 0% respectively).

Cellulitis at the injection site was the most commonly reported treatment-related serious adverse event (1.7% talimogene laherparepvec; 0% GM-CSF). In some cases, inflammation at the tumor injection site may have been difficult to discern from cellulitis events.

Table 18. Treatment-Emergent Serious Adverse Events by Preferred Term With ≥1 % Subject Incidence in Either Treatment Group (Primary Melanoma Analysis Set)

Preferred Term	GM-CSF (N = 127) n (%)	Talimogene Laherparepvec (N = 292) n (%)	Total (N = 419) n (%)
Number of subjects reporting serious treatment-emergent adverse events	17 (13.4)	75 (25.7)	92 (22.0)
Disease progression	2 (1.6)	9 (3.1)	11 (2.6)
Cellulitis	1 (0.8)	7 (2.4)	8 (1.9)
Pyrexia	0 (0.0)	5 (1.7)	5 (1.2)
Tumour pain	0 (0.0)	4 (1.4)	4 (1.0)
Cerebral haemorrhage	0 (0.0)	3 (1.0)	3 (0.7)
Deep vein thrombosis	0 (0.0)	3 (1.0)	3 (0.7)
Gastrointestinal haemorrhage	0 (0.0)	3 (1.0)	3 (0.7)
Infected neoplasm	0 (0.0)	3 (1.0)	3 (0.7)
Metastases to central nervous system	1 (0.8)	3 (1.0)	4 (1.0)
Metastatic malignant melanoma	0 (0.0)	3 (1.0)	3 (0.7)
Pleural effusion	0 (0.0)	3 (1.0)	3 (0.7)

N = Number of subjects in the analysis set.
Treatment-emergent adverse events include all adverse events that began between the first administration of study treatment and 30 days after the last administration of study treatment.
Primary Melanoma Analysis Set is defined as all randomized subjects who received ≥ 1 dose of study treatment.
Coded using MedDRA version 15.1
Source: Study 005/05 Primary CSR Table 14-6.2.2

5.2.4 Adverse Events of Grade 3 or Higher

The incidence of grade 3 or higher adverse events was 36.0% in the talimogene laherparepvec arm and 21.3% in the GM-CSF arm (Table 19). The most frequently reported grade 3 or higher adverse events (> 1%) were disease progression, cellulitis, dyspnea, fatigue, deep vein thrombosis, dehydration, hypokalemia, hyponatremia, pain in extremity, tumor pain, and vomiting. The remaining grade 3 adverse events were reported for ≤ 1% of subjects. Most of these events were not related to treatment. Disease progression was the most commonly reported grade 3 or higher adverse event in the talimogene laherparepvec arm (2.7%); the majority of these events were fatal. The incidence of treatment-related grade 3 or higher events was 11% in the talimogene laherparepvec arm and 5% in the GM-CSF arm.

Table 19. Most Frequent (≥ 1% Incidence) Treatment Emergent Grade 3 or Greater Adverse Events by Preferred Term (Primary Melanoma Analysis Set)

Preferred term	GM-CSF (N = 127) n (%)	Talimogene Laherparepvec (N = 292) n (%)	Total (N = 419) n (%)
Number (%) of Subjects with Treatment Emergent Adverse Event Grade 3 or Greater	27 (21.3)	105 (36.0)	132 (31.5)
Disease Progression	2 (1.6)	8 (2.7)	10 (2.4)
Cellulitis	1 (0.8)	6 (2.1)	7 (1.7)
Dyspnoea	3 (2.4)	3 (1.0)	6 (1.4)
Fatigue	1 (0.8)	5 (1.7)	6 (1.4)
Deep Vein Thrombosis	0 (0.0)	5 (1.7)	5 (1.2)
Dehydration	0 (0.0)	5 (1.7)	5 (1.2)
Hypokalaemia	1 (0.8)	4 (1.4)	5 (1.2)
Hyponatraemia	1 (0.8)	4 (1.4)	5 (1.2)
Pain In Extremity	1 (0.8)	4 (1.4)	5 (1.2)
Tumour Pain	0 (0.0)	5 (1.7)	5 (1.2)
Vomiting	0 (0.0)	5 (1.7)	5 (1.2)
Anaemia	1 (0.8)	3 (1.0)	4 (1.0)
Back Pain	0 (0.0)	4 (1.4)	4 (1.0)
Metastases To Central Nervous System	1 (0.8)	3 (1.0)	4 (1.0)
Pleural Effusion	1 (0.8)	3 (1.0)	4 (1.0)

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N = Number of subjects in the analysis set.
Primary Melanoma Analysis Set includes all randomized and treated subjects from Study 005/05. Randomized subjects who do not receive at least one dose of study treatment are excluded. Subjects are analyzed using the treatment received.
Coded using MedDRA 15.1
Treatment-emergent adverse events include all adverse events that began between the first administration of study treatment and 30 days after the last administration of study treatment.
Non-CTCAE grade is mapped using the following rule: mild = grade 1, moderate = grade 2 and severe = grade 3.
Source: Study 005/05 Primary CSR Table 14-6.2.5

5.2.5 Fatal Adverse Events

Fatal adverse events were reported for 10 subjects (3.4%) in the talimogene laherparepvec arm and 2 subjects (1.6%) in the GM-CSF arm, and were most often due to disease progression (8 of 10 events in the talimogene laherparepvec arm and both events in the GM-CSF arm). The remaining two events in the talimogene laherparepvec arm (myocardial infarction and sepsis) were considered to be due to other underlying

disease processes. No fatal events were reported as treatment-related. The risk of fatal adverse events over time was similar between treatment arms (Cox model estimate of hazard ratio = 1.02, 95% CI: 0.21, 4.89).

5.2.6 Adverse Events Leading to Discontinuation

Adverse events were reported as the primary reason for discontinuing study treatment in 11 subjects (3.8%) in the talimogene laherparepvec arm and 3 subjects (2.4%) in the GM-CSF arm (based on the End of Treatment case report form). These data are distinct from adverse event data based on the Adverse Event case report form, in which 29 subjects (9.9%) in the talimogene laherparepvec arm and 8 subjects (6.3%) in the GM-GSF arm experienced adverse events with an "action taken" of treatment discontinuation. The most common adverse event with an action of treatment discontinuation in both treatment arms was disease progression (1.4% in the talimogene laherparepvec arm and 0.8% in the GM-CSF arm), followed by metastatic malignant melanoma (0.7%, 0%); the remaining events occurred in no more than 1 subject in either treatment arm. Seven subjects (2.4%) in the talimogene laherparepvec arm had treatment-related adverse events (as determined by the investigator) with an action taken of treatment discontinuation: one event each of bronchial hyperreactivity, glomerulonephritis, influenza-like illness, lymphadenopathy, obstructive airways disorder, pneumonitis, and tumor hemorrhage.

5.2.7 Adverse Events of Interest

Adverse events of special interest were defined for talimogene laherparepvec based upon events identified in emerging clinical data, the mechanism of action of the product, potential risks as defined by nonclinical data, and events identified with other products. Adverse events of special interest included immune-mediated adverse events, cellulitis, flu-like symptoms, herpes simplex virus (HSV-1 infections), hypersensitivity reactions, injection site reactions, vitiligo (based on general occurrence of this event in subjects with melanoma and in subjects receiving other forms of immunotherapy), impaired wound healing at the injection site, plasmacytoma at the injection site, and other neoplastic events.

Table 20 provides a summary of the subject incidence rates of adverse events and serious adverse events of interest by category. The subject incidence rates of the adverse events of interest reflect all cases that were reported with preferred terms identified using a predefined search strategy (Standardized MedDRA Query [SMQ] or Amgen-specified strategy) and do not imply a causal drug event association. The cases

identified were then medically reviewed to determine if they met the case definition in order to assess a potential causal drug event association.

Table 20. Subject Incidence of Adverse Events of Interest by Category (Primary Melanoma Analysis Set)

Event of Interest Category	GM-CSF (N = 127) n (%)	Talimogene Laherparepvec (N = 292) n (%)	Total (N = 419) n (%)
IMMUNE-MEDIATED EVENTS (AUTOIMMUNE DISORDERS)[a]			
Adverse event	2 (1.6)	5 (1.7)	7 (1.7)
Serious adverse event	0 (0)	1 (0.8)	1 (0.2)
CELLULITIS AT THE INJECTION SITE (BACTERIAL CELLULITIS)			
Adverse event	2 (1.6)	18 (6.2)	20 (4.8)
Serious adverse event	1 (0.8)	7 (2.4)	8 (1.9)
FLU LIKE SYMPTOMS			
Adverse event	83 (65.4)	264 (90.4)	347 (82.8)
Serious adverse event	0 (0.0)	9 (3.1)	9 (2.1)
HERPES SIMPLEX VIRUS (HSV) INFECTIONS			
Adverse event	2 (1.6)	16 (5.5)	18 (4.3)
Serious adverse event	0 (0.0)	0 (0.0)	0 (0.0)
HYPERSENSITIVITY			
Adverse event	25 (19.7)	53 (18.2)	78 (18.6)
Serious adverse event	0 (0.0)	0 (0.0)	0 (0.0)
INJECTION SITE REACTIONS			
Adverse event	64 (50.4)	122 (41.8)	186 (44.4)
Serious adverse event	0 (0.0)	0 (0.0)	0 (0.0)
VITILIGO			
Adverse event	2 (1.6)	15 (5.1)	17 (4.1)
Serious adverse event	0 (0.0)	0 (0.0)	0 (0.0)
IMPAIRED WOUND HEALING AT THE INJECTION SITE[a]			
Adverse event	3 (2.4)	16 (5.5)	19 (4.5)
Serious adverse event	1 (0.8)	0 (0.0)	1 (0.2)

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N = Number of subjects in the analysis set

Primary Melanoma Analysis Set is defined as all randomized subjects who received ≥ 1 dose of study treatment.

[a] The incidence rates in this table reflect only the number of cases/events that were reported with preferred terms using the search strategy (SMQ or Amgen-specified strategy) and do not imply a causal drug event association. The cases/events identified in this table were medically reviewed to determine if they met the case definition in order to provide a true ascertainment of the subject incidence of the event shown.

Source: Table IAS-6.11.41, Table IAS-6.11.42, Table IAS-6.11.47, Table IAS-6.11.48

Table 20. Subject Incidence of Adverse Events of Interest by Category (Primary Melanoma Analysis Set)

Event of Interest Category	GM-CSF (N = 127) n (%)	Talimogene Laherparepvec (N = 292) n (%)	Total (N = 419) n (%)
OTHER NEOPLASTIC EVENTS (MALIGNANT OR UNSPECIFIED TUMORS)			
Adverse event	3 (2.4)	16 (5.5)	19 (4.5)
Serious adverse event	1 (0.8)	9 (3.1)	10 (2.4)
PLASMACYTOMA			
Adverse event	0 (0.0)	1 (0.3)	1 (0.2)
Serious adverse event	0 (0.0)	1 (0.3)	1 (0.2)

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N = Number of subjects in the analysis set
Primary Melanoma Analysis Set is defined as all randomized subjects who received ≥ 1 dose of study treatment.
[a] The incidence rates in this table reflect only the number of cases/events that were reported with preferred terms using the search strategy (SMQ or Amgen-specified strategy) and do not imply a causal drug event association. The cases/events identified in this table were medically reviewed to determine if they met the case definition in order to provide a true ascertainment of the subject incidence of the event shown.
Source: Table IAS-6.11.41, Table IAS-6.11.42, Table IAS-6.11.47, Table IAS-6.11.48

5.2.7.1 Immune-mediated Adverse Events (Autoimmune Adverse Events)

Based on Amgen's medical review, 7 subjects, (5/292 [1.7%] in the talimogene laherparepvec arm; 2/127 [1.6%] in the GM-CSF arm) experienced adverse events that met the criteria for the definition of an immune-mediated event.

Four of the subjects in the talimogene laherparepvec arm had immune-mediated adverse events that were considered possibly related to talimogene laherparepvec during Amgen's medical review (one case each of glomerulonephritis, pneumonitis, psoriasis, and vasculitis); however, other possible contributory factors were present, and therefore causality was not clearly established. In two cases (pneumonitis and psoriasis), the subjects had a prior history of autoimmune disease; in addition, the subject with pneumonitis had prior treatment with an agent (mesalamine) that may have contributed to the development of an immune-mediated adverse event. The subject with acute renal failure had a plausible alternative etiology (bacterial and/or antibiotic associated glomerulonephritis following cellulitis), and per the investigator, the event was related to the administration of an antibiotic and not investigational product.

5.2.7.2 Cellulitis

Adverse events in the bacterial cellulitis category were reported in 18 subjects (6.2%) in the talimogene laherparepvec arm and 2 subjects (1.6%) in the GM-CSF arm. The most frequently reported preferred term was cellulitis (5.8% and 1.6%, respectively). Most events were grade 1 or 2; 6 grade 3 events and no grade 4 or 5 events were reported. One event led to study treatment discontinuation. Seven subjects (2.4%) in the talimogene laherparepvec arm and 1 subject (0.8%) in the GM-CSF arm experienced serious adverse events of cellulitis; 5 of the events (all in the talimogene laherparepvec arm) were considered to be possibly related to study treatment. Fever, elevated white blood cell count, bacteremia or sepsis, and hospitalization for treatment with intravenous antibiotics were reported in 5 of the 7 subjects. All serious cases resolved within 8 days of onset, with the exception of 1 case that persisted for approximately 5 months and for which pathology indicated a nonspecific dermatitis with no evidence of melanoma. None of the serious cellulitis events resulted in study treatment discontinuation.

5.2.7.3 Flu-like Symptoms

The subject incidence of adverse events in the flu-like symptoms category was 90.4% in the talimogene laherparepvec arm and 65.4% in the GM-CSF arm. The most frequently reported preferred term was fatigue (50.3% and 36.2% respectively). Other flu-like symptoms reported with a $>$ 5% difference between the talimogene laherparepvec arm compared with the GM-CSF arm included chills (48.6% vs 8.7%), pyrexia (42.8% vs 8.7%), nausea (35.6% vs 19.7%), influenza-like illness (30.5% vs 15.0%), headache (18.8% vs 9.4%), myalgia (17.5% vs 5.5%), and oropharyngeal pain (5.8% vs 0.8%).

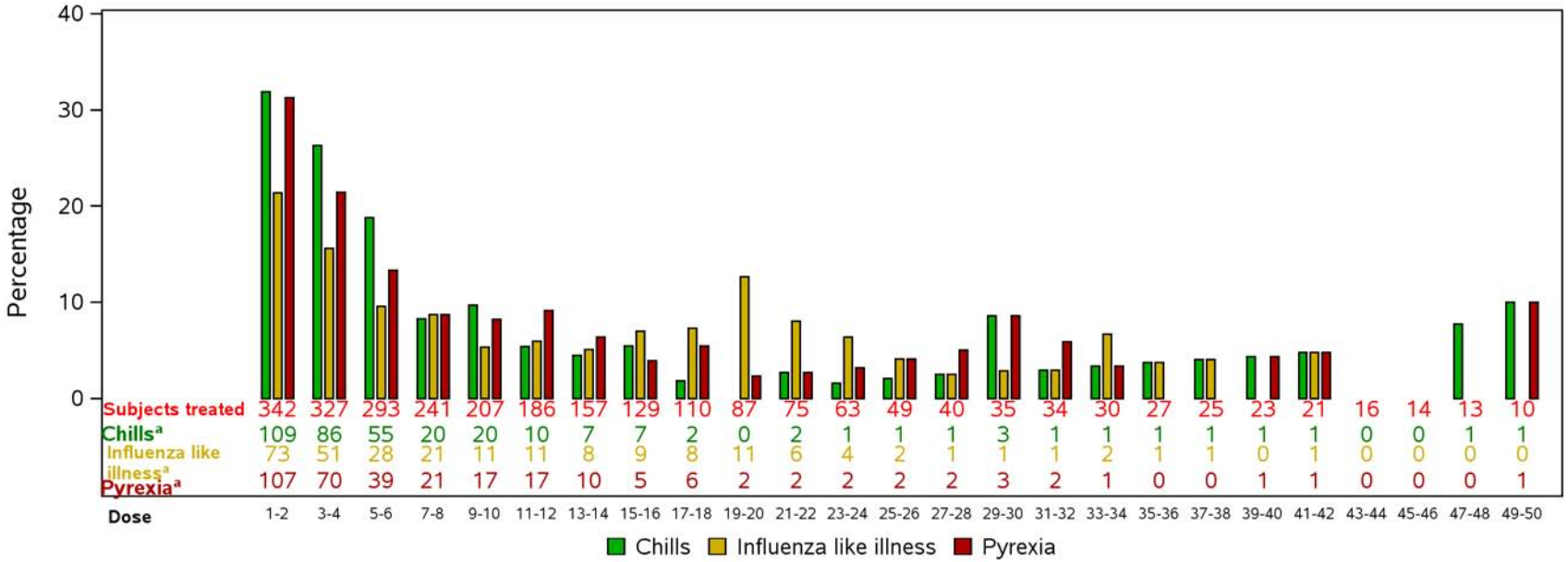
Nine subjects (3.1%) in the talimogene laherparepvec arm reported serious adverse events in this category, including pyrexia (n = 5), asthenia (n = 1), chills (n = 1), influenza-like illness (n = 1), and musculoskeletal pain (n = 1). One serious event of influenza-like illness resulted in study treatment discontinuation (grade 3 event). No other serious adverse events of flu-like symptoms resulted in study treatment discontinuation. No serious adverse events in this category were reported for subjects in the GM-CSF arm.

In a combined analysis of data from Studies 005/05, 002/03, and their respective extension studies, events of pyrexia, chills, and influenza-like illness were reported most often in the first 3 monthly cycles of talimogene laherparepvec treatment but were also

reported at any time during treatment (Figure 15). Most of these events were mild to moderate in severity and did not lead to discontinuation of study treatment.

When adjusted for duration of exposure, the subject incidence of events such as pyrexia and influenza-like illness were higher in subjects receiving talimogene laherparepvec who were HSV-1 seronegative at baseline compared with those who were HSV-1 seropositive.

Figure 15. Subject Incidence of Treatment Emergent Pyrexia, Chills, and Influenza Like Illness Over Time in Subjects who Received Talimogene Laherparepvec (Supportive Melanoma Analysis Set)



[a] Number of subjects who started a new episode of the specified preferred term in the dosing interval.
No treatment emergent pyrexia, chills, or influenza like illness was observed on or after the 51st dose.
The Supportive Melanoma Analysis Set will consist of all subjects enrolled in a talimogene laherparepvec melanoma clinical study (005/05, 002/03) who received at least 1 dose of talimogene laherparepvec or GM-CSF. Data from subjects treated on 005/05 and 002/03 extension studies will be combined with data from the parent study on the subject level prior to being summarized in this analysis set. Subjects will be analyzed according to the treatment they received.

Program: /userdata/stat/amg678/meta/bla_201310_mela/analysis/css/figures/f-ae-over-time.sas
Output: fias-06-014-ae-over-time-supm-l.rtf (Date Generated: 19MAR14 16:40) Source Data: adsl, adae, adex

5.2.7.4 Herpes Simplex Virus

The subject incidence of adverse events in the category of herpes simplex virus infections was 5.5% (n = 16) in the talimogene laherparepvec arm and 1.6% (n = 2) in the GM-CSF arm; these rates are lower than the background rates in the normal population. The most frequently reported preferred term was oral herpes (4.8%; [n = 14] and 1.6% [n = 2], respectively). The median duration for this event was 10.3 days (range 3 to 46 days). One event each mapping to preferred terms of herpes simplex and herpes keratitis were reported; the latter occurred in a subject who had a history of this event due to wild-type HSV-1 before enrollment. None of the events were reported as serious.

Of the 14 subjects who reported an event that mapped to the preferred term of oral herpes, 6 subjects were HSV-1-seronegative at baseline. Whether any of these events was due to talimogene laherparepvec or wild-type HSV could not be confirmed, as viral testing was not routinely performed during Study 005/05. At the discretion of the investigator, swabs were to be collected only if lesions were oozing or weeping and suspected to be herpetic in origin.

Most of the oral herpetic events (57%) were treated with concomitant medications, including topical acyclovir or docosanol. Nearly all events of oral herpes (93%) had resolved by the end of study treatment.

5.2.7.5 Hypersensitivity

Using the SMQ narrow search strategy, the subject incidence of adverse events in the category of hypersensitivity reactions was 18.2% in the talimogene laherparepvec arm and 19.7% in the GM-CSF arm. Rash was the most frequently reported preferred term (8.9% and 7.9% respectively). No serious hypersensitivity events were reported in either treatment arm.

Using the SMQ broad search strategy, 2 serious adverse events were reported in the talimogene laherparepvec arm: asthma and bronchial hyperreactivity in 1 subject following a viral respiratory infection that were considered to be possibly related to study treatment by the investigator. The latter event led to study treatment discontinuation and resolved approximately 3 weeks later.

5.2.7.6 Injection Site Reactions

The subject incidence of adverse events in the category of injection site reactions was 41.8% in the talimogene laherparepvec arm and 50.4% in the GM-CSF arm. In the

talimogene laherparepvec arm, the most common adverse event reported in the injection site reactions category was injection site pain (27.7% talimogene laherparepvec, 6.3% GM-CSF). Most events were of mild or moderate severity. Three events of injection site pain were reported as severe, 2 of which were considered probably related to talimogene laherparepvec. All subjects recovered with or without concomitant treatment and no subjects were discontinued from treatment. No serious injection site reaction adverse events were reported in either treatment arm.

5.2.7.7 Vitiligo

The incidence of preferred terms in the category of vitiligo (pigmentation disorder, skin discoloration, skin hypopigmentation, and vitiligo) was 5.1% in the talimogene laherparepvec arm and 1.6% in the GM-CSF arm. No serious adverse events of vitiligo were reported.

5.2.7.8 Impaired Wound Healing at the Injection Site

The incidence of adverse events in the impaired wound healing category was 5.5% (n = 16) in the talimogene laherparepvec arm and 2.4% (n = 3) in the GM-CSF arm. Preferred terms of wound complication, wound secretion, and wound infection were reported in 1.4%, 1.4%, and 1.0% of talimogene-laherparepvec-treated subjects respectively, and upon medical review of cases, were reported in the context of infection. Most adverse events resolved while on study treatment, and none resulted in permanent study treatment discontinuation.

No serious wound healing events were reported in the talimogene laherparepvec arm during the study and follow-up period. One serious adverse event of impaired healing was reported in an elderly subject in the talimogene laherparepvec arm that resulted in a left leg amputation below the knee approximately 7 months after completion of study treatment. Although several confounding factors were present, including advanced age, location on the lower extremity, peripheral vascular disease, prior radiation and infection at the site, a possible contributory role of study treatment could not be ruled out.

5.2.7.9 Plasmacytoma at the Injection Site

A single case of plasmacytoma at the injection site was identified in a subject with a pre-existing smoldering multiple myeloma. The development of the plasmacytoma in proximity to the injection site is considered to be possibly related to treatment with talimogene laherparepvec.

5.2.7.10 Other Neoplastic Events

The incidence of other neoplastic events was 5.5% (n = 16) in the talimogene laherparepvec arm and 2.4% (n = 3) in the GM-CSF arm. Based on a review of the "Malignant and Unspecified Tumors" high-level group term from a combined analysis of Studies 005/05, 002/03 and their respective extension studies, most events of malignancy reported were due to melanoma disease progression. A review of the remaining cases did not identify a safety signal.

5.3 Adverse Drug Reactions

Table 21 displays adverse drug reactions observed in Study 005/05. Adverse drug reactions were defined as adverse events with a ≥ 2% greater incidence in subjects receiving talimogene laherparepvec compared to GM-CSF, or adverse events with < 2% difference between treatment groups, but with a biologically plausible mechanism and similar medical concept to other adverse events.

Table 21. Adverse Reactions Observed With Talimogene Laherparepvec in Study 005/05

System Organ Class	Adverse Reaction Preferred Term
General disorders and administration site conditions	• Fatigue • Chills • Pyrexia • Influenza like illness • Malaise • Axillary pain • Injection site reactions[a]
Gastrointestinal disorders	• Nausea • Vomiting • Diarrhea • Constipation • Abdominal pain • Abdominal discomfort
Musculoskeletal and connective tissue disorders	• Myalgia • Arthralgia • Pain in extremity • Groin pain
Skin and subcutaneous tissue disorders	• Vitiligo
Infections and infestations	• Cellulitis • Oral herpes • Incision site infection
Nervous system disorders	• Headache • Dizziness
Respiratory, thoracic and mediastinal disorders	• Oropharyngeal pain
Metabolism and nutrition disorders	• Dehydration
Injury, poisoning, and procedural complications	• Contusion • Procedural pain • Wound complication • Wound secretion
Neoplasms benign, malignant and unspecified (including cysts and polyps)	• Tumor pain • Infected neoplasm
Investigations	• Weight decreased
Vascular disorders	• Flushing
Blood and lymphatic system disorders	• Anemia

[a]Injection site reactions include the following individual adverse reactions: Injection site pain, Injection site erythema, Injection site hemorrhage, Injection site swelling, Injection site reaction, Injection site inflammation, Secretion discharge, Injection site discharge, Injection site warmth

5.4 Biodistribution and Shedding

Viral biodistribution was evaluated in blood and urine samples collected in four clinical studies (Study 001/01 [n = 30], Study 002/03 [n = 50], Study 004/04 [n = 17], and

Study 005/04 [n = 17]). Samples were analyzed for the presence of viral DNA (as opposed to infectious virus) by qPCR.

Viral shedding was assessed by the collection of swab samples during four clinical studies (Studies 001/01, 002/03, 004/04, and 005/05). Samples were collected from the surface of injected tumors, from herpes labialis or other noninjected lesions that arose during treatment and that were suspected to be herpetic in origin, from injected tumors that were oozing or weeping, and from the outside of occlusive dressings associated with any of these tumors/lesions. All samples were analyzed for the presence of infectious virus using a plaque assay.

To supplement the existing biodistribution and shedding profile of talimogene laherparepvec, Amgen is conducting a single-arm phase 2 study (20120324) with a planned enrollment of 40 subjects with unresected Stage IIIB to Stage IV M1c melanoma. Interim data from qPCR and 50% tissue culture infective dose ($TCID_{50}$) are available.

Data from these studies are summarized in Section 5.4.1 and Section 5.4.2.

5.4.1 Biodistribution

Across 4 clinical studies (Studies 001/01, 002/03, 004/04, and 005/04), viral DNA was detected by qPCR in blood and urine from approximately 30% and 20% of subjects (respectively) at sporadic time points and in low copy numbers from 1 hour to 1 week after injection. Available samples were negative at 2 weeks after injection.

Interim results from the ongoing biodistribution and shedding study (Study 20120324) indicated that 66 of 176 samples (38%) in 11 of 12 subjects (92%) had detectable talimogene laherparepvec DNA in blood at various time points, and 2 of 177 samples (1%) in 2 of 12 subjects (17%) had detectable talimogene laherparepvec DNA in urine. In a preliminary analysis of updated data from this study, 111 of 309 samples (36%) in 17 of 20 subjects (85%) had detectable talimogene laherparepvec DNA in blood at any timepoint. The proportion of samples and subjects with detectable laherparepvec DNA in blood was highest during the second cycle, decreased during the third cycle, and was 0 at the beginning of the fourth cycle. Six of 306 samples (2%) in 4 of 20 subjects (20%) had detectable talimogene laherparepvec DNA in urine at any time point (all on day 1 of cycle 1 or cycle 2).

5.4.2 Viral Shedding

Across 3 clinical studies (Studies 001/01, 002/03, and 004/04), talimogene laherparepvec was detected at the injection site in 11% of subjects (all within the first 2 weeks after injection). All swabs of the exterior of the dressing were negative for infectious virus at all time points tested across all studies. In Study 005/05, 18 swabs from oozing or weeping lesions (11 of which had been directly injected with talimogene laherparepvec) were collected from 12 subjects. All were negative for infectious virus.

Interim results are available from the ongoing biodistribution and shedding study (Study 20120324). In this study, talimogene laherparepvec DNA was detected on swabs of injected lesions in 65 of 158 samples (41%) in 11 of 12 subjects (92%) and on swabs of exterior occlusive dressings in 11 of 119 samples (9%) in 8 of 12 subjects (67%). Testing for viral infectivity (based on $TCID_{50}$) was negative for all of these samples.

In a preliminary analysis of updated data from Study 20120324, talimogene laherparepvec was detected on swabs of injected lesions in 156 of 302 samples (52%) in 18 of 20 subjects (90%), and on swabs of exterior occlusive dressings in 45 of 266 samples (17%) in 14 of 20 subjects (70%). In addition, swabs of oral mucosa had detectable talimogene laherparepvec DNA in 1 of 140 samples (< 1%) in 1 of 20 subjects (5%). No talimogene laherparepvec DNA was detected in 15 swabs of lesions suspected to be of herpetic origin taken from 7 subjects. The $TCID_{50}$ assay was positive in 3 of 156 swabs of injected lesions (1.9%), and no swabs of exterior occlusive dressings (0 of 43) or oral mucosa (0 of 1).

These data are supportive of a low risk of unintended spread of intact talimogene laherparepvec to close contacts.

5.5 Accidental Exposure From Subjects Administered Talimogene Laherparepvec to Family Members and Health Care Providers

Information on exposure of family members and health care providers to talimogene laherparepvec from subjects receiving the product was collected through a Virus Surveillance Program, which was intended to quantify any potential risk of talimogene laherparepvec transmission to third parties following treatment of cancer patients in Study 005/05. The program included 1217 Family and Caregiver Surveillance Questionnaires from 177 subjects. Fifteen subjects reported that they lived with others, had a caregiver, or had a close contact that had reported signs and symptoms that may be related to the subject's participation in the clinical trial.

A total of 82 Healthcare Staff Surveillance Questionnaires were received from 36 study sites. Among the sites that provided responses, 1 site reported an HCP who experienced 2 episodes of an accidental needle stick (first episode, experienced a herpetic whitlow that resolved with administration of acyclovir), 1 site reported an HCP who accidentally stuck himself while preparing talimogene laherparepvec (resolved with administration of an antiviral), 1 site reported a needle stick in an animal handler with no symptoms, and 1 site reported a splashback to the eye that was asymptomatic.

Overall, the questionnaires returned and reviewed and the follow-up information did not suggest a significant risk of transmission of talimogene laherparepvec to third parties following treatment of patients with talimogene laherparepvec.

6. RISK MANAGEMENT PLAN

A summary of the talimogene laherparepvec pharmacovigilance and risk management activities is provided in Table 22.

Table 22. Summary of the Talimogene Laherparepvec Risk Management Plan

Routine Pharmacovigilance	• Spontaneous reporting • Pregnancy surveillance • Aggregate data review • Signal detection • Periodic reports (PSUR/PBRER)
Additional Pharmacovigilance	• Post-market observational study • Shedding study • Capturing reports of suspected herpetic infection • PCR testing • Questionnaire
Labeling	• Prescribing Information • Medication Guide
Additional Risk Minimization Activities	• REMS – Communication Plan o Dear HCP letter o Patient safety brochure o Dedicated REMS internet site o Presence at American Society of Clinical Oncology and Society of Surgical Oncology meetings

PSUR = periodic safety update report, PBRER = periodic benefit-risk evaluation report, PCR = polymerase chain reaction

6.1 Pharmacovigilance

Routine postmarketing safety surveillance activities will include monitoring of adverse events from clinical trials, postmarketing experience, and the literature; routine review of individual and aggregate adverse event data; submission of periodic safety reports; and identification of new safety signals. Postmarketing experience will be monitored through the collection and analysis of spontaneous adverse event reports according to regional and international regulations and guidelines.

Amgen will also collect data on exposure to talimogene laherparepvec prior to conception and/or during pregnancy and lactation.

New and updated safety information is provided to regulatory authorities consistent with local/regional standards and law. In addition, several targeted pharmacovigilance activities are planned, as described in Section 6.1.1 through Section 6.1.5.

6.1.1 Targeted Follow-up Questionnaires

Talimogene laherparepvec is intended for injection into melanoma lesions by HCPs. Health care providers may be accidentally exposed if a needle stick or splashback to the eyes or mucus membranes occurs, and the product may potentially be transmitted to close physical contacts (secondary exposure). In addition, nonclinical results demonstrated systemic viral infection (including lethal infections) in immunocompromised animals following intratumoral injection of talimogene laherparepvec. Amgen will use targeted follow-up questionnaires to collect information on reported signs and symptoms of potential herpetic infection in patients treated with talimogene laherparepvec, their close contacts, and their HCPs; this questionnaire will also include information on immunocompromised states.

6.1.2 PCR Assay to Detect Talimogene Laherparepvec DNA

For any reports of signs or symptoms of suspected herpetic infection in patients treated with talimogene laherparepvec, HCPs, and close contacts, a PCR assay for detection of talimogene laherparepvec DNA will be available to evaluate whether any are due to talimogene laherparepvec.

6.1.3 Postmarketing Prospective Observational Cohort Study (20130193)

A postmarketing prospective observational cohort study (Study 20130193) will be conducted to evaluate the incidence of suspected herpetic infection, risk of secondary transmission, and risk of herpetic infections in immunosuppressed individuals that are confirmed as being due to talimogene laherparepvec. The study will enroll approximately 920 subjects with melanoma who are treated with talimogene laherparepvec. Subjects will be followed for up to 5 years during or following treatment to obtain long term safety data. Subjects will also be periodically evaluated while on treatment to identify late herpetic events, immune-related events, plasmacytoma at the injection site, and impaired healing.

6.1.4 Observational Registry Study (20120139)

This is an ongoing international, multicenter, observational registry program for subjects who received at least one dose of talimogene laherparepvec in an Amgen-sponsored clinical trial and who have permanently ended treatment on that trial; subjects who participated in a Biovex-sponsored trial before Biovex was acquired by Amgen are also eligible for participation. No experimental intervention is involved. Thus, a subject will undergo clinical assessments and receive the standard of care treatment as determined by the subject's physician. Subjects who consent to and are eligible to enroll in this

registry study will be monitored for adverse events deemed by the investigator to be related to talimogene laherparepvec and for OS every 3 months (± 15 days) until withdrawal of consent, death, or end of study, whichever occurs first.

A formal hypothesis will not be tested in this study. The number of subjects planned for enrollment is not capped, and the study will continue until it is determined, in consultation with the regulatory authorities, that the collection of long-term safety and survival data are no longer necessary.

6.1.5 Clinical Biodistribution and Shedding Study (20120324)

Clinical biodistribution and shedding data are being collected in an ongoing, single-arm, phase 2 study in subjects with unresected, stage IIIB to stage IV M1c melanoma (Study 20120324). Approximately 40 subjects will be enrolled in this study and will receive treatment with talimogene laherparepvec until the earliest occurrence of any of the following:

- a CR
- all injectable lesions disappear
- development of clinically relevant progressive disease per World Health Organization criteria beyond 6 months of treatment (as described in the protocol), or
- intolerance to treatment

Therefore, the length of treatment will vary for each subject. This treatment plan is consistent with Study 005/05 and the proposed prescribing information.

Biodistribution will be evaluated by the collection of blood and urine samples for analysis by qPCR. Shedding will be evaluated by the collection of swabs from the exterior of occlusive dressings, surface of injected lesions, oral mucosa, and any lesions suspected to be of herpetic origin; samples will be analyzed by qPCR and $TCID_{50}$ assay (if appropriate). The study will also incorporate a periodic survey to gather data on exposure of close contacts and HCPs.

6.2 Risk Minimization

Routine risk minimization activities are risk communications through prescribing information, labeling, or packaging. The important identified and potential risks associated with the use of talimogene laherparepvec, and the relevant management of events, will be discussed under the appropriate sections of the prescribing information.

An additional risk minimization activity is a communication plan as part of a Risk Evaluation and Mitigation Strategy (REMS) to inform healthcare providers and patients

about the risks of herpetic infection and accidental exposure associated with talimogene laherparepvec. The goals of the REMS are to inform HCPs and patients about the risks of herpetic infections and accidental exposure associated with talimogene laherparepvec. The components of the REMS include the following:

- The Dear Healthcare Provider letter will provide information about disseminated herpetic infection in severely immunocompromised patients, accidental exposure of health care providers and close contacts to talimogene laherparepvec, and potential harm to the fetus or neonate in pregnancy.
- The patient safety brochure, designed in a patient-friendly format for patients and close contacts, will provide information on the important risks associated with talimogene laherparepvec noted above and safe use to prevent accidental exposure.

7. BENEFITS AND RISKS CONCLUSIONS

Melanoma is the fifth most common cancer type and the most common cancer in adults 25 to 49 years of age. Although a number of systemic therapies have been approved that demonstrate objective tumor responses and improvement in survival, complete response rates can be low with the immune checkpoint inhibitors, and the duration of responses with the targeted agents can be limited due to innate or acquired resistance. There are also specific toxicities associated with these 2 classes of agents, and their overall benefit-risk profiles have been determined primarily in patients with the most advanced stages of melanoma. Therefore, there is a need for additional treatment options. Talimogene laherparepvec, a novel oncolytic immunotherapy, has the potential to offer a new treatment option for patients with injectable regionally or distantly metastatic melanoma.

7.1 Summary of Benefits

In phase 3 Study 005/05, talimogene laherparepvec resulted in a statistically significant improvement over GM-CSF in DRR, the primary endpoint. In the ITT population, a difference of 14% ($p < 0.0001$) was observed favoring talimogene laherparepvec. Analyses to assess potential bias (eg, due to differences in early discontinuations) indicated a robust treatment difference favoring talimogene laherparepvec. Durable response was associated with a 95% reduction in the risk of death, a 67% reduction in the risk of subsequent therapy, and improvements in quality of life and the appearance of lesions. Anti-tumor effects were also consistently observed across other efficacy endpoints, including overall response rate and time to treatment failure. The Kaplan-Meier probability of maintaining a response for at least 12 months was 65% in the talimogene laherparepvec arm. Although unresectable at baseline, after treatment with talimogene laherparepvec, 9 subjects were able to undergo surgery that successfully resulted in no residual disease. Evidence of a systemic effect of talimogene laherparepvec was demonstrated, with responses observed in both injected lesions and in noninjected lesions (including visceral lesions) on a time course consistent with a delayed, systemic anti-tumor response, as well as a decreased risk of developing visceral metastases in subjects receiving talimogene laherparepvec compared with those receiving GM-CSF. Median OS was 4.4 months longer for talimogene laherparepvec than for GM-CSF, which, though only trending toward statistical significance, is clinically meaningful. The emergence of a plateau in the Kaplan-Meier survival curves was apparent by 3 years, with more than one-third of subjects still alive

in the talimogene laherparepvec arm. Separation in the survival curves by treatment arm persisted through 5 years. Finally, benefits were particularly pronounced in subjects who had stage IIIB/C and stage IV M1a disease (57% of the phase 3 study population). This group of patients is typically not at imminent risk of death from melanoma, and would particularly benefit from effective treatment that is associated with durable response and minimal toxicity.

7.2 Summary of Risks

Safety results for talimogene laherparepvec have demonstrated a low incidence of grade 3 or higher adverse events, and no treatment-related deaths. The most frequently reported adverse events included pyrexia, chills, and influenza-like illness. The majority of adverse events (74% talimogene laherparepvec, 87% GM-CSF) were nonserious. The most frequently reported serious adverse events (talimogene laherparepvec, GM-CSF) were disease progression (3.1%, 1.6%) and cellulitis (2.4%, 0.8%). Immune-mediated adverse events were reported for 1.7% of subjects in the talimogene laherparepvec arm and 1.6% of subjects in the GM-CSF arm. Herpetic events were reported for 5.5% of talimogene laherparepvec-treated subjects (4.8% oral herpes); no serious herpes complications were reported. In 4100 treatment visits, there were 5 accidental exposures to talimogene laherparepvec in 4 individuals, which were asymptomatic or resolved with acyclovir. Secondary transmission to either HCPs or close contacts of the study subjects was not reported. These and other important and identified risks can be managed through pharmacovigilance, risk minimization measures including appropriate product labeling, and additional risk communication.

7.3 Overall Assessment of Benefit-Risk

An analysis of the benefits and risks of talimogene laherparepvec, as compared with GM-CSF, is provided in Table 23. Based on this analysis, if 100 patients were treated with talimogene laherparepvec:

- In terms of benefit, an average of 14 additional patients would achieve a durable response by 18 months compared with 2 patients receiving GM CSF.
- In terms of benefit, an average of 21 additional patients would achieve an overall response by 18 months compared with 6 patients receiving GM- CSF.
- In terms of risk, an average of 3 additional events of oral herpes would be observed compared with GM-CSF.
- In terms of risk, an average of 5 additional events of bacterial cellulitis would be observed compared with GM-CSF.

- Because immune-mediated events were rare in this program, on average, over 700 patients would need to be treated with talimogene laherparepvec to result in 1 additional immune-mediated event.

Based on this analysis, talimogene laherparepvec has a positive benefit-risk profile for the treatment of patients with injectable regionally or distantly metastatic melanoma. The benefit-risk profile of talimogene laherparepvec is further improved in patients with earlier stages of disease (IIIB/IIIC/IVM1a) (Table 24).

Table 23. Analysis of Benefits and Risks for Talimogene Laherparepvec

Effects	Endpoint	GM-CSF (N=141)	Talimogene Laherparepvec (N=295)	Difference (95% CI)
Benefit	Durable response by 18-mo	2.1%	16.3%	14.1% (8.2-19.2)
	Overall response by 18-mo	5.7%	26.4%	20.8% (13.4-27.0)
	Prob. Survival > 18-mo	52.2%	57.0%	4.8% (-5.4-14.9)
	Prob. Failure-free > 18-mo	12.6%	34.0%	21.4% (10.7-32.1)
	Prob. No new therapy > 18-mo	15.5%	34.9%	19.5% (10.3-28.6)
Risks[a]	Immune-mediated event by 18-mo	1.6%	1.7%	0.1% (-4.6-2.9)
	Oral herpes by 18-mo	1.6%	4.8%	3.2% (-1.8-6.8)
	Bacterial cellulitis by 18-mo	1.6%	6.2%	4.6% (-0.6-8.4)

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[a] Risks endpoints were analyzed with the Safety Population, which includes all treated subjects (N = 127 for GM-CSF and N = 292 for Talimogene Laherparepvec).

Source: t14-11-400-benefit-risk-itt-l.rtf (Date Generated: 16MAR2015:15:29)

Table 24. Analysis of Benefits and Risks for Talimogene Laherparepvec (Stage IIIB/IIIC/IVM1a)

Effects	Endpoint	GM-CSF (N=86)	Talimogene Laherparepvec (N=163)	Difference (95% CI)
Benefit	Durable response by 18-mo	1.2%	25.2%	24.0% (15.2-31.6)
	Overall response by 18-mo	2.3%	40.5%	38.2% (28.2-46.4)
	Prob. Survival > 18-mo	59.8%	72.8%	13.1% (0.4-25.7)
	Prob. Failure-free > 18-mo	4.2%	42.4%	38.2% (26.9-49.6)
	Prob. No new therapy > 18-mo	16.6%	40.3%	23.6% (11.6-35.7)
Risks[a]	Immune-mediated event by 18-mo	1.3%	3.1%	1.8% (-5.3-6.3)
	Oral herpes by 18-mo	1.3%	3.1%	1.8% (-5.3-6.3)
	Bacterial cellulitis by 18-mo	1.3%	6.7%	5.4% (-2.1-10.9)

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[a] Risks endpoints were analyzed with the Non-visceral (Stage IIIB-C, IVM1a) subgroup within Safety Population, which includes all treated Non-visceral (Stage IIIB-C, IVM1a) subjects (N = 76 for GM-CSF and N = 163 for Talimogene Laherparepvec).

Source: t14-11-401-benefit-risk-early-stage-itt-l.rtf (Date Generated: 16MAR2015:15:27)

7.4 Conclusions

Melanoma is a complex cancer that requires the use of multiple treatment modalities for patients over the evolution of their disease. Despite recent advances in therapy, not all patients currently benefit, and there is a need for additional treatment options in this population. Based on talimogene laherparepvec's consistent anti-tumor efficacy, positive trend in survival, and minimal incidence of grade 3 adverse events observed in the phase 3 study, talimogene laherparepvec has a positive benefit-risk profile for the treatment of patients with injectable regionally or distantly metastatic melanoma. The benefit-risk profile of talimogene laherparepvec is further improved in patients with earlier stages of disease (IIIB/IIIC/IVM1a), a patient population with unmet medical need that could particularly benefit from additional treatment options.

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