FDA Briefing Document

Cellular, Tissue, and Gene Therapies Advisory Committee
and
Oncologic Drugs Advisory Committee Meeting

April 29, 2015

BLA 125518

talimogene laherparepvec

(Amgen)

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the members of the advisory committee. The FDA background package often contains assessments, conclusions, and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We bring the talimogene laherparepvec BLA with the Applicant's proposed indication to this Advisory Committee to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

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Glossary

ACS	American Cancer Society
ACOD	Analysis Cut-Off Date
AE	Adverse Event
AJCC	American Joint Committee on Cancer
BLA	Biologics License Application
BORR	Best Overall Response Rate
CI	Confidence Interval
CMV	Cytomegalovirus
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	Cutaneous T- Cell Lymphoma
CTGTAC	Cellular, Tissue, and Gene Therapies Advisory Committee
cuSCC	Cutaneous squamous cell carcinomas
D	Day
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DOR	Duration of Response
DR	Durable Response
DRG	Dorsal Root Ganglia
DRR	Durable Response Rate
DTIC	Dacarbazine
EAC	Endpoint Assessment Committee
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiography
eCTD	Electronic Common Technical Document
EOS	End of Study
EOT	End of Treatment
FACT-BRM	Functional Assessment of Cancer Treatment-Biological Response Modifier
FDA	Food and Drug Administration
F/U	Follow-up
GM-CSF/hGM-CSF	Human Granulocyte Macrophage Colony-Stimulating Factor
HCP	Healthcare Providers
HR	Hazard Ratio
HSV-1	Herpes Simplex Virus Type-1
IA	Interim Analysis

IL-2	High-Dose Interleukin-2
IMM	Irreversible Morbidity or Mortality
IND	Investigational New Drug Application
Ipi	Ipilimumab
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
ITT	Intent-To-Treat
IVRS	Interactive Voice Response System
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
mDOR	Median Duration of Response
MOA	Mechanism of Action
mOS	Median Overall Survival
mPFS	Median Progression-Free Survival
MRI	Magnetic Resonance Imaging
N	Number of Subjects
NCI	National Cancer Institute
ND	Not Done
NDA	New Drug Application
NOS	Not Otherwise Specified
NR	Not Reached
ODAC	Oncologic Drugs Advisory Committee
ORR	Objective Response Rate
OS	Overall Survival
pA	Polyadenylation Signal
PD	Progressive Disease
PDcns	Central Nervous System Progressive Disease
PDr	Clinically Relevant Progressive Disease
PDn	Non-Clinically Relevant Progressive Disease
PFU	Plaque Forming Unit
PI	Package Insert
PP	Per Protocol
PR	Partial Response
QOL	Quality Of Life
QPCR	Quantitative Polymerase Chain Reaction
PET	Positron Emission Tomography
Pre	Sampling Done Before Injection
RECIST	Response Evaluation Criteria in Solid Tumors
REMS	Risk Evaluation and Mitigation Strategy
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Stable Disease

SPA	Special Protocol Assessment
Std Dev	Standard Deviation
TCID50	Tissue Culture Infectious Dose 50
T-E	Treatment - Emergent
TNM	Tumor, Node, Metastasis
TOI	Trial Outcome Index
T-VEC	talimogene laherparepvec
ULN	Upper Limit of the Normal Range
US	United States
USPI	United States Product Insert
WHO	World Health Organization

1 Purpose of Advisory Committee Meeting

FDA convenes this joint advisory committee meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) and the Oncologic Drugs Advisory Committee (ODAC) to discuss the biologics license application (BLA) submitted by Amgen for talimogene laherparepvec for the treatment of injectable regionally or distantly metastatic melanoma. FDA is considering talimogene laherparepvec for a traditional approval for the proposed indication.

In this BLA, the primary evidence of effectiveness comes from Study 005/05. In this randomized, Phase 3 study, subjects who received intralesional injections of talimogene laherparepvec had a statistically significant higher durable response rate, including complete or partial responses maintained for at least 6 months, compared with subjects who received subcutaneous injections of granulocyte-macrophage colony stimulating factor (GM-CSF).

The safety data for talimogene laherparepvec also came primarily from Study 005/05. Additional safety data were obtained from five Phase 1 and Phase 2 studies in melanoma and a variety of solid tumors. The most common treatment-emergent adverse events associated with talimogene laherparepvec in Study 005/05 were fatigue, chills, pyrexia, nausea, influenza-like illness, and injection-site pain. The most common serious adverse events associated with talimogene laherparepvec in Study 005/05 were cellulitis, pyrexia, and tumor pain. Other safety concerns included impaired wound healing and immune-mediated disease. Shedding data are limited, and an ongoing Phase 2 study is being conducted to provide shedding data for talimogene laherparepvec. The applicant has proposed a pharmacovigilance plan to collect postmarketing safety data from patients, close contacts, and healthcare providers.

FDA review of this BLA identified several issues for consideration by this joint Advisory Committee. Please refer to Section 10 of this document for details.

DRAFT Questions for the Advisory Committee:

1.1 Assessment of Benefits and Risks

1.1.1 Benefits

Study 005/05 met its primary objective by demonstrating a higher durable response rate (DRR) in the talimogene laherparepvec group than in the control (GM-CSF) group. Concerns regarding the study results include uncertainty regarding the clinical meaningfulness of the durable responses (e.g., considering the limited evidence of a systemic effect), and uncertainty regarding an effect on overall survival.

Discussion: Please discuss the benefit of talimogene laherparepvec for the proposed indication.

1.1.2 Safety

In Study 005/05, the most common treatment-emergent adverse events that occurred more commonly with talimogene laherparepvec included fatigue, chills, pyrexia, nausea, influenza-like illness, and injection site pain. Serious adverse events attributed to the study treatment included cellulitis at the injection site and injection site reactions.

Discussion: Please discuss the safety of talimogene laherparepvec for the proposed indication.

1.1.3 Patient Population

The proposed patient population includes patients with other potential treatment options including surgery, radiation, and a number of medical therapies. There may be subgroups of the proposed indicated population for whom talimogene laherparepvec would have a more favorable benefit-risk profile. For example, some patients (e.g., patients with Stage IIIB or IIIC melanoma; patients whose tumors do not have a BRAF mutation) may have few treatment options and want a treatment that avoids the potential toxicities associated with the currently approved therapies.

Discussion: Considering the evidence of effectiveness and safety of talimogene laherparepvec, and the current landscape of available therapies for melanoma, please discuss whether talimogene laherparepvec has an overall favorable benefit-risk profile for some population other than the proposed indicated population. If for some other population, please describe that population.

1.2 Dosing

The Study 005/05 protocol specified that talimogene laherparepvec (up to 4 mL total) was to be injected into one or more cutaneous or subcutaneous (SC) or nodal melanoma lesions every 2 weeks until clinically relevant disease progression occurred or there was no residual tumor to inject. However, the actual dose administered, and the dosing regimen, were subject to investigator discretion, and varied considerably among the study subjects.

Discussion: Please discuss whether the dosing instructions (including both dose and regimen, for both individual lesions and for the subject) provided for Study 005/05 would be sufficient to inform the use of talimogene laherparepvec by healthcare providers in clinical practice. If not, please discuss any additional dosing instructions that would be helpful.

1.3 Shedding and Pharmacovigilance

Talimogene laherparepvec is a replication-competent virus derived from an attenuated Herpes Simplex Virus-1 (HSV-1) isolate. As such, talimogene laherparepvec is expected to have biological properties that are similar to wild type HSV-1 with regard to viral shedding and potential transmission and

latency/symptomatic reactivation. However, to date, there are limited data on talimogene laherparepvec shedding, which serves as a proxy for transmission. Thus, there are concerns that viral shedding may expose healthcare providers (HCP) and close patient contacts to talimogene laherparepvec.

Discussion: Regarding the shedding and potential transmission of talimogene laherparepvec from patients treated with the product:

a) Please discuss the available data from the ongoing shedding study and the potential risk for transmission to close contacts (e.g., immunocompromised, infants, pregnant women) and health care providers (HCP).

b) Please discuss Amgen's proposed postmarketing protocol 20130193 and identify any recommendations for modification of the protocol. Please consider whether the protocol design is adequate to capture (with qPCR confirmation) cases of talimogene laherparepvec transmission to close contacts, should they occur. Are there additional measures that should be included in the postmarketing study to ensure that samples can be collected and testing can be performed in a timely manner for suspected herpetic lesions in close contacts or HCPs?

1.4 Overall benefit-risk profile

The proposed indication for talimogene laherparepvec is for the "treatment of injectable regionally or distantly metastatic melanoma." Please consider the background information and evidence of benefit and safety provided in the briefing document, as well as the presentations and discussions during this meeting.

Voting Question: Does talimogene laherparepvec have an overall favorable benefit-risk profile for the treatment of injectable regionally or distantly metastatic melanoma? In voting, please consider only whether the available evidence would support traditional approval, not Accelerated Approval.

2 Melanoma

2.1 Melanoma Overview

American Cancer Society (ACS) estimated that there were 76,100 new melanoma cases and 9,710 deaths from melanoma in the U.S. in 2014 (American Cancer Society: Cancer Facts and Figures 2014) (ACS, 2014).

Stage at diagnosis is the strongest predictive factor for survival in melanoma. The American Joint Committee on Cancer (AJCC) Melanoma Staging system is widely accepted as a useful prognostic indicator (Balch et al., 2009). Staging is based on thickness of the tumor at diagnosis, presence or absence of ulceration, and local or distant lymph node involvement and visceral metastasis (Table 1). Study 005/05 enrolled only subjects with unresectable stage IIIB, stage IIIC, or stage IV melanoma, based on staging at the time of enrollment. Subjects may not have had stage IIIB, stage IIIC, or stage IV melanoma at the time of initial diagnosis.

Table 1. Staging and Prognosis of Stage III and Stage IV Melanoma

AJCC Stage	Clinical Status	5-year survival (%)
IIIA	**1 lymph node**	**65-70**
IIIB	**1-3 involved nodes + ulceration**	**40-60**
IIIC	**1-3 nodes + nodal macrometastasis + ulceration**	**20- 35**
IVM1a	**Distant skin, nodal**	**30**
IVM1b	**Lung**	**20**
IVM1c	**Other visceral**	**10**

Source: (Balch et al., 2009)

2.2 Treatment of Unresectable Stage III, Stage IV, and Recurrent Melanoma

Until five years ago, the treatment options for patients with unresectable stage III, stage IV, and recurrent melanoma were limited to high-dose interleukin-2 (IL-2) and dacarbazine (DTIC), neither of which has been demonstrated to prolong overall survival (OS) (Balch et al., 2009) (Howard et al., 2012) (Howlader N, 2014). Within the last five years, however, therapeutic options for patients with unresectable or metastatic melanoma have expanded (Table 2 below). The current standard care options for the initial treatment of these patients include not only IL-2, but also ipilimumab, an immune checkpoint inhibitor, and BRAF signal transduction inhibitors (for patients whose tumors express the BRAF V600E mutation), such as vemurafenib, dabrafenib and trametinib. Both ipilimumab and vemurafenib have been shown to prolong OS. In addition, dabrafenib and trametinib were approved in 2014, based on an effect on progression-free survival, for treatment of patients with unresectable or metastatic melanoma and BRAF V600E mutations (see Section 12 for detailed discussion regarding the approvals for these therapies). Programmed death 1 (PD-1) inhibitors pembrolizumab and nivolumab were granted Accelerated Approval in 2014. These therapies have demonstrated improvements in durable objective response rates, and ongoing clinical trials are being conducted to verify their clinical benefit. Thus, patients with unresectable or metastatic melanoma now have multiple systemic treatment options.

Accelerated Approval is one of the FDA's expedited programs intended to facilitate and expedite development and review of new drugs that address unmet medical need in the treatment of a serious or life-threatening condition. FDA may grant Accelerated Approval to "a product for a serious or life-threatening disease or condition . . . upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM), that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. For drugs granted Accelerated Approval, postmarketing confirmatory trials have been required to verify and describe the anticipated effect on IMM or other clinical benefit." (FDA Guidance:

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf)

In addition to systemic therapies, palliative radiation therapy may alleviate symptoms in patients with brain and bone metastases as well spinal cord compression, although melanoma is a relatively radiation-resistant tumor.

Table 2. FDA-Approved Therapies for Advanced Melanoma

FDA-Approved Products	Approval Year/ indication	Endpoint(s)	Clinical Benefit / Effect
DTIC (dacarbazine)	**1975**	**ORR**	**ORR of 5-20%**
Proleukin (Interleukin-2)	**1998**	**ORR (WHO)**	**ORR 16% (CR 6%); CR: 59+ (range 3 to 122+ months) PR or CR: 59 months+ (range 1-122+ months)**
Yervoy (Ipilimumab)	**March 25, 2011 treatment of unresectable or metastatic melanoma**	**OS ORR (WHO)**	**Ipi vs. gp100: OS: HR 0.66 (95% CI: 0.51, 0.87) median 10 vs. 6 months BORR: 10.9% vs. 1.5% Ipi+gp100 vs. gp100: OS: HR 0.68 (95% CI: 0.55, 0.85) median 10 vs. 6 months BORR: 5.7% vs. 1.5%**
Patients with unresectable or metastatic melanoma and BRAF V600E mutations			
Zelboraf (Vemurafenib)	**2011**	**OS PFS**	**Vemurafenib vs. DTIC mOS: 13.6 vs. 10.3 months HR: 0.44 (95% CI: 0.33, 0.59) mPFS: 5.3 vs. 1.6 months HR: 0.26 (95% CI: 0.20, 0.33)**
Tafinlar (Dabrafenib)	**2013**	**PFS**	**Dabrafenib vs. Dacarbazine mPFS: 5.1 vs. 2.7 months HR: 0.33 (95% CI: 0.20, 0.54)**
Mekinist (Trametinib)	**2013**	**PFS**	**Trametinib vs. Chemotherapy mPFS: 4.8 vs. 1.5 months HR: 0.47 (95% CI: 0.34, 0.65)**
Tafinlar and Mekinist (Dabrafenib and Trametinib)	**2014 Accelerated Approval**	**ORR***	**Dabrafenib plus or minus Trametinib ORR 76% vs. 54% mDOR : 10.5 months (95% CI : 7, 15) vs 5.6 months (95% CI : 5, 7)**
Patients with unresectable or metastatic melanoma with disease progression following ipilimumab and/or BRAF inhibitor			

FDA-Approved Products	Approval Year/ indication	Endpoint(s)	Clinical Benefit / Effect
Keytruda (Pembrolizumab)	**2014 Accelerated Approval**	**ORR***	**24% (95% CI: 15, 34) CR(1) PR (20), 86% ongoing response (1.4 – 8.5 months)**
Opdivo (Nivolumab)	**2014 Accelerated Approval**	**ORR***	**32% (95% CI: 23, 41) CR(4) PR (34)**

Source: FDA, and Proleukin (USPI); Yervoy (USPI); Zelboraf (USPI); Dacarbazine (USPI; (Huncharek et al., 2001)); Tafinlar (USPI); Mekinist (USPI). *ORR was assessed by RECIST v1.1criteria
Abbreviations in Table: BORR, best overall response rate; CR, complete response; DOR, duration of response; HR, hazard ratio (95% C.I.); Ipi, ipilimumab; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; NR, not reached; ORR, objective response rate; OS, overall survival; PR, partial response.

The detailed approval information for therapies listed in Table 2 is further described in the Appendix at the end of this document. The Appendix provides further background for discussion and consideration of talimogene laherparepvec in the context of the currently available therapies in the treatment of patients with injectable regionally or distantly metastatic melanoma, the proposed indication of talimogene laherparepvec.

3 Product Description

The investigational product, talimogene laherparepvec, is an attenuated replication-competent herpes simplex virus type 1 (HSV-1) that can constitutively express a biologically active form of human GM-CSF. The biology, derivation of talimogene laherparepvec, and its proposed mechanism of action are described in this section.

3.1 Oncolytic HSV

Herpes simplex virus type 1 (HSV-1) is a ubiquitous enveloped DNA virus that causes most human cold sores. Sixty-five percent of the US population has antibodies to HSV-1 (Wald A., 2007). Biological characteristics of HSV-1 include 1) the capacity to infect different cell types, 2) the inability to integrate into the host genome, 3) well characterized virulence genes, and 4) the susceptibility to anti-viral therapeutics, including replication inhibitors such as acyclovir, valcyclovir, famciclovir and penciclovir.

Biological characteristics of HSV-1 that raise concerns regarding its use as an oncolytic viral product include risks associated with HSV-1 infection, such as viral latency and recombination in vivo with other strains of HSV-1. In very rare cases (~2 to 4 in 10^6 people/year) wild type HSV-1 enters the central nervous system (CNS) and causes meningoencephalitis, or disseminates and causes multi-organ disease (Slifkin et al., 2004) (Kennedy, 2005) (Kimberlin, 2007). In addition, because HSV-1 is a replication-

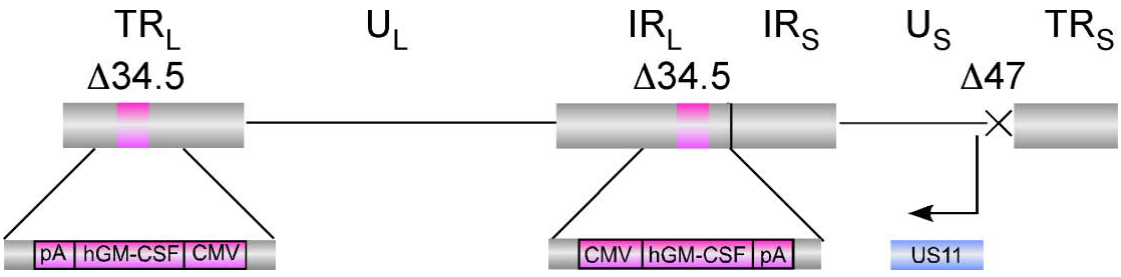
competent virus, viral shedding from treated patients may lead to the exposure of HCPs and close patient contacts. The risk of infection may be higher in immunocompromised individuals who are close patient contacts.

Some of these risks associated with using HSV-1 as an oncolytic viral product can be mitigated by introducing genetic mutations into viral genes associated with neurovirulence (e.g., ICP34.5) and immune response modulation (e.g., ICP47). These mutations attenuate the virus, while still preserving the ability of the virus to replicate in tumor cells, leading to lysis of tumor cells. HSV-1 mediates 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).

3.2 Talimogene Laherparepvec

Talimogene laherparepvec was derived from a novel primary HSV-1 isolate (JS1, ECACC Accession Number 01010209) that demonstrates enhanced oncolytic activity towards tumor cells, as compared to the commonly used laboratory strains (e.g., 17syn+) and other primary isolates (Liu et al., 2003). To produce talimogene laherparepvec, the JS1 strain was genetically modified by deleting the virulence genes that code for ICP34.5 and ICP47. Wild type HSV-1 contains two copies of the gene for ICP34.5, and both copies were functionally deleted in talimogene laherparepvec by inserting two copies of human GM-CSF gene sequences. Deletion of the ICP47 gene also resulted in converting the HSV-1 late gene US11 into an immediate early gene, under the ICP47 promoter (Cassady et al., 1998). A schematic of the talimogene laherparepvec genome is shown in Figure 1.

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 talimogene laherparepvec manufacturing process consists of expansion of the virus in Vero cells, followed by harvest, recovery, purification, and sterile filtration. The filtered product is formulated to

nominal drug product doses of either 10^6 plaque-forming units/mL (PFU/mL) or 10^8 PFU/mL. The drug product is supplied in 2mL vials, each containing a recoverable product volume of 1mL, and is stored at -80°C ± 10°C until use.

3.3 Proposed Mechanism of Action (MOA)

Deletion of the viral gene coding for ICP34.5 reduces the neurovirulence of talimogene laherparepvec compared to wild type HSV-1, and contributes to tumor-selective viral replication. Deletion of the gene for ICP47 (antigen processing inhibitor encoded by HSV-1) prevents down-regulation of antigen presentation molecules and increases the expression of the HSV US11 gene, which enhances viral replication in tumor cells. Talimogene laherparepvec constitutively expresses human GM-CSF under the control of a cytomegalovirus (CMV) immediate-early promoter.

Talimogene laherparepvec has been designed for (1) replication of the virus in tumor cells, resulting in the destruction of injected tumors, and (2) local expression of GM-CSF encoded in the virus, by the infected tumors. The combination of tumor destruction and release of tumor antigens with local GM-CSF expression is proposed to enhance tumor antigen presentation to the immune system and induction of immune responses to the tumors.

3.4 Virus Biodistribution

Biodistribution of talimogene laherparepvec in pre-clinical studies helps determine the extent and capacity of the attenuated virus to infect animals and spread from the site of administration to other tissues. Animal models may serve as a surrogate for virus biodistribution in, and potential shedding from, infected subjects.

Following repeat intratumoral administration of talimogene laherparepvec into a tumor-bearing murine model, viral DNA was detected in tumor, blood, lymph nodes, spleen, and liver. Lower levels of viral DNA were detected in the heart, kidney, lung, and brain. At 25 days following administration of talimogene laherparepvec into the footpad of Balb/c mice, infection in the dorsal root ganglia (DRG) was observed. These results in animals indicate the potential for talimogene laherparepvec to spread to uninjected tissues in exposed subjects.

4 Study 005/05

4.1 Trial Design

Study 005/05 was a multicenter, randomized, open-label, Phase 3 study to assess talimogene laherparepvec monotherapy vs. control (GM-CSF) injections in subjects with unresectable stage IIIB, IIIC, and IV melanoma. FDA concurred on the study protocol as part of a Special Protocol Assessment in 2008.

Talimogene laherparepvec contains human GM-CSF gene sequences and might be expected to produce measurable systemic blood levels. At the time that Study 005/05 was initiated, GM-CSF was in clinical studies for treatment of melanoma. Therefore, GM-CSF was chosen as the comparator to control for any activity, either therapeutic or adverse, due to GM-CSF alone. However, it is unclear whether GM-CSF, as administered in this study, was reasonably likely to have had any therapeutic activity. Regardless, GM-CSF served as the comparator for the assessment of the superiority of the effectiveness of talimogene laherparepvec.

Eligible subjects were randomized in a 2:1 allocation ratio to receive talimogene laherparepvec or control. Talimogene laherparepvec was administered intralesionally. The control was administered subcutaneously.

Subjects were to receive treatment until Week 24 (even in the presence of disease progression, including the appearance of new lesions), or achievement of a CR, unless other therapy for melanoma was required (Figure 2). After 24 weeks, subjects were to remain on study until clinically relevant disease progression (disease progression associated with a decline in performance status and/or alternative therapy was required in the opinion of the investigator), up to 12 months. Subjects in response at 12 months were to continue treatment for up to an additional 6 months or disease progression, whichever was earlier.

Subjects were to be followed for OS for at least 36 months from the date the last subject was randomized or until the last study subject had died, whichever was earlier.

4.2 Objectives

The objective of Study 005/05 was to evaluate the efficacy and safety of treatment with talimogene laherparepvec in melanoma patients with unresectable stage IIIB, IIIC, and stage IV disease.

4.3 Major Eligibility Criteria

4.3.1 Inclusion Criteria:

1. Males or females age ≥ 18 years.
2. Histologically confirmed diagnosis of malignant melanoma.
3. Stage IIIB, IIIC or stage IV disease that is not surgically resectable.
4. Measurable disease defined as:
   - at least 1 melanoma lesion that can be accurately and serially measured in at least 2 dimensions and for which the greatest diameter is ≥ 10 mm as measured by contrast enhanced or spiral computed tomography (CT) scan for visceral or nodal/soft tissue disease (including lymph nodes) and/or;
   - at least 1 ≥ 10 mm superficial cutaneous melanoma lesion as measured by calipers and/or;
   - at least 1 ≥ 10 mm subcutaneous melanoma lesion and/or;
   - multiple superficial melanoma lesions which in aggregate have a total diameter of ≥ 10 mm.

5. Injectable disease (i.e., suitable for direct injection or through the use of ultrasound guidance) defined as:
   - at least 1 injectable cutaneous, subcutaneous, or nodal melanoma lesion ≥ 10 mm in longest diameter or,
   - multiple injectable melanoma lesions which in aggregate have a longest diameter of ≥ 10 mm.
6. Serum LDH levels ≤ 1.5 x ULN.
7. ECOG Performance Status of 0 or 1.
8. Life expectancy greater than 4 months from the date of randomization.

FDA comment: Inclusion criterion "multiple superficial melanoma lesions which in aggregate have a total diameter of ≥ 10 mm" allowed enrollment of subjects who had only small or very small lesions. Inclusion of such subjects raises concerns regarding the reliability of injection, and particularly reliability of measurement, both at the baseline and during assessments of response.

4.3.2 Exclusion Criteria:

1. Clinically active cerebral or any bone metastases. Patients with up to 3 cerebral metastases may be enrolled, provided that all lesions have been adequately treated with stereotactic radiation therapy, craniotomy, gamma knife therapy, with no evidence of progression, and have not required steroids, for at least two months prior to randomization.
2. For patients with ≤ 3 visceral metastases, no lesion > 3 cm., and liver lesions must meet RECIST criteria for SD for at least 1 month prior to randomization.
3. Any underlying medical condition, which in the opinion of the investigator, would make administration of the study drugs hazardous or make it difficult to monitor adverse effects.
4. History of second cancer unless disease-free for greater than 5 years.
5. Primary ocular or mucosal melanoma.
6. Evidence of immunosuppression for any reason.
7. Open herpetic skin lesions.

4.4 Treatment and Study Drug Administration Schedule

4.4.1 Talimogene Laherparepvec Treatment Group

The initial dose of talimogene laherparepvec was up to 4 mL total, at a concentration of 10^6 PFU/mL, which was injected into 1 or more skin or subcutaneous (SC) tumors.

Subsequent doses began 3 weeks after the first dose and consisted of talimogene laherparepvec up to 4 mL total, at a concentration of 10^8 PFU/mL, every 2 weeks.

All reasonably injectable lesions (cutaneous, SC, and nodal disease that could be injected with or without ultrasound guidance) were to be injected, up to the maximum dosing volume available, with the largest injectable lesion(s) dosed first.

On any individual dosing Day, any new lesions, newly measurable lesions, and newly documented lesions that were injectable should be injected before the pre-existing lesions, up to the 4 mL dosing volume available.

If any injected lesion progressed, the injection frequency could be increased to once per week for 4 weeks for the progressing lesion(s) only ("accelerated dosing"). Up to 3 sets of 4 accelerated injections could have been given, providing that (after each set) clinically relevant disease progression did not occur and there was still residual tumor to inject. The dose remained the same during periods of accelerated dosing. The total injection volume for each treatment visit could be up to a maximum of 4 mL. The same lesion(s) could be injected on more than one treatment visit. The volume of talimogene laherparepvec to be injected into each lesion depended on the size of the lesion and should have been determined according to Table 3 below.

4.4.2 Control (GM-CSF) Group

The control was administered at a dose of 125 μg/m^2/day subcutaneously, on an every four week schedule, consisting of daily doses for 14 days, followed by a 14-day rest period.

4.4.3 Treatment in the Presence of New Lesions and Progressive Disease

Subjects who had new lesions and progressive disease within 24 weeks after randomization would continue their treatment unless they met conditions for off-treatment described in Section 4.5. Subjects who had new lesions and progressive disease after week 24 could be treated if the progressions or new lesions were judged "non-clinically relevant" progressive disease by the investigators. "Clinically relevant" progressive disease was defined as disease progression associated with a decline in performance status, and/or alternative therapy was required, in the opinion of the investigator.

Table 3. Talimogene Laherparepvec Injection Dose Based on Lesion Size

Lesion size (longest dimension)	Talimogene laherparepvec injection volume	Dose [concentration: 10^6 PFU/mL]	Dose [concentration: 10^8 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**

[Source: Reproduced from BLA Submission]

Note: The initial dose of talimogene laherparepvec was at a concentration of 10^6 PFU/mL, up to 4 mL total. Subsequent doses were at a concentration of 10^8 PFU/mL, up to 4 mL total. The volume of talimogene laherparepvec to be injected into each lesion depended on the size of the lesion and was determined by investigators.

4.5 Study and Treatment Duration

- Day 0 to Week 24: Subjects were to receive treatment, even in the presence of disease progression (even the appearance of new lesions), unless one of the following occurred:

    1) Complete response (disappearance of all disease)
    2) All injectable tumors disappear

3) Intolerable toxicity
4) The investigator believed that it was in the best interest of the subject to stop treatment or to be given other therapy for melanoma.
5) Subject withdrew consent

If any of events 1) – 4) occurred, the subject was to discontinue study treatment, have an end-of-study / early termination visit (including response assessment), and then continue to be followed for survival.

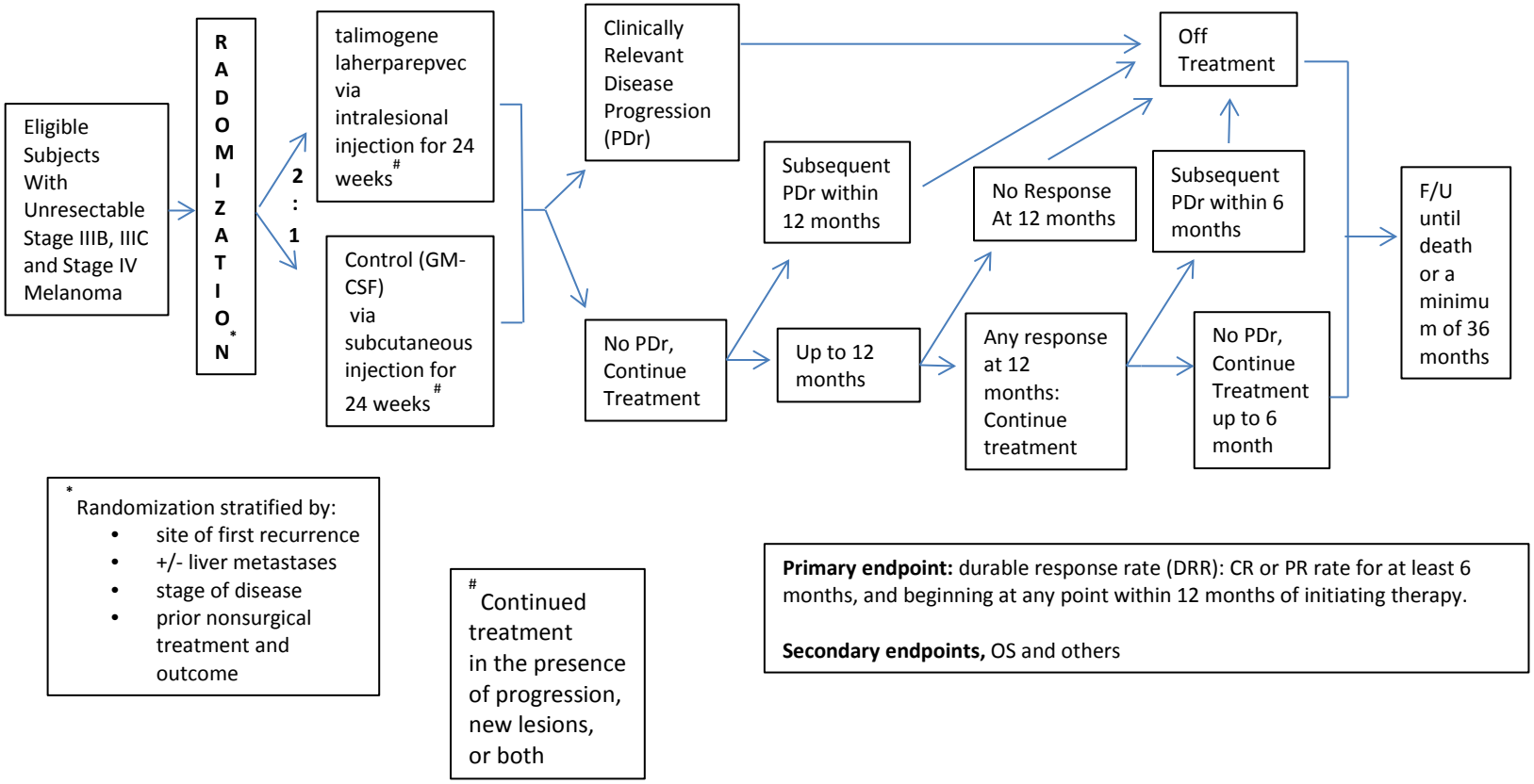
If the subject withdrew consent (i.e., event 5 above occurred), then the subject discontinued study treatment, and no new information other than survival status was to be collected from that subject and added to the database. All subjects who discontinued scheduled follow-up visits were to be followed for survival, including search of public records to gather survival data.

- Week 24 to Month 12: Subjects were to continue treatment through Month 12, unless one of the events 1-5 above occurred, or the subject had clinically relevant disease progression (PDr) (i.e., disease progression associated with a decline in performance status and/or alternative therapy was required in the opinion of the investigator).
- Month 12 to Month 18: Subjects who were not incomplete response (CR) or partial response (PR) at Month 12 discontinued treatment at that time. Subjects in response at Month 12 were to continue treatment for any injectable lesions through Month 18, unless any of events 1 – 5 above occurred, or the subject had disease progression, either clinically relevant (PDr) or not clinically relevant (PDn).
- All subjects were to be followed for overall survival (OS) for at least 36 months from the date the last patient was randomized, or until the last subject had died, whichever was earlier (Figure 2).

4.6 Trial Endpoints and Analyses

Study 005/05 was designed to show an improvement in durable response rate (DRR) for subjects treated with talimogene laherparepvec compared with subjects treated with control (GM-CSF). The responses were assessed by investigators using multiple modalities, including clinical assessments, ultrasound, CT and PET imaging, photography, and biopsies. Investigators were responsible for evaluating both measurable and non-measurable lesions. The assessment of disease status (e.g., disease progression; complete response; partial response; stable disease) involved a calculation of the tumor burden associated with lesions that had been present at baseline, and a separate calculation of the tumor burden associated with new lesions. Those subjects assessed by the investigators to have reached 9 months on therapy, or CR, or PR, were referred to the Endpoint Assessment Committee (EAC) for a determination of durable response, the primary endpoint. The EAC response assessment was based on clinical information provided by the investigators, along with measurements provided by dermatologists and radiologists blinded to treatment arm and based on review of imaging data. Thus, the outcome assessment in Study 005/05 was a complex process.

Figure 2. 005/05 Study Design



Source: FDA figure.

4.6.1 Trial Endpoints

The primary endpoint of Study 005/05 was durable response rate (DRR): rate of CR or PR maintained for at least 6 months, and beginning at any point within 12 months of initiating therapy.

Overall survival was a secondary endpoint. Other secondary endpoints included objective response rate (ORR) [PR+CR], time to response, duration of response, and time to treatment failure [time from randomization until the first episode of clinically relevant disease progression where there is no response achieved after the progression event or until death].

Exploratory endpoints included impact of response on survival, and "quality of life" patient-reported outcomes using the FACT-BRM instrument.

4.6.2 Primary Endpoint Evaluation

4.6.2.1 Patient Assessments

Patients underwent the assessment procedures described in Table 4 with the frequencies shown in Table 5 below to evaluate melanoma tumor status.

4.6.2.2 Lesion Definition

Lesions were put into two categories: measurable lesions and non-measurable but evaluable lesions.

Measurable lesion was defined by the ability to measure a lesion bi-dimensionally with surface area determined by multiplying the longest diameter by the diameter perpendicular to the longest diameter.

Lesions considered to be non-measurable but evaluable included: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, lymphangitis cutis, multiple small lesions, and serum markers (i.e., elevated LDH). These non-measurable but evaluable lesions were assessed by clinical, radiological (e.g., CT, MRI, PET, PET/CT), and laboratory evaluations.

4.6.2.3 Lesion Assessments

Assessments for both measurable lesions and non-measurable lesions were performed at baseline and at the beginning of each treatment cycle.

Table 4. Subject Assessment Modalities

Modalities	Details
Clinical measurement	Clinical measurements were based on tumor measurement by physical measurement and photographs of superficial lesions, at baseline, Day 1 of each cycle, and 30 days after last injection of the product
CT	Whole body (i.e., including the head and both upper and lower extremities in addition to chest, abdomen and pelvis) scans should be performed for all subjects during screening. CT scans of the chest, abdomen, and pelvis and all other areas where disease was noted at baseline should be performed every 12 weeks from the start of therapy to assess disease response. If a response (CR or PR) was suspected to have initiated since the last visit based on clinical assessment, CT scans and any other confirmatory procedures should be performed within one week. Subjects who completed treatment and were in response should continue to be followed every 12 weeks by CT for disease assessment until PDr (clinical relevant disease progression) or 18 months following randomization, whichever was the earliest.
Ultrasonograms	Ultrasonograms of nodal or other soft tissue masses may be performed at baseline as clinically indicated. Ultra-sonograms performed to assess response should be repeated every 12 weeks from the start of therapy. Ultrasound was not acceptable for measurement of deep tissue/visceral lesions, although may be used for soft tissue lesions which were not effectively imaged by CT.
PET or PET/CT	Whole body PET or whole body PET/CT scan was required at screening for all subjects. For subjects who reach 9 months of therapy but for whom a PR or CR had not been recorded, a whole body PET or whole body PET/CT scan should be performed and representative biopsies taken from residual masses, as far as was clinically feasible, to aid in determining status.
MRI	Brain MRIs are required at screening for all subjects. MRI of the brain should be performed every 16 weeks (or at any time when in the judgment of the investigator for the subjects with signs or symptoms of CNS disease progression).

[Source: Reproduced from BLA Submission]

Table 5. Subject Assessment Schedules

	Screening	Treatment Period			Scan Schedule			End of Treatment/ Early Termination	Follow-up
Assessments	**Day 28 to -1**	**Day 1 Cycle 1**	**Subsequent Injections (28-day cycle)**		**Q12 weeks (± 14 d)**	**Q16 weeks (± 14 d)**	**9 months (± 7 d)**	**30 days after last injection (± 7 d)**	
			Day 1 (± 3 d)	**Day 15[a] (± 3 d)**					
Medical history, TNM Staging, ECG	X								
Physical exam	X							X	
Photography	X	X	X					X	
Clinical measurements	X	X	X					X	
Whole body CT[j]	X				X				X
Whole body PET or PET/CT[k]	X						X		
Ultrasonograms	X				X				
Brain MRI[l]	X					X			
Biopsy of residual lesions[n]	**A biopsy of residual pigmented areas or other residual masses suspected to no longer contain tumor could be obtained at any time point.**								
Response assessment by modified WHO			X					X	

[j] Whole body CT scans or CT CAP and CT of any other areas where disease was noted at baseline or where disease has appeared post baseline were to be repeated every 12 weeks from the start of therapy to assess disease response. If a response (CR or PR) was suspected to have initiated at any visit, then the CT and any other procedures required to confirm response were to be performed within 1 week. All screening CT scans and scans of those subjects considered in response were to be submitted to the central reader and approved by BioVex prior to randomization. Subjects who completed treatment and were in response continued to be followed every 12 weeks by CT for disease assessment until PDr or end of study, whichever was earliest.

[k] Whole body PET or PET/CT was required at screening for all subjects; for subjects who reached 9 months on therapy without PR or CR having been recorded, PET or PET/CT was to be repeated.

[l] Brain MRIs were required at screening for all subjects.

[n] At any stage, a biopsy of residual pigmented areas or other residual masses suspected to no longer contain tumor could be obtained at any time point.

Source: Reproduced from BLA submission

4.6.2.3.1 Measurable Lesions

- For lesions present at baseline: tumor burden for all measurable lesions was calculated by summation of the products of all measurable lesions. At the beginning of each treatment cycle, the tumor burden of these same lesions present at the baseline was calculated and compared with the tumor burden at baseline, according to the assessment criteria described below.
- If new measurable lesions appeared during the treatment, the tumor burden for new lesions was calculated by summation of the products of all these new lesions. At the beginning of each treatment cycle, the summated tumor burden of these new lesions was calculated. This calculated tumor burden was compared with the tumor burden calculated based on the summation of the product of all of the new lesions, using the time when each new lesion first appeared. For example, for a subject who had three new lesions that appeared at different times, to determine whether the tumor burden of new lesions had changed, the summated tumor burden at a visit was compared to the sum of the original tumor burden for the three lesions, which were measured at the three different times when each lesion had first appeared.
- Response Criteria for lesion assessment (modified World Health Organization Criteria):
  - Complete Response (CR):
    - Tumor burden for lesions present at baseline decreased by 100%, and
    - Tumor burden for new lesions decreased by 100%
  - Partial Response (PR)
    - Tumor burden for lesions present at baseline decreased by 50%, and
    - Tumor burden for all new lesions decreased by 50%.
  - Stable Disease (SD): Neither sufficient overall tumor shrinkage to qualify for response (PR or CR) nor sufficient tumor increase to qualify for PD.
  - Progressive Disease (PD): A greater than25% 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.

- Non-clinically relevant progressive disease (PDn): PD in subjects who did not suffer a decline in performance status and/or in the opinion of the investigator did not require alternative therapy. Subjects showing PDn were allowed to continue study treatment.

- Clinically relevant progressive disease (PDr): PD that is associated with a decline in performance status and/or in the opinion of the investigator the subject required alternative therapy. Subjects with PDr were allowed to remain on study until 24 weeks of therapy unless, in the opinion of the investigator, other treatment is warranted.

- CNS progressive disease (PDcns): Progression in the central nervous system (brain).

4.6.2.3.2 Non-measurable Lesions

Assessment for responses of non-measurable but evaluable lesions to the treatment:

- Complete Response (CR): Disappearance of all non-measurable but evaluable tumors.
- Incomplete Response/Stable Disease (SD): Persistence of one or more non-measurable but evaluable tumor(s).
- Progressive Disease (PD): Unequivocal appearance of one or more non-measurable but evaluable tumors.

4.6.2.4 Evaluation of Overall Melanoma Response to the Treatment

Evaluation of overall melanoma response to treatment integrated responses of both measurable lesions (those present at the baseline and the new lesions during the treatment) and non-measurable but evaluable lesions is shown in Table 6 below.

Overall response evaluation was performed by the investigators at the beginning of each treatment cycle or subsequent to study withdrawal according to Table 6 below, based on the assessment of both measurable lesions and non-measureable lesions.

Table 6. Evaluation of Overall Melanoma Response to the Treatment

Measurable Lesions including new lesions	Non-measurable Lesions	Overall Melanoma Response
CR	CR	CR
PR	CR	PR
SD	CR	SD
CR or PR	SD	PR
SD	SD	SD
Any	PD	PDr
PDn	Not PD	PDn
PDr	Any	PDr
PDcns	Not PD	PDcns

Source: Reproduced from the BLA 125518 Submission
CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease; PDr=clinically relevant PD; PDn=clinically not relevant PD; PDcns=central nervous system.

4.6.3 Primary Endpoint: Durable Response Rate

The primary endpoint of durable response rate was defined as rate of subjects who experienced an overall complete or partial response (CR or PR) that began at any point within 12 months after initiating therapy and was maintained for at least 6 months. The primary efficacy results were based on Endpoint Assessment Committee (EAC) determination of durable CR or PR. The EAC was blinded to treatment assignment. However, the EAC did not review results for all subjects. Instead, the EAC evaluated information sent by investigators only for subjects who had investigator-determined CR or PR, or who reached nine months on therapy.

The EAC used a 2-step process: first, tumor measurements were determined by a radiologist and dermatologist and provided to the EAC; then EAC Oncologists determined if a subject was in response (CR or PR) using available clinical information except for treatment assignment. Thus, in cases where the assessments were based on radiological or photographic information, the EAC may have based response assessments on measurements and/or lesions that were different than the measurements and lesions that were used by the investigators. For example, the EAC may have disagreed with the investigators regarding what constituted a lesion, or whether a lesion was measurable. These differences between the EAC and the investigators with regard to the data reviewed, and with regard to lesion assessment, may

have contributed to observed differences between the EAC and the investigators with regard to the assessment of durable responses.

FDA comment: The definition of the primary endpoint allowed a subject to be counted as "durable responder" (DR) even if the subject developed new lesions, relapse, or progression of disease after the 6-month period when the durable response was recorded (See Section 6.1).

4.6.4 Secondary Endpoint: Overall Survival

Overall survival was defined as the time from the date of randomization to the date of death due to any cause. After concluding the treatment period of the trial, all subjects were to be followed for mortality at 3-month intervals until End of Study (EOS). EOS was defined as 36 months from the date the last subject was randomized, or until the last subject died, whichever was earlier. The follow-up plan included subjects who discontinued after randomization but prior to receiving the first dose of study treatment. If the survival status was unknown, including situations when death was not confirmed, survival time was to be censored at the last date the subject was known to be alive. Subjects were censored at the date of randomization if no additional follow-up data were obtained.

4.6.5 Additional Secondary and Exploratory Endpoints

Additional secondary endpoints to further characterize tumor responses included best overall response and disease burden, response onset, time to treatment failure, duration of response, and response interval. Subjects' "quality of life" was assessed by the FACT-BRM questionnaire as an exploratory endpoint.

4.7 Statistical Considerations

4.7.1 Randomization

Subjects were to be randomized 2:1 to talimogene laherparepvec or control, stratified by

- Site of first recurrence (3 levels): in transit or distant skin, lymph node, visceral.
- Presence of liver metastases (2 levels): no, yes.
- Stage of disease (3 levels): IIIB/C, IVM1a or IVM1b, IVM1c.
- Prior treatment and time to recurrence (3 levels):
    a. No prior nonsurgical melanoma treatment other than adjuvant therapy,
    b. Prior nonsurgical melanoma treatment other than adjuvant therapy and recurrence less than 1 year from primary diagnosis,
    c. Prior nonsurgical melanoma treatment other than adjuvant therapy and recurrence more than 1 year from primary diagnosis.

4.7.2 Sample Size

The applicant planned to randomize 430 subjects, to yield 360 evaluable subjects at 2:1 ratio in the talimogene laherparepvec versus the control arm. With 360 subjects, a level 0.05 2-sided Fisher's exact test would have 90% power to detect a DRR difference of 13% (talimogene laherparepvec) versus 3% (control), or 21% versus 8%. In addition, the primary analysis of the OS endpoint was planned to occur at 290 deaths, to allow 90% power to detect a hazard ratio of 0.67.

4.7.3 Analysis of Durable Response Rate (DRR), the Primary Endpoint

The primary analysis of DRR and all response-based endpoints was scheduled to occur when no further subjects had the possibility of meeting the criteria for durable response, or all subjects reached 18 months from first dose (whichever was earlier). The primary analysis of DRR was a two-sided unadjusted Fisher Exact test. Study success was defined as the test being statistically significant at the 0.0488 level.

4.7.4 Analysis of Overall Survival (OS)

OS was to be tested for superiority in the talimogene laherparepvec arm compared to the control arm at the following occasions.

- Interim analysis (IA) of OS would occur at each IA of DRR and at the time of the primary analysis of DRR, but only in the event of a statistically significant difference on DRR.
- The primary analysis of OS would occur at the time of 290 deaths if that was later than the time of the primary analysis of DRR.
- A descriptive OS analysis would occur when all subjects had been followed for 3 years after randomization (EOS).

The primary analysis of OS was the un-adjusted log-rank test. The Cox proportional hazard model was used to estimate the hazard ratio for the treatment effect. With respect to Type 1 error control, the applicant stated that "a nominal 0.0001 one-sided alpha spending will be used to account for the possibility of an unexpected survival outcome prior to the primary OS analysis (including the analyses at each interim and at the primary DRR analysis if applicable). Given the minimal alpha spending on OS prior to the primary analysis, the primary OS analysis will have one-sided significance level of 0.025." In other words, the primary analysis of OS was compared to a nominal statistical significance level of two-sided 0.05.

In response to an information request from the FDA, the applicant communicated that "Prior to both the primary and 36-month (last planned) survival analyses, sites were instructed to conduct a search of the US Death Index to determine if any subject had died and, if confirmed, to report the date of death on the CRF."

4.7.5 Interim Analysis

Two formal interim analyses (IA) with respect to efficacy were planned. The first IA was to occur after the first 75 subjects had been on study for 9 months. One purpose of this IA was to recalculate sample size and to determine timing of the second IA, based on response rate (PR+CR) and DRR (in the control arm). The alpha for this IA was set to be one-sided 0.0001 for the DRR endpoint.

The second IA was to occur once all planned subjects had been randomized and on study for 9 months, at a time to be determined by the DMC after performing the first IA. After the first IA, the DMC recommended performing the second IA once there had been 42 EAC-confirmed DRs. The alpha for this IA was set to be one-sided 0.0005 for the DRR endpoint.

The second IA was eventually cancelled. The applicant stated that the timing of the second IA would have occurred within one month of the primary (final) DRR analysis, which was to occur after the last randomized subject reached 18 months on study. The reason was that the EAC did not start response assessment until October 2012, only 2 months before the data cut-off date for the primary analysis of DRR. Alpha spend for both IAs, however, was accounted for in the primary analysis of DRR. That is, the primary analysis of DRR used a nominal significance level of one-sided 0.0244 (=0.025-0.0001-0.0005), or 2-sided 0.0488.

4.7.6 Analysis Population

The populations for analysis are defined below**.**

The Intent-to-Treat (ITT) population is defined to include all subjects who had been randomized to receive study treatment.

The safety population is defined as all randomized and treated subjects.

The Per Protocol (PP) population is defined as all subjects who were randomized, eligible and treated, received at least 2 cycles of therapy and completed the assessment after 8 weeks (and at other time of termination for those who stay on study past 8 weeks), unless taken off therapy due to progression or due to safety issues before two cycles had been received. Subjects with major protocol violations were excluded from this population. All major protocol violations were determined following the Applicant's standard operating procedures prior to the data base lock.

Unless noted otherwise, the primary analysis of endpoints used the ITT population and the analysis using the PP population was supportive.

5 Study 005/05 Population and Subject Disposition

The study period was from 29 April 2009 (date first subject enrolled) to 21 December 2012 (data cutoff date); no subjects were still receiving treatment as of the cutoff date for this BLA submission. At the data cutoff for the primary analysis of the primary endpoint, the median follow-up times for subjects in the talimogene laherparepvec arm, the control arm, and in both arms of the ITT population were 20.6 months, 18.5 months, and 19.9 months, respectively.

5.1 Study Populations

The primarily efficacy analysis was based on the intent-to-treat population of 436 subjects.

Safety Population includes all subjects randomized and treated, including one subject who was disqualified for efficacy analysis but received talimogene laherparepvec. The primary safety analysis was

performed on 419 subjects in Study 005/05; 292 received talimogene laherparepvec and 127 received control (GM-CSF).

5.2 Subject Characteristics

There were 295 subjects enrolled in the talimogene laherparepvec arm, and 141 subjects enrolled in the control arm (Table 7). Overall, 57.3% were men and 97.9% were white. The mean (range) age was 63 (22 to 94) years. Most subjects (70%) had an ECOG performance status of 0. The Baseline demographics were generally balanced between the talimogene laherparepvec and control arms and were similar across the ITT population, first-line therapy population, second-line population, and the per-protocol population. Most subjects had recurrent disease, and were restaged at screening.

The subject disease staging was based on tumor, node, metastasis (TNM) staging performed during screening for enrollment to the study, not the stage at the initial diagnosis of melanoma. Thirty percent subjects had stage IIIB and IIIC, 27% had IVM1a, and 43% of subjects had more advanced disease (i.e., stage IVM1b and IVM1c). Twenty-two percent of subjects in both arms were stage IV M1c. BRAF mutation status was not known for two thirds of the study subjects in both arms. Demographic characteristics are summarized in Table 7.

The two groups were reasonably well balanced with respect to baseline prognostic characteristics. The population was predominantly male, Caucasian, with good performance status. Approximately two thirds of subjects had received some type of prior non-surgical therapy; approximately one third had received prior biological therapy. BRAF status was known in approximately one third of subjects.

The study initially required that subjects have undergone prior therapy, but Amendment 2 allowed subjects to enroll who had not undergone previous therapy. For those who had undergone prior surgery, the median time from the initial diagnosis to first recurrence was approximately one year. There were 277 (93.6% of 295) subjects in the talimogene laherparepvec group and 123 (87.2% of 141) subjects in the control group that had prior surgery before enrollment to the study (Table 8).

Table 7. Demographic Characteristics

	Talimogene laherparepvec (n = 295)	**Control (n = 141)**
Median age, years	**63**	**64**
Female gender	**122 (41%)**	**64 (45%)**
Race: White	**289 (98%)**	**138 (98%)**
ECOG PS 0	**209 (71%)**	**97 (69%)**
Disease stage		
IIIB	**22 (8%)**	**12 (9%)**
IIIC	**66 (22%)**	**31 (22%)**
IV M1a	**75 (25%)**	**43 (31%)**
IV M1b	**64 (22%)**	**26 (18%)**
IV M1c	**67 (23%)**	**29 (21%)**

	Talimogene laherparepvec (n = 295)	Control (n = 141)
LDH >ULN	15 (5.1%)	5 (3.5%)
BRAF status Mutation Wild-type Unknown / Missing	46 (15.6%) 45 (15.3%) 204 (69.2%)	23 (16.3%) 23 (16.3%) 95 (67.4%)
HSV-1 status Negative Positive Unknown	 97 (33%) 175 (59%) 23 (7.8%)	 45 (32%) 78 (55%) 18 (13%)

[Source: Reproduced from BLA submission]

Ipilimumab and vemurafenib (BRAF inhibitor) were approved just as the Study 005/05 was finishing accrual thus most of the subjects enrolled in Study 005/05 did not receive these therapies. However, a few subjects (3 subjects in the GM-CSF group and 11 subjects in the talimogene laherparepvec group) had prior ipilimumab treatment at screening.

Table 8. Summary of Prior Therapies

CATEGORY Subcategory	Talimogene laherparepvec n = 295 (%)	Control n = 141 (%)
PRIOR SURGERY	277 (93.9)	123 (87.2)
Excision *	240 (81)	108 (76)
Lymphadenectomy	165 (55.9)	65 (46.1)
Amputation	15 (5.1)	5 (3.5)
PRIOR NON SURGICAL THERAPY	203 (68.8)	88 (62.4)
Biologic therapy interferon alfa-2b interleukin-2	99 (33.6) 72 (24.4) 39 (13.2)	45 (31.9) 35 (24.8) 17 (12.1)
Chemotherapy	87 (29.5)	40 (28.4)
Ipilimumab (investigational)	11 (3.7)	3 (2.1)
Limb perfusion	33 (11.2)	16 (11.3)
Radiation therapy	79 (26.8)	23 (16.3)

[Source: Reproduced from BLA submission] * BLA Dataset PR
N = Number of subjects in the analysis set. The subcategories within each category were not mutually exclusive.

5.3 Subject Disposition

A total of 437 subjects were randomized into the study. One subject who was randomized 3 times at 3 different study centers (twice to the control group and then once to talimogene laherparepvec) was excluded from the ITT population. In the ITT population, 436 subjects were randomized at 64 study centers in the US, Canada, South Africa, and United Kingdom. A total of 418 subjects received ≥ 1 dose of study treatment (291 talimogene laherparepvec, 127 control).

As of the primary analysis cutoff date, all ITT subjects had discontinued from study treatment. Table 9 lists the reasons for discontinuation of study treatment. The most common reason was progressive disease (Table 9).

Table 9. Subject Disposition

	Talimogene laherparepvec n = 295 (%)	**Control n = 141 (%)**
Subjects who never received treatment	**4 (1.4%)**	**14 (9.9%)**
Subjects who received Study treatments	**291 (98.6%)**	**127 (90.1%)**
Subjects who Discontinued Study Treatments due to:		
Maximum allowed dose without CR or PR	**26 (8.8)**	**9 (6.4)**
PR or CR for at least 6 continuous months	**42 (14.2)**	**0**
Adverse event	**11 (3.7%)**	**3 (2.1%)**
Consent withdrawn	**10 (3.4%)**	**12 (8.5%)**
Deaths	**5 (1.7%)**	**3 (2.1%)**
Physician decision	**6 (2.0%)**	**5 (3.5%)**
Progressive disease	**191 (64.7%)**	**95 (67.3%)**

[Source: FDA analysis and reproduced BLA submission CSR Table 14-1.1 and Applicant's response on 3-17-2015]

Table 9 indicates that, cumulatively, the percentage of subjects who discontinued study treatment because of the most common reason, "progressive disease", was comparable between the study arms, at 64.7% versus 67.3%. However, the percentage of subjects who did not receive any study treatment was higher in the control arm than in the talimogene laherparepvec arm, at 9.9% versus 1.4%. These 14 subjects in the control arm and 4 subjects in the talimogene laherparepvec arm were designated as non-responders and not assessed for tumor response.

5.4 Study Conduct

5.4.1 Duration of Response Assessment

The protocol stipulated that "subjects were to receive treatment until Week 24 (even in the presence of disease progression, including the appearance of new lesions), or achievement of a CR." Differential early discontinuation of study treatment and response assessment, in particular by Week 24 (Month 6), may reflect subject or investigator bias, based on knowledge of the treatment assignment. Table 10 lists, in 3-month increments, the number of subjects who discontinued study treatment. There were more control group subjects than talimogene laherparepvec group subjects who discontinued study treatment at or before 3 months, 56.0% versus 29.2%. This imbalance in drop-outs could have created bias, in terms of assessment of responses, that would favor the talimogene laherparepvec arm.

Table 10. Cumulative Number of Subjects who Discontinued Treatment at Different Evaluation Time Points

Study Arm	Number of subjects at randomization	At or before 3 Months	At or before 6 Months	At or before 9 Months	At or before 12 Months	At or before 16 Months	At or before 18 Months
Talimogene laherparepvec	**295**	**86 (29.2%)**	**172 (58.3%)**	**226 (76.6%)**	**266 (90.2%)**	**277 (93.9%)**	**291 (98.6%)**
Control	**141**	**79 (56.0%)**	**106 (75.2%)**	**111 (78.7%)**	**124 (87.9%)**	**125 (88.7%)**	**127 (90.1%)**

Source: Adapted from BLA eCTD ISS (Integrated Summary of Safety): Figure IAS-1.1.

While a subject was receiving study treatment, the response assessment schedule included monthly clinical visits, and imaging scans every 12 weeks. When a subject discontinued treatment, he or she should return in 30 days for the End of Treatment (EOT)/Early Termination visit, when the last response assessment would occur. After the EOT visit, the subject would not receive any additional response assessments, but would be followed for survival at 3-month intervals. However, subjects who temporarily stopped treatment because they did not have any remaining injectable lesions did not have an EOT visit; rather, these subjects continued to be followed for response. Therefore, the comparatively much higher percentage of subjects in the control arm who discontinued study treatment by Week 24, suggests that control subjects may have been assessed for tumor response for a shorter time than talimogene laherparepvec subjects. For example, eight (5.7%) of the control group subjects, but none of the talimogene laherparepvec group subjects, had their last tumor assessment within the first 28 days. This differential follow-up may have influenced the study results for the primary endpoint, and may have also influenced the study safety results.

5.4.2 Protocol Deviations

Eligibility violations were reported for 26 subjects in the talimogene laherparepvec arm and seven subjects in the control arm. Protocol deviations, including missing more than one clinical assessment, were reported in 36 (12.2%) subjects in the talimogene laherparepvec arm and five (3.5%) subjects in the control arm. Most protocol deviations were about eligibility violations and missing scans. FDA analysis showed that nine subjects in the talimogene laherparepvec arm and four subjects in the control arm were missing more than 1 sequential response assessment. FDA analysis of protocol deviations suggested that these had no more than a minor effect on the study results.

5.4.3 Surgical Interventions During Study

Two subjects in the talimogene laherparepvec arm received a surgical treatment for melanoma during the course of the study, which may have contributed to determination that both subjects had Complete Response.

6 Efficacy Results

6.1 Primary Endpoint

The primary endpoint of Study 005/05 was durable response rate (DRR): CR or PR rate for at least 6 months, and beginning at any point within 12 months after initiating therapy, as described in Section 4.6.

6.1.1 Primary Endpoint Results

The primary endpoint, durable response rate, was assessed by the EAC, which only reviewed those subjects who had investigator-determined CR or PR, or who had reached nine months on therapy. These subjects accounted for approximately one third of ITT subjects' results (143/436), representing 42% of treatment arm subjects vs. 13% of control (GM-CSF) arm subjects.

The investigators identified 56 durable responders in the talimogene laherparepvec arm and two in the control arm; the EAC identified 51 durable responders, 48 in the talimogene laherparepvec arm and three in the control arm. Thus, the rate of durable response assessed by the EAC was 16.3% in the talimogene laherparepvec arm, compared to 2.1% in the control arm. The unadjusted odds ratio of DRR was 8.9 with 95% confidence interval (CI): 2.7 to 29.2; p value was less than 0.0001. At the data cutoff for the primary analysis of the primary endpoint, the median follow-up times for the durable responders in the talimogene laherparepvec arm and the control arm were 30.2 months and 33.2 months, respectively.

FDA reviewed available clinical response data including Case Report Forms (CRFs) and datasets for all 51 durable responders. A comparison of DRR results assessed by the investigators, the EAC and FDA is in Table 11, below. Please note that although the table provides percentages, based on the number of subjects in the ITT group, only a subset of subjects were evaluated by the EAC, and only the EAC-identified responders were evaluated by FDA.

The results of the analysis of DRR by investigators, EAC and FDA show a statistically significant difference in DRR in favor of the talimogene laherparepvec arm. FDA disagreed with the EAC assessment of DRR for two subjects on the talimogene laherparepvec arm. In addition, due to missing tumor status assessments, the FDA was unable to confirm a durable response for one of the subjects on the GM-CSF arm.

The analysis of study conduct suggested that that the interpretation of study results could have been confounded by bias due to asymmetric dropouts, early study discontinuations in subjects in the control arm, and missing study assessments (See Section 5.4).

Table 11. Determinations of DRR by Investigators, EAC, and FDA

	Talimogene laherparepvec, N (%)	Control N (%)	Odds ratio (95% CI)
Investigator	**56 (19.0%)**	**2 (1.4%)**	**16.3 (3.9, 67.8) P< 0.0001**
EAC[#]	**48 (16.3%)**	**3 (2.1%)**	**8.9 (2.7, 29.2) P< 0.0001**
FDA*	**46 (15.6%)**	**2 (1.4%)**	**12.8, (3.1, 53.7) P< 0.0001**

[Source: FDA analysis and reproduced table from BLA submission]
[#]EAC reviewed 19 subjects in Control arm, and 124 subjects in talimogene laherparepvec arm; *FDA analyzed 51 subjects with DRR classified by the EAC. FDA performed Fisher's exact test for calculating the odds ratio; CI = confidence interval

In addition, investigator bias in this open-label study may have influenced the primary endpoint evaluation. As described in Section 4.6.3, although the primary endpoint results were to be based on EAC evaluation, the EAC was blinded to treatment assignment, and the EAC did not review results for all subjects. Instead, the EAC evaluated information of only 143 subjects who had investigator- determined CR, or PR or who reached nine months on therapy. Investigators based on their evaluation for CR, PR or SD on clinical assessment results with photographic documentation and original imaging scans (MRI, CT, ultrasonogram, PET, or PET/CT). Upon receiving the information, the EAC performed the following tasks: 1) categorizing the lesions, i.e., measurable or non-measurable; 2) choosing lesions for measurements. The lesions that the EAC chose to measure, based on the imaging studies and photographs (clinical assessments), may or may not have been the same as those evaluated by the investigator.

Table 12. Comparison of DRR Evaluation by EAC to DRR Evaluation by Investigator

Durable Response per EAC	**Durable Response per Investigator**		
	Durable Responder	**Non-Durable Responder**	**Total**
Durable Responder - n (%)	**44 (30.8)**	**7 (4.9)**	**51 (35.7)**
Non-Durable Responder - n (%)	**14 (9.8)**	**78 (54.5)**	**92 (64.3)**
Total - n (%)	**58 (40.6)**	**85 (59.4)**	**143 (100.0)**

[Source: Reproduced from BLA Submission]

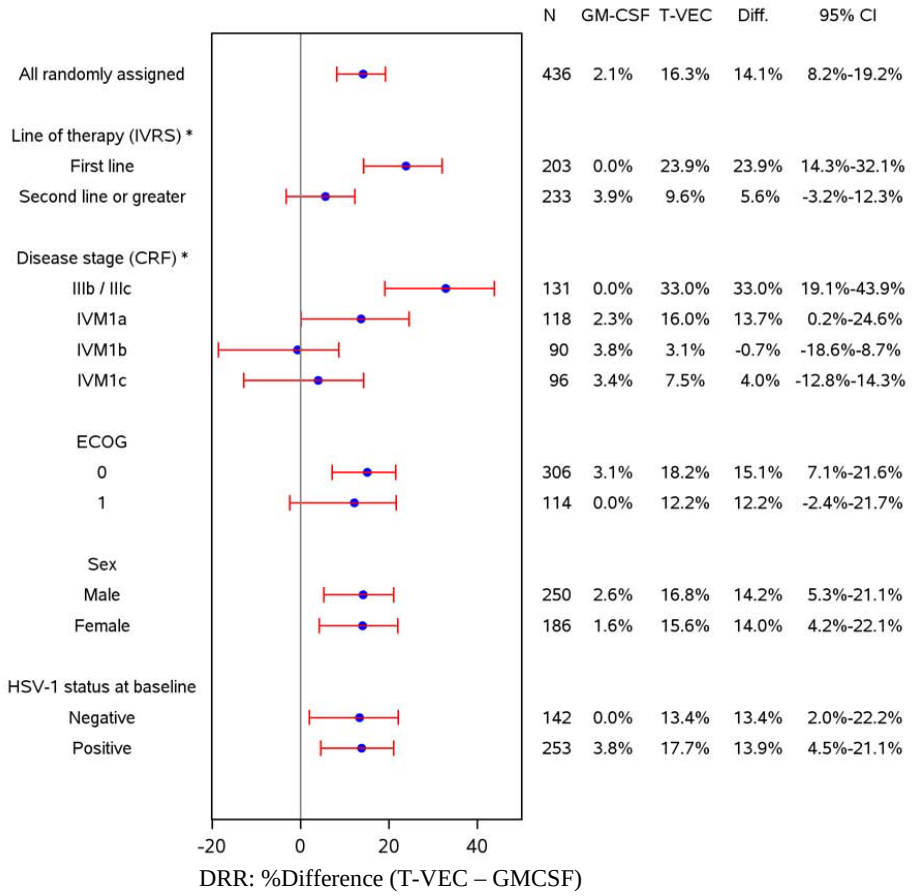
As can be seen from Table 12, the investigators and EAC agreed on approximately 85% of assessments. There was discordance in 21/143 (15%) of subjects between the EAC and investigators with respect to durable responders. The EAC assessed 14 subjects as non-durable and seven subjects as durable compared with the investigators. Investigators assessed a total of seven additional subjects as DR's as compared with the EAC. These results suggest some possible bias in the investigator assessment of DR's in this open-label study. However, the magnitude of the observed treatment effect on the primary endpoint makes it unlikely that the overall study conclusions would have been changed by these issues.

6.1.2 Durable Complete Responders

The Applicatant reported 24 subjects who had durable response with a best overall response of CR. To investigate the number of subjects who experienced a continuous complete response lasting more than 6 months (durable complete responders), FDA reviewed EAC CRFs for these 24 durable responders. FDA identified five of these subjects who did not meet the criteria for durable complete responses. Therefore, FDA considered that there were only 19 durable complete responders (5.4 %) from Study 005/05 per protocol definition.

6.1.3 Subgroup Analysis of Durable Response Rate (EAC)

Figure 3. Applicant's Analysis of EAC Durable Response Subgroups



T-VEC: talimogene laherparepvec
[Source: Reproduced from BLA Submission]

Results for DRR by randomization factors and other covariates, including tumor stage and previous treatment history, are shown in Figure 3 above. The red color bars were Durable Response Rate (DRR) percentage difference between talimogene laherparepvec and control. The subgroup analyses suggest that a higher durable response rate in the talimogene laherparepvec group was seen in Stage III, ECOG Performance Status of 0, and first-line untreated subjects.

6.1.4 Baseline Size of Measurable Lesions

To better understand the baseline characteristics of the subject population and the responders, FDA performed several analyses to examine the distribution of baseline size of measurable lesions, among both the ITT population and the durable responders. Because the investigators at the study sites and the EAC selected baseline lesions for assessment of responses independently from each other, and because they might have reported different sizes for the same lesions that both investigator and EAC happened to choose, both data from the investigators and the EAC are used in FDA analyses. Note that in this document, the size was determined by "multiplying the longest diameter by the greatest diameter perpendicular to the longest diameter." Thus, the size may or may not have matched the actual surface area of a lesion, depending on the actual shape of the lesion. The results of these analyses are presented in Table 13, Table 14, and Figure 4.

Table 13. Distribution of Subjects according to Baseline Size of the Largest Baseline Measurable Lesions Recorded by Investigators in the ITT Population (by treatment arm and status of being durable responder)

	Talimogene laherparepvec			Control		
Largest Lesion Size at Baseline (cm^2)	**All (N=289)**	**Durable Responder (N=46)**	**Not Durable Responder (N=243)**	**All (N=127)**	**Durable Responder (N=2)**	**Not Durable Responder (N=125)**
<0.5	**12 (4.2%)**	**7 (15.2%)**	**5 (2.1%)**	**7 (5.5%)**	**0**	**7 (5.6%)**
0.5 to (<1)	**17 (5.9%)**	**7 (15.2%)**	**10 (4.1%)**	**6 (4.7%)**	**0**	**6 (4.8%)**
1 to (<2)	**34 (11.8%)**	**11 (23.9%)**	**23 (9.5%)**	**16 (12.6%)**	**0**	**16 (12.8%)**
2 to 1164	**226 (78.2%)**	**21 (45.7%)**	**205 (84.4%)**	**98 (77.2%)**	**2 (100%)**	**96 (76.8%)**

The table is generated using 3442 records of measurable lesions on 416 subjects
[Source: FDA Analysis]

Table 13 lists the number and percentage of subjects whose largest baseline lesion fell within one of four size categories: < 0.5 cm^2, 0.5 to 1, 1 to 2, or 2 to 1164 (the largest lesion among all subjects), based on measurements recorded by the investigators. (For reference, the product of the diameters of a US dime is 1.79^2=3.21cm^2, and 2.43^2=5.88 cm^2 for a US quarter.) The distributions in these size categories are comparable between the two treatment arms, as expected (gray columns). However, among the durable responders (DR), a larger proportion (30.4%) of subjects had only very small lesions (< 1 cm^2) compared to the overall subject population (10.1%). This suggests that subjects who had larger lesions were less likely to respond to talimogene laherparepvec. The predominance of subjects with only very small baseline lesions also raises concern regarding errors and inaccuracies in response assessment for lesions

with these small sizes. On the other hand, 45.7% of the DRs in the talimogene laherparepvec arm had at least one lesion that were greater than 2 cm^2.

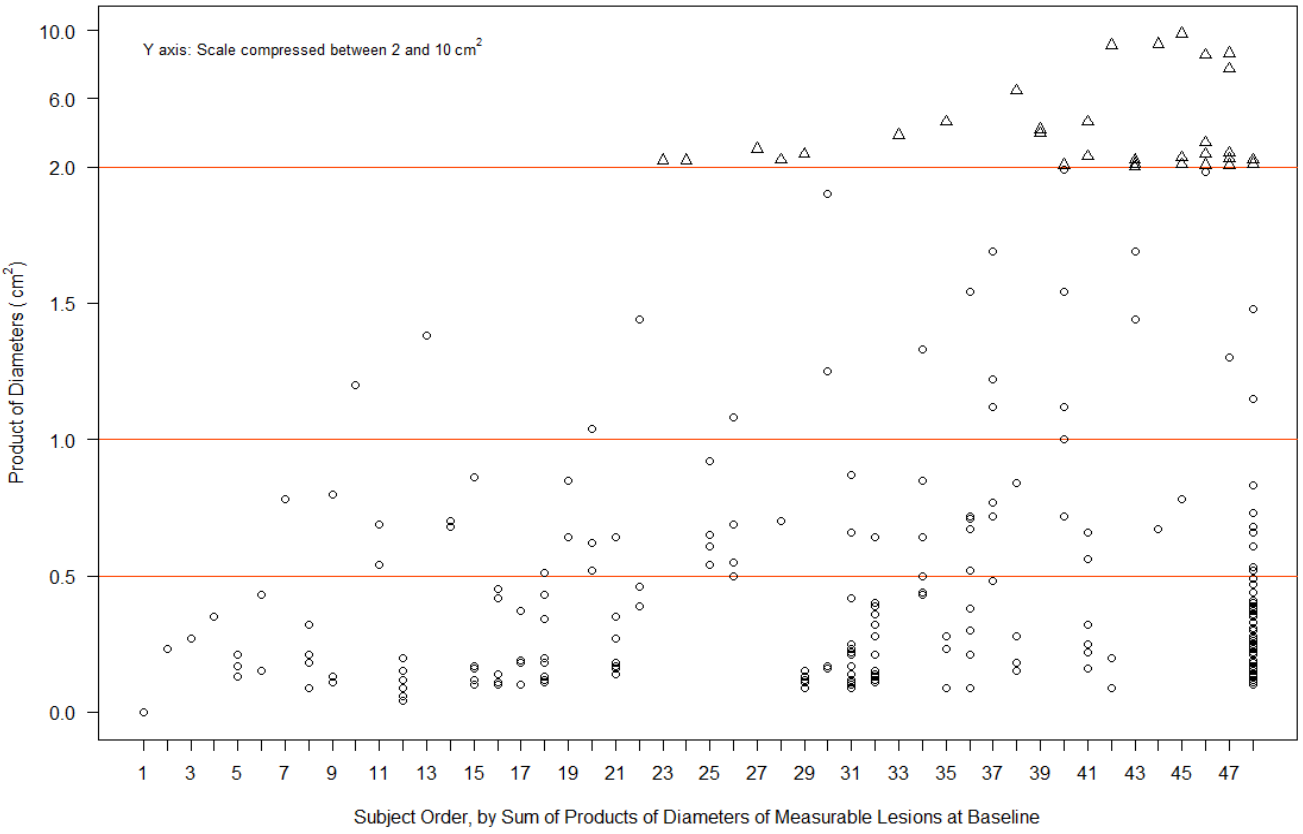
Table 14. Distribution of Baseline Measurable Lesions According to Baseline Size of the Largest Baseline Lesions Based on EAC Measurements in the 48 Durable Responders

Size interval (cm^2)	# Lesions (N = 284) n (%)	# Subjects with largest lesion in interval (N = 48) n (%)
< 0.5	182 (64.1%)	10 (20.8%)
0.5 to (<1)	48 (16.9%)	11 (22.9%)
1 to (<2)	22 (7.7%)	9 (18.8%)
2 to 9.82	32 (11.3%)	18 (37.5%)

[Source: FDA analysis]

Table 14 above summarizes the EAC-reported baseline size of all 284 baseline measurable lesions in the 48 DRs. There are more subjects whose largest lesions are small (< 1 cm^2) using the EAC data (43.7%, Table 14) than using the investigator data (30.4%) as seen in Table 13. This observation indicates that there are differences between the investigators and the EAC in the determination of which lesions were measurable at baseline and also in the measurements of the same lesions, despite the fact that the information reviewed by the EAC were submitted by the investigators.

Figure 4 below shows the baseline size of all 284 measurable lesions at baseline in the 48 DRs. The y-axis gives the baseline size of individual measurable lesions. On the x-axis, the 48 DRs are arranged from the left to the right in increasing order by the sum (total tumor burden) of size of all measurable lesions at baseline within each DR. Each circle represents a lesion up to 2 cm^2 and each triangle represents a lesion larger than 2 cm^2. As can be seen from Figure 4, the majority of the baseline measurable lesions in these 48 DRs had measurements of 0.04 cm^2 to 0.5 cm^2 (64.1% of all lesions), illustrated by circles below the bottom red line, raising concern regarding potential inaccuracies in the measurements and response assessment for these lesions.



6.2 Secondary Endpoint: Overall Survival

An interim analysis (IA) of OS occurred at the time of the primary analysis of DRR, when DRR was statistically significant in the comparison between the two arms. At this time, 250 deaths had been recorded. This IA of OS yielded a p-value of 0.075 (Applicant's analysis). Therefore the primary analysis of OS was to occur at 290 deaths. No other IA of OS occurred. The descriptive analysis of OS at the end of study (EOS) identified one additional death in the talimogene laherparepvec arm during the additional follow-up period between the time of primary analysis of OS and EOS.

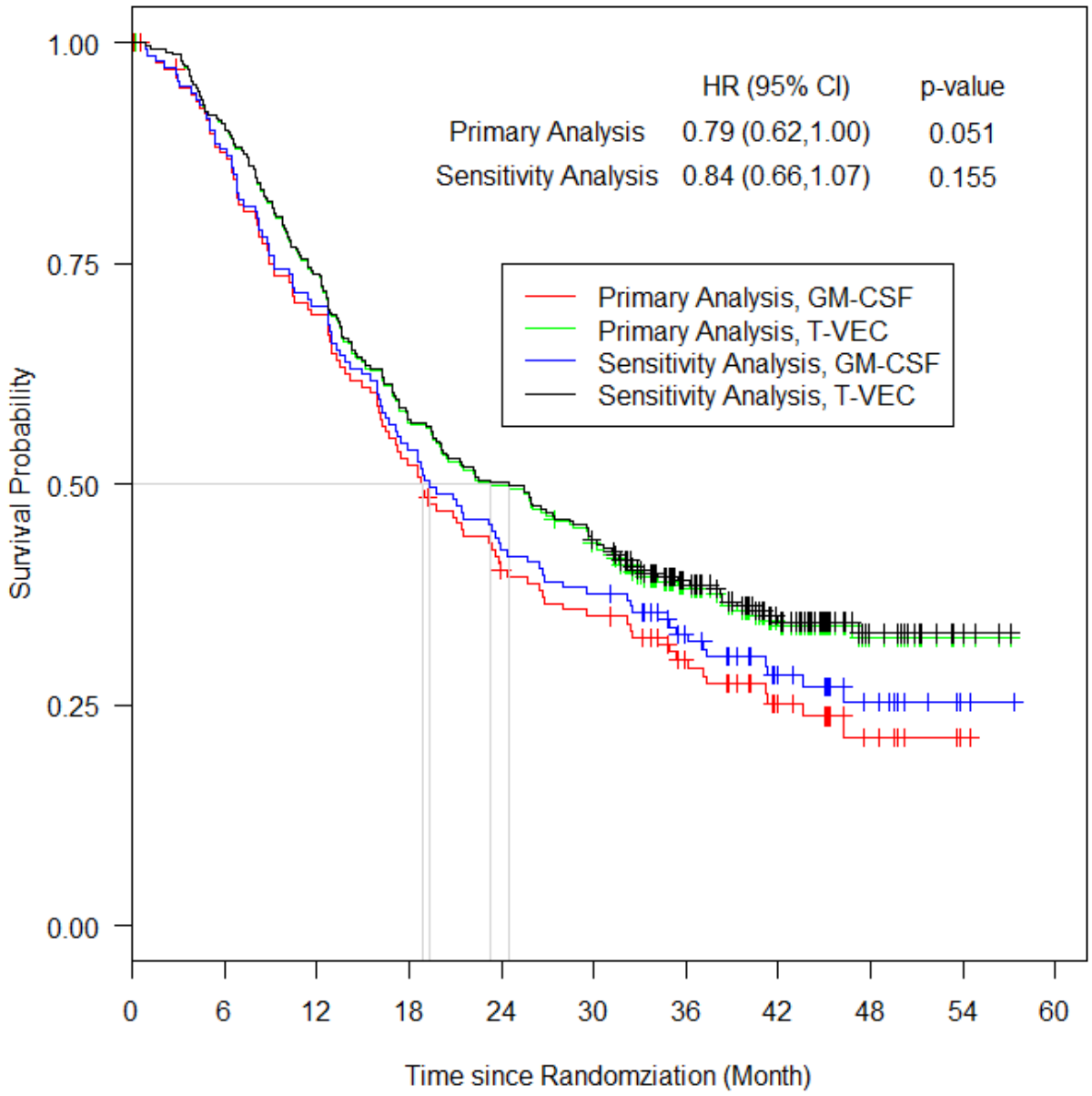
The event-driven OS primary analysis, at 290 events, set the analysis cut-off date (ACOD) to March 31, 2014. As of the ACOD, there were 189/295 (64%) confirmed deaths in the talimogene laherparepvec arm and 101/141 (72%) confirmed deaths in the control arm. The primary analysis using the un-adjusted log-rank test yielded a p-value of 0.051. The estimates of median OS (in months) and the 95% confidence

intervals (CIs) were 23.3 (19.6, 29.7) for the talimogene laherparepvec arm and 18.9 (16.2, 24.0) for the control arm. The estimate of the hazard ratio was 0.79 (0.62, 1.00).

The proportion of subjects who were randomized but not treated was 4/295 (1.4%) in the talimogene laherparepvec arm and 14/141 (9.9%) in the control arm. Due to this substantial difference between the two arms, the FDA performed a detailed analysis of time of event/censoring and reason for censoring, to examine the potential for bias due to censoring that may be related to risk of death ("informative censoring") or to arm assignment.

Censoring due to the ACOD is considered non-informative. The FDA identified a total of 10 subjects who were censored for reasons other than the ACOD and therefore may represent informative censoring. Seven of these 10 observations were censored soon after randomization, with six censored within 16 days and one censored on Day 86. The potentially informative censoring distributed disproportionately in the control arm (7/141, 5%), compared to the talimogene laherparepvec arm (3/295, 1%). For the seven subjects in the control arm, the "reason for ending study" was "consent withdrawn" in six subjects and "lost to follow-up" in one subject. For the three subjects in the talimogene laherparepvec arm, the "reason for ending study" was "consent withdrawn" in two subjects and "subject randomized in error; subject was ineligible [for enrollment] due to brain mets" in one subject. Thus, the "reason for ending study" was "consent withdrawn" in eight of the 10 subjects with potentially informative censoring. As of the analysis cut-off date, the survival status of these 10 subjects is unknown. The FDA performed several post hoc sensitivity analyses on OS by varying the survival status and censoring times of these 10 subjects. One such FDA sensitivity analysis imputed the censoring times of these 10 subjects using the ACOD as the last known alive date. This sensitivity analysis yielded a p-value of 0.155 and a hazard ratio of 0.84 (0.66, 1.07). Please refer to Figure 5 for a comparison of the results between the primary analysis and this sensitivity analysis. While the survival curves between the two arms, in the sensitivity analysis, continue to visually suggest some difference in time to death, the presence of potentially informative censoring increases the uncertainty about the presence and magnitude of comparative effect on OS in the talimogene laherparepvec arm.

Figure 5. Overall Survival: Primary Analysis Versus a Sensitivity Analysis* by FDA



* This post hoc sensitivity analysis uses the analysis cut-off date (March 31, 2014) as the censoring time for the 10 subjects who were censored for reasons other than the ACOD. The potentially informative censoring distributed disproportionately in the control arm (7/141, 5%), compared to that in the talimogene laherparepvec arm (3/295, 1%). For the control arm, the sensitivity analysis changes the estimate of median OS from 18.9 months (16.2, 24.0), by the primary analysis, to 19.3 months (16.5, 26.4). For the talimogene laherparepvec arm, the change is from 23.3 months (19.6, 29.7) to 24.5 months (19.6, 29.9).
T-VEC: talimogene laherparepvec.

6.3 Additional Secondary and Exploratory Endpoints

Additional secondary endpoints included best overall response and disease burden, response onset, time to treatment failure, duration of response, and response interval. Subjects' "quality of life" (QOL) was assessed by the FACT-BRM questionnaire as an exploratory endpoint.

There was no provision in the applicant's statistical analysis plan to control the type 1 error rate in testing these additional secondary endpoints. In addition, OS, as the first endpoint listed in the secondary endpoints, did not reach statistical significance, at the time of the primary analysis of DRR. The results of these additional secondary endpoints are also susceptible to the same potential biases identified previously in the consideration of DRR, the primary endpoint. The FACT-BRM result is not readily interpretable; the data are limited by the low rate of completion of questionnaires in the GM-CSF group compared with the talimogene laherparepvec group during the study.

6.4 Systemic Effects

In Study 005/05, primary sites of injection of talimogene laherparepvec were cutaneous, subcutaneous, and lymph node tumor lesions. Talimogene laherparepvec was not directly administered into visceral melanoma metastases. The applicant performed an analysis showing that among 2116 evaluable baseline or new individual lesions directly injected with talimogene laherparepvec, 1361 (64.3%) decreased in size by ≥ 50% and 995 (47.0%) completely resolved. The Applicant reported that of 981 evaluable non-injected non-visceral lesions, 212 (21.6%) completely resolved. Of 177 evaluable visceral lesions, 16 (9.0%) lesions completely resolved.

The BLA includes photographs of some study subjects who had numerous cutaneous lesions at baseline and no visible cutaneous lesions at follow-up response assessment; some of those lesions that were not present at follow-up were uninjected lesions. In addition, in some cases, a skin biopsy of the area did not find any evidence of residual melanoma. These examples support that talimogene laherparepvec can have a systemic effect on cutaneous melanoma lesions. However, FDA review of the purported responses in other uninjected lesions raised several concerns. For example, some lesions reported as uninjected appeared to be too small for reliable assessment. In addition, uninjected visceral lesions were assessed based on imaging studies; it was difficult to be sure that the imaging slices used for the baseline assessment were comparable to the imaging slices used in the follow-up assessment of response. In addition, no immunologic biomarker correlative studies were submitted to support the existence of systemic effects. During the course of the study, 10 talimogene laherparepvec group subjects received additional surgery and four additional talimogene laherparepvec group subjects received radiation therapy; however, the extent to which this surgery or radiation therapy contributed to the resolution of any uninjected lesions is unclear. Thus, the evidence that talimogene laherparepvec has a systemic effect was limited and difficult to quantitate.

7 Safety Results

The primary safety analysis was performed on the findings from Study 005/05, including 292 subjects who received at least one dose of talimogene laherparepvec. Supportive safety data were obtained from 116 subjects who received talimogene laherparepvec in Phase 1 and Phase 2 studies for a variety of solid tumors, including melanoma.

Safety was evaluated based on recorded adverse events, physical examinations, and clinical laboratory assessments. If a subject experienced multiple episodes of a single adverse event, the greatest severity and strongest investigator assessment of relation to study drug was assigned to the adverse event.

Baseline demographics for Study 005/05 are described in the Section 5.2, Table 7.

7.1 Drug Exposure

7.1.1 Exposure

Median duration of treatment was 23 weeks (range 0.1-78.9 weeks) in the talimogene laherparepvec arm and 10 weeks (0.6-72 weeks) in the control (GM-CSF) arm (Table 15).

Table 15. Exposure: Treatment Duration for the Talimogene Laherparepvec Arm Versus the Control Arm (Study 005/05 Safety Analysis)

	Talimogene laherparepvec	**Control**
Subjects (n)	**292**	**127**
Mean (weeks)	**26.8**	**15.8**
Standard Deviation (weeks)	**18.4**	**15.8**
Median (weeks)	**23.0**	**10.0**
Min, Max (weeks)	**0.1, 78.9**	**0.6, 72.0**

[Source: BLA Submission]

Exposure to talimogene laherparepvec occurred at two dose levels. The initial dose was for up to 4 ml of 10^6 PFU/ml, on cycle 1, Day 1 only. All subsequent doses were up to 4 ml of 10^8 PFU/ml of talimogene laherparepvec. Subjects received a mean dose of 2.68 x 10^8 PFU with a mean volume of 2.69 ml for the non-accelerated dosing regimen. The mean dose increased to 3.21 x 10^8 PFU with a volume of 3.21 ml in the accelerated dosing group (82 of 292 subjects) (Table 16). Thus, subjects who received accelerated dosing had a higher overall exposure to talimogene laherparepvec.

Table 16. Exposure to Talimogene Laherparepvec for the 005/05 Safety Analysis

		Talimogene laherparepvec (Accelerated Dosing)	Talimogene laherparepvec (No Accelerated Dosing)	Total Talimogene laherparepvec
Subjects (n)		**82**	**210**	**292**
Dose at cycle 1; Day 1 (10^6 PFU)				
	Mean			**2.8**
	SD			**1.2**
	Median			**3.0**
	Min, Max			**0.4, 4.0**
Average dose post-cycle 1; Day 1 (10^8 PFU)				
	Mean	**3.2**	**2.7**	**2.8**
	SD	**1.0**	**1.3**	**1.2**
	Median	**3.7**	**2.9**	**3.3**
	Min, Max	**0.5, 4.0**	**0.3, 4.4**	**0.3, 4.4**

[Source: BLA Submission]

7.2 Adverse Events in 005/05 Safety Analysis

7.2.1 Definitions

Treatment-emergent event: any adverse event that occurred after the administration of the first dose of study drug and through 30 days after the last dose, or any event that was present at baseline and continued after the first dose but worsened in intensity.

Adverse Events were graded as Grade 1 through 5, with Grade 5 being death. A serious adverse event was any untoward medical occurrence regardless of grade that resulted in death, was life-threatening, required or prolonged hospitalization, resulted in significant disability/incapacity, or was a congenital anomaly/birth defect.

7.2.2 Treatment-Emergent Adverse Events

The incidence of treatment-emergent adverse events in Study 005/05 subjects is described for the talimogene laherparepvec and control arms in Table 17. A total of 290 subjects (99.3%) exposed to talimogene laherparepvec had at least one treatment-emergent adverse event (grades 1-5). Of these, 82 subjects (28.1%) experienced Grade 3 and 13 subjects (4.5%) experienced Grade 4 adverse events in the talimogene laherparepvec arm. One hundred eighty-five subjects (63%) experienced Grade 1 or Grade 2 treatment-emergent adverse events. Overall, 75 subjects (25.7%) experienced treatment-emergent adverse events that were considered serious in the talimogene laherparepvec arm (Section 7.2.3).

Table 17. Summary of Treatment-Emergent Adverse Events (005/05)

	Talimogene laherparepvec n* =292 (%)	Control n =127 (%)
Treatment-emergent Adverse Events (TEAEs)	**290 (99.3%)**	**121 (95.3%)**
Grade 3	**82 (28.1%)**	**21 (16.5%)**
Grade 4	**13 (4.5%)**	**4 (3.1%)**
Serious TEAEs	**75 (25.7%)**	**17 (13.4%)**
Deaths within 30 days of last study treatment	**10 (3.4%)**	**2 (1.6%)**
Discontinuation due to TEAEs	**29 (9.9%)**	**8 (6.3%)**

*subject
[Source: BLA Submission]

The most frequent treatment-emergent adverse events for the talimogene laherparepvec arm are in Table 18. For the talimogene laherparepvec group, the most common adverse events were fatigue, chills, pyrexia, and nausea. These specific events are typical manifestation of a flu-like illness, which is the next most common adverse event. The adverse events for control are consistent with its known safety profile. Flu-like symptoms were common in both arms, but more frequent in the talimogene laherparepvec arm.

Table 18. Most Frequent Treatment-Emergent Adverse Events (occurring in ≥ 5% of Subjects in Talimogene Laherparepvec Arm (Study 005/05)

Treatment-Emergent Adverse Events	Talimogene laherparepvec n=292 (%)	Control n=127 (%)
Any treatment-emergent adverse event	**290 (99.3%)**	**121 (95.3%)**
Fatigue	**147 (50.3%)**	**46 (36.2%)**
Chills	**142 (48.6%)**	**11 (8.7 %)**
Pyrexia	**125 (42.8%)**	**11 (8.7%)**
Nausea	**104 (35.6%)**	**25 (19.7%)**
Influenza-like Illness	**89 (30.5%)**	**19 (15%)**
Injection site pain	**81 (27.7%)**	**8 (6.3%)**
Vomiting	**62 (21.2%)**	**12 (9.4%)**
Diarrhea	**55 (18.8%)**	**14 (11%)**
Headache	**55 (18.8%)**	**12 (9.4%)**
Myalgia	**51 (17.5%)**	**7 (5.5%)**
Extremity Pain	**48 (16.4%)**	**12 (9.4%)**
Pain	**47 (16.1%)**	**13 (10.2%)**
Oedema peripheral	**35 (12.0%)**	**12 (9.4%)**
Constipation	**34 (11.6%)**	**8 (6.3%)**
Cough	**31 (10.6%)**	**10 (7.9%)**
Decreased Appetite	**30 (10.3%)**	**14 (11.0%)**
Upper Respiratory Tract Infection	**29 (9.9%)**	**8 (6.3%)**
Pruritus	**28 (9.6%)**	**19 (15.0%)**

Treatment-Emergent Adverse Events	Talimogene laherparepvec n=292 (%)	Control n=127 (%)
Dizziness	**28 (9.6%)**	**4 (3.1%)**
Back Pain	**27 (9.2%)**	**8 (6.3%)**
Abdominal Pain	**26 (8.9%)**	**3 (2.4%)**
Rash	**26 (8.9%)**	**10 (7.9%)**
Tumor Pain	**22 (7.9%)**	**7 (5.5%)**
Hyperhidrosis	**23 (7.9%)**	**9 (7.1%)**
Erythema	**21 (7.2%)**	**9 (7.1%)**
Insomnia	**21 (7.2%)**	**6 (4.7%)**
Anxiety	**19 (6.5%)**	**2 (1.6%)**
Cellulitis	**18 (6.2%)**	**2 (1.6%)**
Oropharyngeal Pain	**17 (5.8%)**	**1 (0.8%)**
Weight Decreased	**17 (5.8%)**	**1 (0.8%)**
Anemia	**15 (5.1%)**	**2 (1.6%)**
Depression	**15 (5.1%)**	**3 (2.4%)**
Dyspepsia	**15 (5.1%)**	**9 (7.1%)**
Vitiligo	**15 (5.1%)**	**2 (1.6%)**
Injection Site erythema	**15 (5.1%)**	**33 (26%)**

[Source: Applicant BLA submission]

7.2.3 Serious Adverse Events

Treatment-emergent serious adverse events occurred in 75/292 subjects (25.7%) in the talimogene laherparepvec arm and 17/127 subjects (13.4%) in the control arm in the 005/05 safety population. The most common treatment-emergent serious adverse events were disease progression and cellulitis.

Table 19 (below) lists all the treatment-emergent serious adverse events with a subject incidence of greater than or equal to 1% in the talimogene laherparepvec with a comparison for that event for the control arm.

Table 19. Treatment-Emergent Serious Adverse Events that Occurred in ≥ 1% of Subjects in the Talimogene Laherparepvec Arm

Treatment-Emergent Serious Adverse Events	Talimogene laherparepvec n*=292 (%)	Control n*=127 (%)
Any treatment-emergent serious adverse event	**75 (25.7%)**	**17 (13.4%)**
Disease Progression	**9 (3.1%)**	**2 (1.6%)**
Cellulitis	**7 (2.4%)**	**1 (0.8%)**
Pyrexia	**5 (1.7%)**	**0 (0%)**
Tumor Pain	**4 (1.4%)**	**0 (0%)**
Cerebral Hemorrhage	**3 (1.0%)**	**0 (0%)**
Deep Vein Thrombosis	**3 (1.0%)**	**0 (0%)**
Gastrointestinal Hemorrhage	**3 (1.0%)**	**0 (0%)**
Infected neoplasm	**3 (1.0%)**	**0 (0%)**

CNS metastases	**3 (1.0%)**	**1 (0.8%)**
Metastatic melanoma	**3 (1.0%)**	**0 (0%)**
Pleural Effusion	**3 (1.0%)**	**0 (0%)**

*subjects
[Source: Applicant BLA submission]

Cellulitis at the site of the injection is an important adverse event due to the intratumoral injection route of administration of talimogene laherparepvec. In the talimogene laherparepvec arm, a total of eighteen subjects (6.2%) developed cellulitis; seven of these events (2.4%) were categorized as serious, requiring hospitalization. One subject with streptococcal cellulitis at his injection site developed glomerulonephritis, with a biopsy possibly consistent with an infectious origin.

In addition to the serious adverse events noted above, there were individual important serious adverse. Additional adverse events of concern are discussed here and in Section 7.2.4.
Three individual Grade 4 adverse events were reported in the talimogene laherparepvec arm:

- Plasmacytoma in a subject with smoldering multiple myeloma
- Glomerulonephritis, distinct from the above subject, and
- Obstructive airway disorder: complicated history and influenced by site of tumor.

In an 86 year-old male in the talimogene laherparepvec arm, there was one serious adverse event categorized as flu-like illness that required hospitalization.

In addition, there was a late serious adverse event reported in the talimogene laherparepvec arm in an 84 year-old woman (a durable responder). Prior to the study, she had a history of melanoma lesions in the left foot, radiation, surgery to the region, and a non-healing wound. During the study treatment, she was injected in the left foot as a site of disease recurrence. Six months after the last dose of therapy, preceded by 3 months of unsuccessful medical interventions, the subject underwent a below-the-knee amputation for a non-healing, infected wound in the left foot. The intratumoral injection of the talimogene laherparepvec may have contributed to the event.

7.2.4 Adverse Events of Special Interest

Adverse events of special interest were identified by the applicant based on the mechanism of action and preclinical or emerging clinical data. Cellulitis is discussed in Section 7.2.3. The adverse event of flu-like symptoms is consistent with the treatment with a viral vaccine with a proposed immunological mechanism of action. The increased incidence of documented herpes simplex-1 infection in the talimogene laherparepvec arm is difficult to categorize since the documentation of the infectious agent is not available. Hypersensitivity was almost equal in both groups (Table 20).

Table 20. Adverse Events of Interest By Category* (Safety Population 005/05)

Adverse Events of Special Interest	**Talimogene laherparepvec n*= 292 (%)**	**Control n*= 127 (%)**

Subjects reporting T-E AEs of Special Interest	**275 (94.2%)**	**108 (85%)**
Flu-like symptoms	**264 (90.4)**	**83 (65.4)**
Injection site reactions	**122 (41.8)**	**64 (50.4)**
Hypersensitivity	**53 (18.2)**	**25 (19.7)**
Cellulitis injection site	**18 (6.2)**	**2 (1.6)**
Herpes simplex virus infections	**16 (5.5)**	**2 (1.6)**
Vitiligo	**15 (5.1)**	**2 (1.6)**

*subjects
[Source: Applicant Statistical Analysis Plan]

Additional isolated adverse events of special interest that are relevant to the safety assessment included immune-mediated adverse events and neoplasms other than melanoma.

Immune-Mediated Adverse Events (Auto-immune Adverse Events):

- Talimogene laherparepvec arm (n=6)
  - Glomerulonephritis developed in a 49 year-old white male with hematuria, papillary necrosis, and acute renal failure after one year of therapy. There was a history of singular kidney, hypertension and diabetes. Treatment was discontinued. This event is previously described as Grade 4 event in Section 7.2.3.
  - Acute renal failure/glomerulonephritis developed in a 57 year-old white male. Previously described in Section 7.2.3 associated with cellulitis.
  - Interstitial pneumonitis developed in a 65 year-old white male while on therapy for pre-existing ulcerative colitis (certulizumab pegol and mesalamine) and melanoma (3 months on therapy). Treatment for melanoma continued.
  - Vasculitis developed in a 41 year-old white female on Day 259 of therapy and caused a one dose delay.
  - Psoriasis was diagnosed in a 73 year-old white male prior to his diagnosis of melanoma, the subject had two Grade 1 exacerbations of psoriasis.
  - Hypothyroidism (Grade 2) developed in a 60 year-old white male on Day 77.
- Three subjects in the control arm had auto-immune events: an exacerbation of rheumatoid arthritis, alopecia, and a rash.

Other Neoplastic Events:

- 7 subjects in the talimogene laherparepvec arm developed malignancies other than melanoma.
  - 57 year-old white male with metastatic squamous cell carcinoma after 18 cycles of talimogene laherparepvec. Diagnosis 957 days after last dose.
  - 73 year-old female former smoker with adenocarcinoma of the lung at the time of enrollment to the talimogene laherparepvec study.
  - 80 year-old male smoker with developed transitional cell carcinoma of the bladder one month after last dose of talimogene laherparepvec.

- 89 year-old male former smoker with transitional cell bladder carcinoma that developed 3 months into talimogene laherparepvec therapy.
- 81 year-old white male with prior history of prostate cancer, recurred on Day 237 of 681 days of talimogene laherparepvec therapy.
- 67 year-old white male squamous cell carcinoma of skin on Day 319/443 of talimogene laherparepvec.
- 70 year-old white female with tonsillar neoplasm (NOS) on Day 148/205 of talimogene laherparepvec therapy.

- Two subjects in the control arm developed tumors: An 87 year-old with a meningioma and a 70 year-old with adenoma of the prostate and squamous cell carcinoma of the left cheek.

Subgroup analyses of adverse events, serious adverse events, and discontinuation of treatment for talimogene laherparepvec versus control did not show a higher safety risk in the talimogene laherparepvec arm by age, race, gender, region, or disease stage.

7.3 Clinical Test Results

There were no clinically important laboratory values in the talimogene laherparepvec arm in Study 005/05. There were no Grade 3 or 4 laboratory values from baseline of Grade 0 to 1 for bilirubin, alkaline phosphatase, ALT, and AST.

7.4 Deaths

In Study 005/05, a total of 12 deaths occurred within 30 days of the last dose of study treatment, 10 in the talimogene laherparepvec arm; two deaths occurred within 30 days of the last dose of talimogene laherparepvec on the 005/05 Extension Study, and two in the control arm. Progressive disease was the cause of death in nine subjects who received talimogene laherparepvec and both subjects who received the control. The remaining three deaths after talimogene laherparepvec treatment were due to myocardial infarction, cardiac arrest, and sepsis. The deaths post the talimogene laherparepvec treatment occurred from Days 24 to 648 after initiation of therapy. The deaths in the control arm occurred on Days 27 and 29 after initiation of therapy. For all other studies in the safety database, progressive disease was the main cause of death on study within 30 days of the last dose of talimogene laherparepvec. One-hundred -sixty-four (164) subjects in the talimogene laherparepvec arm and 86 subjects in the control arm died while on therapy or in follow-up.

7.5 Additional Safety Data for Talimogene Laherparepvec

The applicant provided additional safety data from a Phase 2 melanoma study (002/03) and Phase 1-2 Studies 001/10 (solid tumors), 004/04 (head and neck cancer, epithelial), 005/04 (pancreatic cancer), and 006/09 (head and neck cancer, squamous cell). The nature and frequency of adverse events in this additional safety data were generally similar to the safety profile of Study 005/05. The exception is that these other studies had an increased incidence of certain treatment-emergent adverse events that were

attributable to, and particular to, the specific disease or its concomitant therapy (for example, an increased incidence of ascites in Study 005/04, the pancreatic cancer study). There was one additional report of cellulitis at the injection site and no additional reports of glomerulonephritis.

7.6 Safety Conclusions

- 90% of subjects who received talimogene laherparepvec experienced "flu-like symptoms" (Table 20).
- The most common treatment-emergent adverse events with talimogene laherparepvec were fatigue, chills, pyrexia, nausea, influenza-like illness and injection site pain.
- 63% of subjects experienced adverse events that were Grade 1-2, and 37% subjects experienced adverse events Grade 3 or above in the talimogene laherparepvec arm.
- The incidence of treatment-emergent adverse events, regardless of severity, was greater in the talimogene laherparepvec arm than in the control arm.
- Cellulitis at the injection site, impaired wound healing, herpes simplex-1 infections, injection site reactions, and vitiligo were identified by the applicant as adverse events of special interest for subjects who received talimogene laherparepvec.
- After talimogene laherparepvec administration, a wound became resistant to medical therapy, and required a below-the-knee amputation.
- Immune-mediated events occurred in both arms. Four of six such events (glomerulonephritis (n=2); vasculitis (n=1), and hypothyroidism (n=1)) were de novo after talimogene laherparepvec therapy.
- Disease progression was the most common Grade 3 or above adverse event, the most common reason for early discontinuation, the most common treatment-emergent serious adverse event, and the most common preferred term for treatment-emergent fatal event.

Overall, a slightly higher percentage of subjects in the talimogene laherparepvec arm (99.3%) than in the control arm (95.3%) had treatment-emergent adverse events. Treatment-emergent serious adverse events occurred in 25.7% of subjects in the talimogene laherparepvec arm and 13.4% of subjects in the control arm. The GM-CSF safety profile was similar to the description in the FDA label.

8 Shedding and Pharmacovigilance

Talimogene laherparepvec has been attenuated to reduce virulence; however, it is expected to have biological properties that are similar to wild type HSV-1 with regard to viral shedding and potential for transmission and life-long latency/symptomatic reactivation. To date, there are limited data on product shedding from treated subjects, which serves as a proxy for transmission.

The applicant has an active clinical protocol (Amgen 20120324) that is designed to collect and evaluate samples for shedding with validated assay methods. The applicant expects this study to be completed by

the end of 2015 at which time a more complete shedding profile for talimogene laherparepvec is expected to become available.

During the Phase 3 clinical trial (005/05), there was one confirmed exposure of HCP to talimogene laherparepvec[1]. In order to monitor and evaluate transmission of talimogene laherparepvec to HCPs and close contacts, the applicant has also proposed a postmarketing study.

The trial design and preliminary shedding information for talimogene laherparepvec from the ongoing shedding protocol (Amgen 20120324) are described in Table 21 and Table 22. The trial design for the proposed postmarketing study (Protocol #20130193) is described in Table 23 and summarized in the following sections.

8.1 Shedding Protocol (Amgen 20120324)

Table 21. Clinical Shedding Protocol

Study Title	A Phase 2, Multicenter, Single-arm Trial to Evaluate the Biodistribution and Shedding of Talimogene Laherparepvec in Subjects With Unresected, Stage IIIB to IVM1c Melanoma
Study Design	Phase 2, multicenter, single-arm study to evaluate the biodistribution and shedding of talimogene laherparepvec
Study Population	30-40 subjects with unresected, Stage IIIB to IVM1c melanoma
Primary Objectives	To estimate the proportion of subjects with detectable talimogene laherparepvec DNA in the blood and urine any time after administration of talimogene laherparepvec within the first 3 treatment cycles.
Secondary Objectives (only shedding related listed)	• To estimate the incidence of clearance of talimogene laherparepvec DNA from blood and urine overall and by baseline herpes simplex virus type 1 (HSV-1) serological antibody status (seronegative versus seropositive) during each of the first 3 treatment cycles • To estimate the rate of detection and subject incidence of talimogene laherparepvec DNA and infectious virus from exterior of occlusive dressing, the surface of injected lesions, the oral mucosa, genital swabs, and in lesions suspected to be herpetic in origin during treatment and at the end of treatment.
Inclusion and Exclusion Criteria	Similar to 005/05 in Section 4.3, above.

[1] Talimogene laherparepvec transmission to HCP via an accidental needle-stick to the finger with subsequent herpetic whitlow lesion at the site of injury (qPCR positive for talimogene laherparepvec), which resolved with acyclovir.

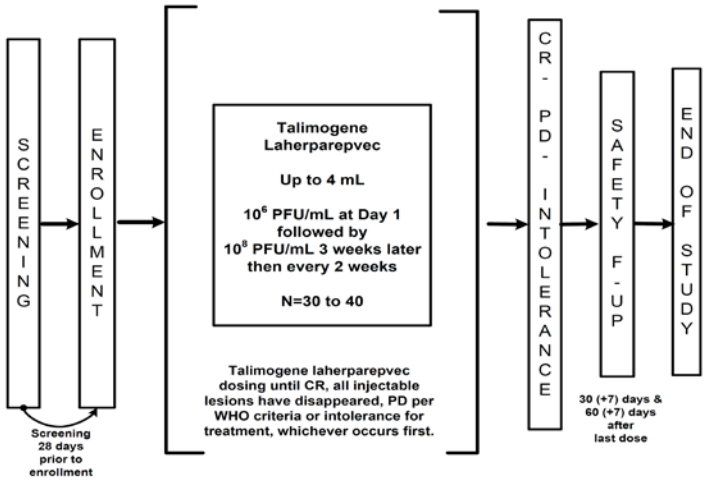
Dose	Talimogene laherparepvec is administered by intralesional injection into injectable cutaneous, subcutaneous, and nodal lesions at an initial dose of up to 4 ml of 10^6 PFU/mL followed by a dose of up to 4 ml of 10^8 PFU/mL 21 days after the initial dose and every 14 (± 3) days thereafter.
Treatment Plan	
Sample Analyses	Samples will be analyzed according to the sampling plan described in Table 22.
Statistical Analysis	Primary analysis triggered once all subjects have completed cycle 4 day 1 to assess the primary endpoint of detectable talimogene laherparepvec DNA in the blood and urine.

Table 22. Sampling Plan for Amgen protocol 20120324[1]

Blood[2]/Urine qPCR	**Occlusive Dressing/injection site swabs[3]: qPCR and TCID50[4]**	**Oral mucosal swab: qPCR and TCID50**	**Other sampling: qPCR**
Cycle 1: Day 1: Pre[5], 1, 4,8 hrs[6] Day 2 Day 3 Day 8 Day 15	**Cycle 1:** Day 1: ND Day 2 Day 3 Day8 Day 15	**Cycle 1:** Day 1 Pre Day 8 Day 15	• Suspected Lesions of herpetic origin (e.g., cold sores or vesicles) swabbed within 3 days of the occurrence. • Genital swabs if

Cycle 2: Day 1: Pre, 1, 4, 8 hrs. Day 2 Day 3 Day 8	**Cycle 2:** Day 1 Pre Day 2 Day 3 Day 8	**Cycle 2:** Day 1 Pre Day 8	talimogene laherparepvec administered to lesions below the waist. • Other unscheduled sampling for whatever reason.
Cycle 3: Day 1: Pre Day 8	**Cycle 3:** Day 1 Pre Day 8	**Cycle 3:** Day 1 Pre Day 8	
Cycle 4: Day 1: Pre	**Cycle 4:** Day 1 Pre	**Cycle 4** Day 1 Pre Day 8	
End of Treatment: Day + 30, off treatment	**End of Treatment** Occlusion dressing: Day +30, off treatment Injection site swabs: Day+30 through day +60, weekly, off treatment	**End of Treatment:** Day +30 through day +60 daily	

[1] Talimogene laherparepvec DNA testing data were not provided for all treated subjects
[2] All subjects will have serological testing for HSV-1at baseline.
[3] Three injection sites were selected on Day 1; swabs were obtained from these sites
[4] PCR positive samples from injection site, occlusive dressing and oral mucosa were tested for infective virus by TCID 50 assay
[5] Pre = sampling done before injection with talimogene laherparepvec
[6] Samples taken at the marked hours after inoculation with talimogene laherparepvec
ND: not done.

Summary of preliminary results[2] from the shedding study: Amgen 20120324:

Overall study status:

- 25 of the 40 planned subjects have been treated under this protocol
  - 20 of the 25 treated subjects have been tested per protocol for cycle 1
  - 17 were tested per protocol after cycle 2
  - 14 were tested per protocol after cycle 3
  - Four subjects have completed 30 days of safety follow up

[2] Study results as of February 6th 2015, submitted to BLA 125518

- 12 subjects had unscheduled testing per protocol and of these seven were tested for suspected herpetic lesions and all were negative.
- Talimogene laherparepvec testing results are not yet available for all treated subjects or for all protocol-specified time points.

Observations from the data available to date (through February 6, 2015) from the ongoing Amgen study 20120324 are summarized below, and the gaps in the data are summarized below.

Study results[2]:

Blood:

The presence of virus in blood may be taken as an indication of virus presence and potential for shedding.

- 17 of 20 subjects (85%) had detectable levels of talimogene laherparepvec DNA in blood at any time during the study.
- Talimogene laherparepvec DNA levels in blood peaked 1 hour after cycle 1 and 2 injections (1 hour data were not collected for subsequent cycles).
- A secondary spike in the mean levels of talimogene laherparepvec DNA was detected in blood on Day 8 (mean of 23.8 copies/ug of cellular DNA, with a range of 1.8 to 62.3 copies/ug) after cycle 1 injection and not in subsequent cycles.
- The mean levels of talimogene laherparepvec DNA in blood of the tested subjects decreased over time following treatment. For the 4 subjects who reached cycle 4, Day 1, the viral DNA levels dropped to below the level of detection.

Urine:

- Four of 20 subjects (20%) had measurable levels of talimogene laherparepvec DNA in urine at any time in the study.
- All positive samples were from Day 1 of cycle 1 or Day 1 of cycle 2. All other tested time points were negative.

Exterior of Occlusive Dressing:

- 14 of 20 subjects had measureable levels of talimogene laherparepvec DNA on the exterior of occlusive dressings during the study.
- The number of positive subjects was higher after cycle 2, Day 2 (50%, 8/16 tested) than cycle 1 Day 2 (20%, 5/20 tested).
- The number of subjects with measurable levels of talimogene laherparepvec DNA on the exterior of occlusive dressing declined over time with no measureable levels in any of the tested subjects on Day 1 of cycle 3 (0 of 13 tested).

- No infectious virus was detected in any of the swabs taken from the exterior of occlusive dressing at any time during the study. However, one of the samples had 230,000 copies (copies/ug) of talimogene laherparepvec DNA on cycle 1 Day 15.

Injection Site Surface:

- 18 of 20 subjects (90%) had measurable levels of talimogene laherparepvec DNA on the injection site surface swabs during the study.
- 15 of 16 subjects (94%) were positive for talimogene laherparepvec DNA on cycle 2, Day 3, and this number reduced to 5/14 on Day 1 of cycle 3.
- Infectious virus was detected in 3/20 subjects positive for talimogene laherparepvec DNA during cycle 1.

Oral Mucosal Swab:

- One of 20 subjects (5%) had measureable levels of talimogene laherparepvec DNA in the oral mucosal swab at cycle 5 (subjects who continued to receive treatment with the investigational agent were tested beyond the protocol mandated 4 cycles).
- This sample tested negative for infectious talimogene laherparepvec virus (by TCID50).
- No other samples tested had measurable levels of talimogene laherparepvec DNA at any time during the study.
- 20 subjects were tested during study follow-up period and all were negative for talimogene laherparepvec DNA.

Unscheduled Testing (for Suspected Herpetic Lesions or Other Reasons):

- 8 individuals, (7 subjects and 1/HCP), who had cold sores during treatment or had herpetic lesions, were tested for the presence of talimogene laherparepvec DNA
- Zero of 8 individuals tested were positive for talimogene laherparepvec DNA.
- Seven of these individuals were tested due to suspected herpetic lesions and were found negative for talimogene laherparepvec DNA.
- Cold sores from one HCP were tested and found negative for the presence of talimogene laherparepvec DNA.

Overall Summary of Shedding Data:

- Talimogene laherparepvec DNA was detected at the injection site by qPCR on all tested days in most subjects.
- Infectious talimogene laherparepvec was detected at the injection site in 3/20 subjects (TCID50 results) after a positive qPCR analysis.
- Peak mean level of talimogene laherparepvec DNA was detected in blood and urine on average one hour after the 2nd injection.

- Talimogene laherparepvec DNA in blood was highest during the second cycle of treatment, decreased during the third cycle, and was 0 at the beginning of the fourth cycle.

8.2 Pharmacovigilance Plan

The applicant proposes routine pharmacovigilance as well as additional measures, such as postmarketing studies and risk minimization activities. Postmarketing studies to evaluate long-term safety include an observational registry study (#20120139) and a postmarketing prospective cohort study (#20130193, see below). In the registry study, subjects previously treated with talimogene laherparepvec will be evaluated with quarterly solicited follow-up for talimogene laherparepvec-related adverse events and survival status. Proposed risk minimization activities include Risk Evaluation and Mitigation Strategy (REMS) and a Medication Guide. The proposed REMS is a communication plan (via Dear Healthcare Provider Letter, patient brochure, and REMS website) to provide information on the risk of disseminated herpetic infection in immunocompromised subjects, the risk of transmission from accidental exposure of HCPs and close contacts, and the risk of talimogene laherparepvec use in pregnant women. The proposed Medication Guide provides information on the product and on the risks of life-threatening herpes infection in immunocompromised subjects; cold sores or serious herpes infection during or after treatment; risk to pregnant/lactating women; risk of transmission to close contacts and ways to reduce accidental exposure; serious AEs and common AEs.

With respect to the transmission risk of talimogene laherparepvec, in premarket studies there was an absence of rigorous follow-up of suspected herpetic infections, in study subjects[3] or contacts[4], to detect possible talimogene laherparepvec infection. The potential risk of talimogene laherparepvec transmission to contacts in the post-licensure period needs to be evaluated. The postmarketing study protocol 20130193 is summarized in Table 23.

[3] In Phase 3 Study 005/05, 16 subjects (5.5%) in the talimogene laherparepvec treatment arm had AEs related to HSV infection, compared to 2 subjects (1.6%) in the GM-CSF control arm; but none were tested for talimogene laherparepvec. Fifteen subjects had lesions of oral herpes and 1 subject developed herpetic keratitis (this subject had a past history of herpetic keratitis due to wild-type HSV-1; qPCR testing for talimogene laherparepvec was not done).
[4] Low compliance with questionnaires for household contacts (49-55%) and medical personnel (14%).

Table 23. Proposed Postmarketing Study (Protocol 20130193)[5]

Study title	A Postmarketing, Prospective Cohort Study of Patients Treated With Talimogene Laherparepvec in Clinical Practice to Characterize the Risk of Herpetic Illness Among Patients, Close Contacts, and Healthcare Providers; and Long-Term Safety in Treated Patients
Study design	Open-label, single-arm, prospective observational cohort, multicenter (US and European Union)
Study population	goal enrollment of 920 subjects with melanoma receiving talimogene laherparepvec in real world clinical practice
Primary Objectives/ Endpoints	• Incidence rate of herpetic lesions containing talimogene laherparepvec DNA in subjects, for 5 years* • Proportion of subjects with a herpetic lesion containing talimogene laherparepvec DNA within 6 months* *time from initiating talimogene laherparepvec treatment
Secondary Objectives/ Endpoints	• Incidence rate of herpetic manifestations, specifically in immunocompromised subjects • Incidence rate of a herpetic lesion, positive for talimogene laherparepvec DNA, occurring more than 30 days after ending use of talimogene laherparepvec, i.e., symptomatic reactivation in subject • Case counts and characterization of herpetic infection containing talimogene laherparepvec DNA in close contacts and HCPs; "occurring during treatment period of subject." • Adverse Drug Reactions, Serious Adverse Drug Reactions • Overall survival (descriptive)
Follow-up and sample collection	**Study subject** • Will record signs/symptoms of suspected herpetic infection and urged to report promptly; will also be asked about suspected lesions in close contacts. • Solicited follow-up: – Biweekly clinic visits during treatment period – Quarterly phone call or clinic visit after ending treatment • Sample collection: swab of lesion during clinic visit; swab sent to central laboratory for qPCR test to detect talimogene laherparepvec DNA. **Contacts** (close contacts and occupational exposure of HCPs) • Passive reporting and unsolicited follow-up Multi-step process of sample collection: Individual reports suspected herpetic infection to Amgen and visits HCP; Amgen sends questionnaire (clinical follow-up regarding nature of lesion, exposure, underlying risk factors) to HCP and provides a list of "acceptable swabs" for sample collection. . HCP determines if

[5] Amgen BLA 125518, (b) (4) (talimogene laherparepvec), module 1.16, United States Risk Management Plan dated 25 June 2014, Appendix 3.

	qPCR testing is required for the suspected herpetic lesion. Individual returns to HCP for swabbing of lesion. Amgen also sends a kit for "qPCR sample retrieval" to HCP office, to aid HCP in shipping swab sample to central laboratory for qPCR test to detect talimogene laherparepvec DNA.
Study Timeline	Protocol originally submitted in BLA 125518 on July 28, 2014. • First subject to be enrolled: Quarter 1 of 2016 • Last subject to be enrolled: Quarter 4 of 2018 • End of data collection: Quarter 4 of 2023 (5 years after last subject enrolled) Annual interim reports will be included in Periodic Safety Update Reports, and will include data on: – Number of subjects enrolled, subject years of observation, number of primary and secondary endpoints, reported number of suspected herpetic lesions that tested positive or negative by qPCR for product DNA. – The co-primary endpoint, incidence proportion of subjects having a herpetic lesion positive for product DNA, "will be analyzed after all enrolled subjects have had a chance to contribute 6 months of observation." – Primary analysis planned when all enrolled subjects contributed 5 years of observation – Estimated milestone: final study report in Quarter 3 of 2024 (within 9 months of end of data collection)
Applicant definitions for: Herpetic lesion – "signs (swelling, papules, vesicles, ulcers, crusts, fissures, erythema, or discharge) or symptoms (pain, burning, itching, tingling, dysuria) on the skin or oral or genital mucosa." Herpetic manifestation –examples of events such as "keratitis, conjunctivitis, uveitis, esophagitis, encephalitis, or disseminated infection with multi-organ failure in the opinion of the treating HCP that is attributable to HSV".	

Postmarketing study 20130193 is proposed for evaluation of talimogene laherparepvec- associated herpetic infection and long-term safety in subjects as well as potential talimogene laherparepvec transmission to contacts. Assessment of potential talimogene laherparepvec transmission is designed via passive reporting involving a lengthy multi-step method of sample collection for outcome assessment. In addition, the onus would be on the primary HCP to determine if qPCR testing is required for the suspected herpetic lesion, collect a sample using the correct type of swab, assumed to be available in the office, and then get the sample to an Amgen laboratory for testing. This process may not be feasible in achieving results in the real world clinical setting. Sample collection from suspected herpetic lesions should be performed during an active infection cycle to increase the ability to detect talimogene laherparepvec in the lesions.

9 Summary

In this BLA, the primary evidence of effectiveness of talimogene laherparepvec comes from Study 005/05. In this randomized, Phase 3 study, subjects who received talimogene laherparepvec had a statistically significant higher durable response rate, including complete or partial response maintained for at least 6 months, compared with subjects who received control (GM-CSF) (15.6% vs. 1.4%; $p < 0.0001$). However, it was unclear whether talimogene laherparepvec administration was also associated with improvement in overall survival.

With regard to safety, the most common treatment-emergent adverse events associated with talimogene laherparepvec were fatigue, chills, pyrexia, nausea, influenza-like illness, and injection-site pain. Serious adverse events associated with talimogene laherparepvec included cellulitis, impaired wound healing, and immune-mediated disease (e.g., glomerulonephritis). Shedding data were limited. The applicant has proposed a pharmacovigilance plan to collect postmarketing safety data.

10 Issues and Discussions

10.1 Evidence of Effectiveness

Study 005/05 provides the primary evidence of the effectiveness of talimogene laherparepvec for the treatment of injectable regionally or distantly metastatic melanoma. FDA review of this BLA has identified concerns regarding both the study design and the study results. These concerns include the appropriateness of the study control; differential outcome assessments in the two arms of the study; the reliability of response assessments; the meaningfulness of the primary endpoint of durable response rate; the absence of a clear effect on overall survival; and limited evidence that the product has a systemic effect. Consideration of these concerns may influence the assessment of the evidence of effectiveness of talimogene laherparepvec.

Study Design, Study Conduct, and Response Assessments

With regard to the study control, talimogene laherparepvec contains human GM-CSF gene sequences and might be expected to produce measurable systemic blood levels of GM-CSF. At the time that Study 005/05 was initiated, GM-CSF was in clinical studies for treatment of melanoma. Therefore, GM-CSF was chosen as the comparator to control for any activity, either therapeutic or adverse, due to the control alone. However, if the study investigators or subjects viewed the control as unlikely to have any therapeutic effect, then their bias in favor of the talimogene laherparepvec arm may have influenced the study conduct and the study results.

The protocol stipulated that “subjects were to receive treatment until Week 24 (even in the presence of disease progression, including the appearance of new lesions), or achievement of a CR.” Four (1.4%) subjects randomized to the talimogene laherparepvec arm never received the drug, and 172 (58.3%) subjects in the talimogene laherparepvec arm withdrew from the study before the protocol-specified 24

weeks (Section 5.4; Table 10). In contrast, 14 (9.9% of subjects randomized to the control arm never received the drug, and 106 (75.1%) of subjects in the control arm withdrew from the study before the protocol-specified 24 weeks. Subject or investigator bias regarding the relative benefit of talimogene laherparepvec and the control may have influenced the determination that it was in the best interest of the subject to stop treatment or to be given other therapy for melanoma. Subjects who dropped out early would not have had any opportunity to receive further treatment or tumor response assessment, and thus had less chance to respond to the treatment or to be assessed as durable responders. Thus, this differential opportunity for assessment may have been influenced by investigator bias, and also may have biased the study results for durable response rate.

The problem of differential opportunity for assessment was also manifest in the proceedings of the EAC. The EAC evaluated information sent by investigators only for subjects who had investigator-determined CR, or PR, or had reached nine months of therapy. The trial design also called for the investigator to determine the response data to submit to the EAC. Thus, the EAC did not review data for all subjects in the trial. The determination of which subject data were submitted to the EAC may have been affected by investigator bias (Section 4.6.2). As seen in Table 12, there was discordance between the EAC and the investigators with regard to durable response in 21 subjects. Compared to the investigator assessment, the EAC assessed 14 subjects as not durable responders and 7 subjects as durable responders. It is impossible to determine whether EAC assessment of all of the study subjects would have resulted in any substantial change in the durable response rate in either arm. However, since a disproportionate number (122/141(87%)) of subjects in the control arm, compared to subjects (171/295 (58%)) in the talimogene laherparepvec arm, were never evaluated by the EAC, there were a disproportionate number of subjects in the control arm who were not evaluated by the EAC for durable response.

The study assessment of durable response rate (DRR) was complex, and involved multiple modalities, including clinical assessment, radiological assessments, photographs, and biopsies. Measurable disease, unmeasurable disease, and new lesions were assessed separately (Section 4.6.2). Some of these assessments (e.g., clinical assessments) were subjective, susceptible to investigator bias, and could ultimately influence the determination of stable disease, CR, and PR; thus, such assessments provide an opportunity for bias to influence the determination of durable response rate.

The size of the lesions may have also influenced the reliability of the outcome assessments. The study inclusion criterion “multiple superficial melanoma lesions which in aggregate have a total diameter of ≥ 10 mm” allowed enrollment of subjects who had only small or very small lesions. Inclusion of such subjects raises concerns regarding the reliability of injection, and particularly reliability of measurement, both at the baseline and during assessments of response. Although only 10% (29/289) of subjects in the talimogene laherparepvec arm of the ITT population had their largest lesion < 1 cm^2, such subjects represented 30.4% (14/46) of the subjects with a durable response (Table 13). In addition, the majority of the baseline measurable lesions in these 48 DRs were small to very small with measurements of 0.04 cm^2 to 0.5 cm^2 (64.8% of all lesions) (Table 14, Figure 4). Such small lesions are more susceptible than larger lesions to measurement error, which could also have been influenced by investigator bias. Thus, the

reliability of the tumor measurements is a factor that could have led to biased determinations of stable disease, CR, and PR, and thus provided an opportunity for bias to influence the determination of durable response rate.

However, the study results for the primary endpoint are statistically robust. Therefore, FDA believes that any bias that might have occurred in the study conduct would not change the study results sufficiently to alter the overall interpretation that talimogene laherparepvec had an effect on durable response rate.

Clinical Meaningfulness of Study Results

A key consideration is the uncertainty regarding the meaningfulness of the observed responses. For example, the small size of the baseline lesions in some of the responders raises concern regarding the clinical meaningfulness of the durable response rate for these subjects. In addition, the definition of the primary endpoint allowed inclusion of durable responders (DRs) who developed new lesions, relapse, or disease progression after the 6-month period when the durable responses were recorded. Thus, the meaningfulness of the DCR rate is unclear.

Overall response rate (ORR) has been used as a primary endpoint to support both traditional approval and Accelerated Approval in oncology. In the contemporary drug development setting, ORR has been used to support a traditional approval when accompanied by an improvement in symptoms (Jakafi, for myelofibrosis), or in cases where deep responses or complete responses occur in larger, more disfiguring skin lesions, where the likelihood for cosmetic improvement is high, as was the case for vismodegib for basal cell carcinoma and depsipeptide for cutaneous T- cell lymphoma (CTCL). A possible distinction between this BLA and instances where FDA has used ORR for traditional approval is that response rate has typically been considered in the context of systemic therapies. For a systemic therapy, it is not just the target lesion shrinking (which would be interpreted as antitumor activity of the study agent), but FDA believes that additional anti-tumor effects occur in both visualized lesions and subclinical micro-metastases. Thus, response rate is typically considered in the context of a systemic therapy and most commonly used as an Accelerated Approval endpoint in solid tumors, which intends to predict a clinical benefit such as symptomatic relief or survival. Most local therapies in oncology, such as palliative radiation therapy or bone-seeking radioisotopes, have used trials with a symptom endpoint (e.g., pain relief) rather than a tumor response endpoint. If the predominant antitumor effect of talimogene laherparepvec is to the injected local tumor in the setting of untreated systemic disease, the benefit is less clear than for a systemic therapy.

For these reasons, it is important to consider the evidence that talimogene laherparepvec has a systemic effect. As discussed in Section 3, the product's proposed mechanism of action involves a combination of tumor destruction and release of tumor antigens with local GM-CSF expression. GM-CSF is intended to enhance tumor antigen presentation to the immune system and induction of systemic immune responses to the tumors. In addition, as described in Section 3.4, there is preclinical evidence of systemic biodistribution of the talimogene virus; however the relevance of that preclinical data to the potential for systemic spread of talimogene laherparepvec to tumors is unclear. Therefore, as noted in Section 6.4,

although there is a scientific basis to support the possibility that systemic effects may occur, the evidence in Study 005/05 that talimogene laherparepvec had a systemic effect was limited and difficult to quantitate.

The assessment of overall survival could have provided additional evidence of both a systemic effect and a clinically meaningful benefit. However, it is not clear whether talimogene laherparepvec had a benefit on overall survival in the ITT population (p=0.051, from primary analysis). In addition, absence of the survival information for 10 subjects who were censored early, potentially informatively, increases the uncertainty about the presence or magnitude of any benefit on survival (Figure 5, p=0.155, from one post hoc sensitivity analysis). Thus the survival results are not robust, and the conduct of the study with regard to a relatively small number of subjects, potentially subject to investigator bias, could have had substantial impact on the results of the survival analysis.

Uncertainty regarding the clinical meaningfulness of the Study 005/05 primary endpoint results, in the absence of a clear effect on overall survival, raises concern regarding both the existence and the magnitude of an overall benefit of talimogene laherparepvec.

Advisory Committee Discussion:

Study 005/05 met its primary objective by demonstrating a higher durable response rate (DRR) in the talimogene laherparepvec group than in the control (GM-CSF) group. Concerns regarding the study results include uncertainty regarding the clinical meaningfulness of the durable responses (e.g., considering the limited evidence of a systemic effect), and uncertainty regarding an effect on overall survival.

Discussion: Please discuss the benefit of talimogene laherparepvec for the proposed indication, particularly considering the results of Study 005/05 and the concerns outlined above.

10.2 Safety Issues

The safety data necessary to support a BLA approval depends on several factors, including the magnitude of the benefit associated with the product. When the benefit of the product is substantial, such as improved survival, there may be greater tolerance of safety concerns, considering that the overall benefit-risk assessment could be favorable. This Advisory Committee is asked to consider whether there is a clinical benefit associated with talimogene laherparepvec. With that in mind, the Committee should also consider the safety issues identified in the BLA.

The most common treatment-emergent adverse events in Study 005/05 subjects treated with talimogene laherparepvec were fatigue, chills, pyrexia, nausea, influenza-like illness, and injection site pain. Sixty-four percent (63%) of subjects experienced adverse events that were grade 1-2, and 37% of subjects experienced adverse events that were grade 3 or above with treatment with talimogene laherparepvec. The

subject incidence of treatment-emergent serious adverse events was 25.7% in the talimogene laherparepvec arm and 13.4% in the control arm.

Cellulitis at the injection site and impaired wound healing occurred in subjects who received talimogene laherparepvec as an intra-lesional injection. One subject required a below-the-knee amputation for an infection that became resistant to medical interventions after talimogene laherparepvec administration; due to several confounders (e.g., treatment of the limb with radiation), the relationship of this event to talimogene laherparepvec is unclear. Immune-mediated events occurred in both arms. However, four of six such events (glomerulonephritis (n=2), vasculitis (n=1), and hypothyroidism (n=1)) were de novo after talimogene laherparepvec therapy.

Advisory Committee Discussion:

In Study 005/05, the most common treatment-emergent adverse events that occurred more commonly with talimogene laherparepvec included fatigue, chills, pyrexia, nausea, influenza-like illness, and injection site pain. Serious adverse events attributed to the study treatment included cellulitis at the injection site and injection site reactions.

Discussion: Please discuss the safety of talimogene laherparepvec for the treatment of injectable regionally or distantly metastatic melanoma.

10.3 Patient Population

Since Study 005/05 was initiated, several therapies (ipilimumab, vemurafenib, dabrafenib, trametinib, pembrolizumab and nibolumab) have been approved for the treatment of melanoma, some with demonstrated improvement in overall survival. Since Study 005/05, products approved for the treatment of patients with unresectable or metastatic melanoma and BRAF V600E mutations include vemurafenib, dabrafenib, and trametinib. The BRAF mutation status is known for only 31% of the subjects in Study 005/05. Therefore, the extent to which the Study 005/05 results are based on a disease population that now has an alternative of the BRAF inhibitors is unclear.

The available therapies for Stage IIIB, IIIC, and Stage IV melanoma include products with clinically important toxicities (see Section 12). Due to concern regarding these potential toxicities, some patients with melanoma may not be willing to take any of the currently available therapies. For such patients, talimogene laherparepvec may offer an important safety advantage over the currently approved therapies.

Considering that melanoma patients now have multiple treatment options, it is unclear whether talimogene laherparepvec offers an acceptable benefit-risk profile for the proposed indicated population. However, there may be melanoma patients for whom talimogene laherparepvec would be an appropriate alternative to the currently approved therapies. For example, 16.3% of subjects in the talimogene laherparepvec group had a durable response, but subgroup analyses showed a durable response in 33.0% of subjects with Stage IIIB or IIIC melanoma who received talimogene laherparepvec, and a durable

response in 23.9% of subjects who received talimogene laherparepvec as first-line therapy. Talimogene laherparepvec's overall benefit-risk profile might be more favorable in such patients, or patients with fewer treatment options, than in the proposed indicated population.

The absence of a potentially curative surgical option (i.e., unresectability) was a key eligibility criterion for Study 005/05. However, the applicant has proposed an indication statement that does not limit the indicated population to patients with unresectable disease. It is unclear whether any benefits and risks of talimogene laherparepvec, as demonstrated in Study 005/05, could be reasonably generalized to this broader population.

Study 005/05 enrollment was not limited to any subgroup, and subgroup analyses are generally not reliable with regard to an intervention's safety or efficacy in the subgroup. In addition, Study 005/05 does not provide any direct comparison of talimogene laherparepvec to available therapies, for the study as a whole or for any subgroups. Nevertheless, there may be patients with melanoma who do not have good treatment options, and for whom talimogene laherparepvec would be safe and effective.

Advisory Committee Discussion:

There may be subgroups of the proposed indicated population for whom talimogene laherparepvec would have a more favorable benefit-risk profile. For example, some patients (e.g., patients with Stage IIIB or IIIC melanoma; patients whose tumors do not have a BRAF mutation) may have few treatment options and want a treatment that avoids the potential toxicities associated with the currently approved therapies.

Discussion: Considering the evidence of effectiveness and safety of talimogene laherparepvec, and the current landscape of available therapies for melanoma, please discuss whether talimogene laherparepvec has an overall favorable benefit-risk profile for some population other than the proposed indicated population. If for some other population, please describe that population.

10.4 Dosing Regimen to Ensure Safe and Effective Use

Talimogene laherparepvec administration was highly variable, with investigator discretion in the selection of lesions to be injected, the number of lesions to be injected, the total dose administered, the dose administered into each lesion, and the frequency of injections. This variability in dosing makes it difficult to assess the relationship between specific aspects of dosing and the study efficacy results. In addition, because investigator discretion was a substantial factor in dosing, there may be insufficient information to inform healthcare providers on the safe and effective use of talimogene laherparepvec.

Question to the Advisory Committee:

The Study 005/05 protocol specified that talimogene laherparepvec (up to 4 mL total) was to be injected into one or more cutaneous or subcutaneous (SC) or nodal melanoma lesions every 2 weeks until clinically relevant disease progression occurred or there was no residual tumor to inject (Section 4.4).

However, the actual dose administered, and the dosing regimen, were subject to investigator discretion, and varied considerably among the study subjects.

Discussion: Please discuss whether the dosing instructions (including both dose and regimen, for both individual lesions and for the subject) provided for Study 005/05 would be sufficient to inform the use of talimogene laherparepvec by healthcare providers in clinical practice. If not, please discuss any additional dosing instructions that would be helpful.

10.5 Shedding Data and Pharmacovigilance Issues

It is difficult to determine the extent of talimogene laherparepvec shedding, based on the available data from the ongoing study Amgen 20120324, because of the following:

- Talimogene laherparepvec DNA testing data are not yet available for all treated subjects, nor for all protocol-specified time points. Individual subject information for all the time points is necessary to determine the time course and magnitude of virus persistence.

- Available data on the number of subjects tested and the number of samples obtained per subject varies for each time point and for each subject.

- The protocol Amgen 20120324 was not designed to test for the presence of infectious virus in the DNA positive urine or blood samples. Potential inhibitors (i.e., neutralizing antibodies in blood, high salt content in urine) in these samples could confound the interpretability of infectivity assays such as TCID50.

- Possible correlations of shedding and HSV-1 serological status of the subjects (anti-HSV-1 antibody titers) cannot be assessed because data are not yet available.

Objectives of the proposed postmarketing study (#20130193) are to evaluate talimogene laherparepvec-associated herpetic infection and long-term safety in patients, and its potential transmission to close contacts and HCPs. However, the proposed pharmacovigilance plan may not achieve these objectives in a real-world setting for the following reasons:

- With respect to passive surveillance of potential transmission, the protocol requires contacts to navigate a lengthy, multi-step process of sample collection for outcome assessment, which may not be feasible with regard to collecting samples from lesions during active infection in a timely manner.
- It may be logistically difficult for the primary HCP to the choose correct type of swabs, maintain a quality sample, and ensure timely and accurate transport to an Amgen laboratory for testing.

Advisory Committee Discussion:

Talimogene laherparepvec is a replication-competent virus derived from an attenuated HSV-1 isolate. As such, talimogene laherparepvec is expected to have biological properties that are similar to wild type HSV-1 with regard to viral shedding and potential transmission and latency/symptomatic reactivation. However, to date, there are limited data on talimogene laherparepvec shedding, which serves as a proxy for transmission. Thus, there are concerns that viral shedding may expose healthcare providers (HCP) and close patient contacts to talimogene laherparepvec.

Regarding the shedding and potential transmission of talimogene laherparepvec from patients treated with the product:

a. Please discuss the available data from the ongoing shedding study and the potential risk for transmission to close contacts (e.g., immunocompromised, infants, pregnant women) and health care providers (HCP).

b. Please discuss Amgen's proposed postmarketing protocol 20130193 and identify any recommendations for modification of the protocol. Please consider whether the protocol design is adequate to capture (with qPCR confirmation) cases of talimogene laherparepvec transmission to close contacts, should they occur. Are there additional measures that should be included in the postmarketing study to ensure that samples can be collected and testing can be performed in a timely manner for suspected herpetic lesions in close contacts or HCPs?

10.6 Overall Benefit-Risk Profile

FDA has the regulatory flexibility to consider this BLA for either traditional approval or Accelerated Approval. FDA could approve the product under the Accelerated Approval pathway for either the proposed indicated population, or for a subgroup of the proposed population. However, the BLA submission does not contain any statements from the Applicant regarding how the available data might support Accelerated Approval. In the absence of a submission that presents the Applicant's position regarding Accelerated Approval, and the absence of FDA review of such a submission, a full and fair consideration of the Accelerated Approval pathway for use of talimogene laherparepvec is not feasible at the time of this Advisory Committee meeting. For this reason, although the Committee discussion may include consideration of Accelerated Approval, FDA asks the Committee to vote only on the question of traditional approval for talimogene laherparepvec.

Question to the Advisory Committee:

The proposed indication for talimogene laherparepvec is for the "treatment of injectable regionally or distantly metastatic melanoma." Please consider the background information and evidence of benefit and safety provided in the briefing document, as well as the presentations and discussions during this meeting.

Voting Question: Does talimogene laherparepvec have an overall favorable benefit-risk profile for the treatment of injectable regionally or distantly metastatic melanoma? In voting, please consider only whether the available evidence would support traditional approval, not Accelerated Approval.

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12 Appendix

12.1 Therapies for Unresectable or Metastatic Melanoma with Traditional Approval

As discussed in Section 2.2, for unresectable or metastatic melanoma, FDA has approved ipilimumab, vemurafenib, dabrafenib, and trametinib under the traditional approval pathway. (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf). Detailed information regarding the efficacy and safety for these approvals is described below.

12.1.1 Ipilimumab

FDA approval of ipilimumab was based on a randomized (3:1:1), double-blind, double-dummy clinical trial (MDX010-20) in patients with unresectable or metastatic melanoma who had received at least one prior systemic treatment for melanoma. Overall survival (OS) was the trial's primary endpoint. Progression-free survival and best overall response rate were also assessed.

The clinical trial enrolled 676 patients with HLA-A2*0201 positive genotype. This HLA-A2*0201 genotype facilitated the immune presentation of the investigational tumor vaccine. The three treatment

arms consisted of ipilimumab, 3 mg/kg intravenously, in combination with the tumor vaccine (n=403), ipilimumab plus vaccine placebo (n=137), and tumor vaccine with placebo (n=136). The trial excluded patients with active autoimmune disease or those receiving systemic immunosuppression for organ transplantation.

The median age of subjects was 57 years with 29% of patients age 65 years or older. More than half the subjects were male; 71% had M1c stage; 12% had histories of previously treated brain metastases; 98% had ECOG performance status of either 0 or 1; and 23% had received prior IL-2 (Hodi et al., 2010).

Overall survival was longer with ipilimumab alone compared to tumor vaccine [HR 0.66 (95% CI: 0.51, 0.87), p=0.0026] with median OS of 10 and 6 months, respectively, for ipilimumab alone and the vaccine arm. The trial also demonstrated a statistically significant improvement in OS for the combination of ipilimumab plus tumor vaccine compared to tumor vaccine alone [HR 0.68 (95% CI: 0.55, 0.85), p= 0.0004, log-rank test)] with median OS of 10 and 6 months, respectively. The best overall response rate (investigator assessed) was 10.9% (95% CI: 6.3%, 17.4%) in the ipilimumab arm, 5.7% (95% CI: 3.7%, 8.4%) in the combination of ipilimumab plus vaccine arm, and 1.5% (95% CI: 0.2%, 5.2%) in the vaccine arm.

Safety data were evaluated in 511 patients who received ipilimumab alone or in combination with the tumor vaccine. The most common (greater than5%) adverse reactions (AEs) were manifestations of ipilimumab's immunological mechanism of action leading to T-cell activation and proliferation. Such immune-mediated adverse reactions included diarrhea, pruritus, rash, and colitis. The most serious AEs were also immune-mediated adverse reactions. Ipilimumab was discontinued due to adverse reactions in 10% of subjects. Thirteen percent of ipilimumab-treated subjects experienced a high grade, immune-mediated AE. The most common of these involved the colon, liver, skin, endocrine system, and nervous system. Management of immune-mediated AEs may include discontinuation of ipilimumab and initiation of high-dose corticosteroids.

FDA has also required a risk evaluation and mitigation strategy (REMS) program for ipilimumab's use. The goal of this REMS is to inform healthcare providers about the serious risks associated with ipilimumab, including risks of severe and fatal immune-mediated adverse reactions (such as fatal immune-mediated enterocolitis (including gastrointestinal perforation), fatal immune-mediated hepatitis (including hepatic failure), fatal immune-mediated toxicities of skin (including toxic epidermal necrolysis), fatal nervous system toxicity, and endocrinopathies), and the management of these reactions.

12.1.2 Available Therapies for Unresectable or Metastatic Melanoma with BRAF Mutations

12.1.2.1 Vemurafenib

FDA approval of vemurafenib was based primarily on an international, randomized, open-label trial in patients with previously untreated metastatic or unresectable melanoma with the $BRAF^{V600E}$ mutation as

detected by the cobas 4800 BRAF V600 Mutation Test (Roche Molecular Systems, Inc.). This companion diagnostic test was approved by the FDA concurrent with vemurafenib's approval.

The trial enrolled 675 subjects; 337 subjects were assigned to vemurafenib, 960 mg orally twice daily, and 338 were assigned to dacarbazine, 1000 mg/m^2 intravenously, every three weeks. Treatment continued until disease progression, unacceptable toxicity, and/or consent withdrawal. All subjects had an ECOG performance status of 0 or 1; 95% of subjects had metastatic disease; and 5% had unresectable stage III disease. The major efficacy outcome measures of the trial were OS and investigator-assessed progression-free survival (PFS). Other outcome measures included confirmed investigator-assessed best overall response rate.

The median follow-up at the time of the OS analysis was 6.2 and 4.5 months for the vemurafenib and dacarbazine arms, respectively. Overall survival was significantly improved in subjects receiving vemurafenib compared to those receiving dacarbazine (HR=0.44; 95% CI: 0.33, 0.59; p< 0.0001, log-rank test). The median survival of subjects receiving vemurafenib had not been reached at the time of approval, but was later updated to 13.6 months (95% CI: 12, 15.3), and was 10.3 months (95% CI: 9.1, 12.8) for those receiving dacarbazine.

Progression-free survival (PFS) was also significantly improved in subjects receiving vemurafenib (HR=0.26; 95% CI: 0.20, 0.33; p<0.0001, log-rank test). The median PFS was 5.3 (95% CI: 4.9, 6.6) and 1.6 months (95% CI: 1.6, 1.7) in the vemurafenib and dacarbazine arms, respectively. Overall response rate (complete plus partial response rates) was 48.4% (95% CI: 41.6%, 55.2%) and 5.5% (95% CI: 2.8%, 9.3%) in the vemurafenib and dacarbazine arms, respectively.

Vemurafenib was also evaluated in a single-arm, multicenter trial that enrolled 132 subjects with $BRAF^{V600E}$ mutation-positive metastatic melanoma who had received at least one prior systemic therapy. An independent review of treatment responses confirmed a best overall response rate of 52% (95% CI: 43%, 61%), with a median response duration of 6.5 months (95% CI: 5.6, not reached).

The most common adverse reactions (≥30%) in subjects treated with vemurafenib were arthralgia, rash, alopecia, fatigue, photosensitivity reaction, and nausea. Cutaneous squamous cell carcinomas (cuSCC), including squamous cell carcinomas of the skin and keratoacanthomas, were detected in approximately 24% of subjects treated with vemurafenib. CuSCCs were managed with excision in clinical trials, and patients were able to continue treatment without dose adjustment. Other adverse reactions, sometimes severe, in vemurafenib-treated subjects included hypersensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis, uveitis, QT prolongation, and liver enzyme laboratory abnormalities.

Confirmation of $BRAF^{V600E}$ mutation-positive melanoma using an FDA-approved test is required before treatment with vemurafenib. Vemurafenib is not recommended for use in patients with wild-type BRAF melanoma. The approval also contains a Medication Guide to inform health care professionals and patients of vemurafenib's potential risks.

12.1.2.2 Dabrafenib

FDA approval of dabrafenib was based on demonstration of improved progression-free survival (PFS) in a multi-center, international, open-label, randomized (3:1), active-controlled trial. This trial enrolled 250 patients with previously untreated, histologically confirmed, unresectable Stage III or Stage IV melanoma determined to be BRAF V600E mutation-positive based upon centralized testing. Subjects were randomized to receive either dabrafenib 150 mg orally twice daily (n=187) or dacarbazine 1000 mg/m^2 intravenously once every 3 weeks (n=63). At the time of disease progression, 28 subjects randomized to dacarbazine received dabrafenib. Of 250 subjects enrolled, 60% were male; the median age was 52 years; 67% had an ECOG performance status of 0; 66% had M1c disease; and 2.8% had unresectable stage III disease (Hauschild et al., 2012).

A statistically significant prolongation of investigator-assessed PFS was demonstrated for subjects randomized to the dabrafenib arm [HR 0.33 (95% CI: 0.20, 0.54); $p < 0.0001$, stratified log-rank test]. The median PFS times were 5.1 and 2.7 months in the dabrafenib and dacarbazine arms, respectively. The PFS analysis based on blinded independent central review was consistent with the investigator results.

The investigator-assessed objective response rates were 52% (95% CI: 45, 59) for the dabrafenib arm, which included a 3% complete response rate, and 17% (95% CI: 9, 29) for the dacarbazine arm. The median duration of response was approximately 5 months in both treatment arms. No statistically significant difference in OS between the two arms was demonstrated. The most frequent (greater than or equal to 20% incidence) adverse reactions associated with dabrafenib were hyperkeratosis, headache, pyrexia, arthralgia, papilloma, alopecia, and palmar-plantar erythrodysesthesia syndrome.
Serious adverse reactions were development of new primary skin cancers (cutaneous squamous cell carcinoma, new primary melanomas, and keratoacanthomas), febrile drug reactions requiring hospitalization, hyperglycemia, and uveitis/iritis. Dabrafenib is approved with a Medication Guide to inform patients of these serious potential risks.

Confirmation of the presence of BRAF V600E is needed prior to initiation of dabrafenib because of the potential risk of tumor promotion in patients with BRAF wild-type melanoma.

12.1.2.3 Trametinib

Trametinib's approval was based on the demonstration of improved progression-free survival (PFS) in a multi-center, international, open-label, randomized (2:1) active-controlled trial enrolling 322 subjects with histologically confirmed Stage IIIC or IV melanoma determined to be BRAF V600E or V600K mutation-positive based upon centralized testing. No more than one prior chemotherapy regimen was permitted. Patients with prior exposure to BRAF inhibitors or MEK inhibitors were ineligible.

Subjects were randomized to receive either trametinib 2 mg orally once daily (n=214) or chemotherapy consisting of either dacarbazine or paclitaxel administered intravenously every three weeks (n= 108). At the time of disease progression, 51 subjects (47%) randomized to chemotherapy received trametinib.

Of 322 subjects enrolled, 54% were male; the median age was 54 years; all had baseline ECOG performance status of 0 or 1; 64% had M1c disease; and 5.6% had unresectable stage IIIC disease (Flaherty et al., 2012). All subjects had tumor tissue with mutations in BRAF V600E (87%), V600K (12%), or both (greater than 1%) on centralized testing.

A statistically significant prolongation of investigator-assessed PFS was demonstrated for subjects randomized to the trametinib arm compared to those receiving chemotherapy [HR 0.47 (95% CI: 0.34, 0.65); $p < 0.0001$, log-rank test]. The median PFS was 4.8 and 1.5 months in the trametinib and chemotherapy arms, respectively. The PFS analysis assessed by blinded independent central review was consistent with the investigator results. The investigator-assessed, objective response rates were 22% (95% CI: 17, 28) for the trametinib arm and 8% (95% CI: 4, 15) for the chemotherapy arm. The analysis of OS was not mature at the time of approval.

There was no evidence of anti-tumor activity with trametinib in subjects who had received prior BRAF inhibitor therapy. This was evaluated in a single-arm, multicenter, international trial enrolling 40 subjects with BRAF V600E or V600K mutation-positive, unresectable or metastatic melanoma, all of whom had received prior treatment with a BRAF inhibitor. None of these 40 subjects achieved a confirmed partial or complete response, as determined by the clinical investigators.

The most frequent (greater than or equal to 20% incidence) adverse reactions from trametinib were rash, diarrhea and lymphedema. Serious adverse drug reactions occurring in subjects taking trametinib included cardiomyopathy, retinal pigment epithelial detachment, retinal vein occlusion, interstitial lung disease, and serious skin toxicity.

Confirmation of BRAF V600E or V600K mutation as detected by an FDA-approved test is needed for trametinib treatment. Concurrent with this approval, FDA approved the THxID BRAF assay (bioMerieux, Inc.) for detection of BRAF V600E and V600K mutations. Trametinib is not indicated for treatment of patients who have received prior BRAF inhibitor therapy.

12.2 Therapies with Accelerated Approval for Unresectable or Metastatic Melanoma with BRAF Mutations

12.2.1 Dabrafenib and Trametinib (Tafinlar and Mekinist)

Approval of the combination therapy of dabrafenib and trametinib was based on the demonstration of durable objective responses in a multicenter, open-label, randomized (1:1:1), active-controlled, dose-ranging trial enrolling 162 subjects with histologically confirmed Stage IIIC or IV melanoma determined to be BRAF V600E or V600K. No more than one prior chemotherapy regimen and/or interleukin-2 was permitted. Patients with prior exposure to BRAF inhibitors or MEK inhibitors were ineligible.

Patients were randomized to receive trametinib 2 mg orally once daily in combination with dabrafenib 150 mg orally twice daily (n=54), trametinib 1 mg orally once daily in combination with dabrafenib 150 mg orally twice daily (n=54), or single-agent dabrafenib 150 mg orally twice daily (n=54). Of the 162 subjects enrolled, 57% were male, the median age was 53 years, all had baseline ECOG PS of 0 or 1, 69% had M1c disease, 31% had IIICM0, IVM1a, or IVM1b, and 81% had not received prior anticancer therapy for unresectable or metastatic disease. All subjects had tumor tissue with mutations in BRAF V600E (85%) or V600K (15%) on local or centralized testing.

The investigator-assessed objective response rates and response duration were 76% (95% CI: 62, 87) and 10.5 months (95% CI: 7, 15), respectively, in the trametinib 2 mg plus dabrafenib combination arm and 54% (95% CI: 40, 67) and 5.6 months (95% CI: 5, 7), respectively, in the single-agent dabrafenib arm. Objective response rates were similar in subgroups defined by BRAF V600 mutation subtype, V600E and V600K. Analyses of objective response rates based on blinded independent central review were consistent with the investigator results.

The incidence of cutaneous squamous cell carcinoma (including squamous cell carcinomas of the skin and keratoacanthomas), the trial's primary safety endpoint, was 7% (95% CI: 2, 18) in the trametinib 2 mg plus dabrafenib combination arm compared to 19% (95% CI: 9, 32) in the single-agent dabrafenib arm.

The most frequent (greater than or equal to 20% incidence) adverse reactions from trametinib in combination with dabrafenib were pyrexia, chills, fatigue, rash, nausea, vomiting, diarrhea, abdominal pain, peripheral edema, cough, headache, arthralgia, night sweats, decreased appetite, constipation, and myalgia. The most frequent grades 3 and 4 adverse events (greater than or equal to 5% incidence) were acute renal failure, pyrexia, hemorrhage, and back pain.

Serious adverse drug reactions occurring in patients taking trametinib in combination with dabrafenib were hemorrhage, venous thromboembolism, new primary malignancy, serious febrile reactions, cardiomyopathy, serious skin toxicity, and eye disorders such as retinal pigmented epithelial detachments.

Granting of this Accelerated Approval is contingent upon the successful completion of the ongoing MEK115306 trial to verify the clinical benefit of trametinib for use in combination with dabrafenib. MEK115306 is an international, multicenter, randomized (1:1), double-blind, placebo-controlled trial comparing the combination of dabrafenib and trametinib to dabrafenib and placebo as first-line therapy in approximately 340 subjects with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E or V600K mutation-positive cutaneous melanoma. The primary endpoint is progression-free survival. Overall survival is a key secondary endpoint.

12.3 Therapies with Accelerated Approval for Unresectable or Metastatic Melanoma with Disease Progression Following Ipilimumab and/or BRAF Inhibitor

12.3.1 Pembrolizumab

Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, thereby releasing PD-1 pathway-mediated inhibition of the immune response, including anti-tumor immune response.

Approval was based on the results of a multicenter, open-label, randomized (1:1), dose-comparative, activity-estimating cohort conducted within Trial P001. In this cohort, 173 subjects with unresectable or metastatic melanoma with disease progression within 24 weeks of the last dose of ipilimumab and, if BRAF V600 mutation positive, prior treatment with a BRAF inhibitor, were randomized to receive pembrolizumab 2 mg/kg (n=89) or 10 mg/kg (n=84) intravenously once every 3 weeks until disease progression or unacceptable toxicity.

Key exclusion criteria were an autoimmune disease, a medical condition that required immunosuppression, and/or a history of severe immune-mediated adverse reactions from treatment with ipilimumab. Severe immune-mediated adverse reactions were defined as any CTCAE Grade 4 toxicity requiring treatment with corticosteroids or Grade 3 toxicity requiring corticosteroid treatment (greater than 10 mg/day prednisone or equivalent dose) for greater than 12 weeks.

Among the 173 subjects, the median age was 61 years (64% less than age 65); 40% female; 97% White; and 66% and 34% with an ECOG performance status 0 and 1, respectively. Disease characteristics were BRAF V600 mutation positive (17%), elevated lactate dehydrogenase (39%), M1c (82%), brain metastases (9%), and two or more prior therapies for advanced or metastatic disease (73%).

The major efficacy endpoints were confirmed overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) as assessed by a blinded independent review committee and duration of response (DOR). The ORR was 24% (95% CI: 15, 34) in the 2 mg/kg arm, consisting of one complete response and 20 partial responses. Among the 21 subjects with an objective response, 3 (14%) had disease progression at 2.8, 2.9, and 8.2 months after initial response. The remaining 18 subjects (86%) have ongoing responses, ranging from 1.4+ to 8.5+ months; 8 subjects have ongoing responses of 6 months or longer. Similar ORR results were observed in the 10 mg/kg arm.

The most common (greater than or equal to 20%) adverse reactions among subjects receiving pembrolizumab 2 mg/kg every 3 weeks were fatigue, cough, nausea, pruritus, rash, decreased appetite, constipation, arthralgia, and diarrhea.

The most frequent (greater than or equal to 2%) serious adverse drug reactions observed with pembrolizumab were renal failure, dyspnea, pneumonia, and cellulitis. Additional clinically significant immune-mediated adverse reactions included pneumonitis, colitis, hypophysitis, hyperthyroidism, hypothyroidism, nephritis, and hepatitis.

As a condition of this Accelerated Approval, Merck is required to conduct a multicenter, randomized trial establishing the superiority of pembrolizumab over standard therapy to verify and describe the clinical benefit of pembrolizumab. Merck has two ongoing multicenter, randomized, controlled, therapeutic confirmatory trials in subjects with unresectable or metastatic melanoma, either ipilimumab refractory (Trial P002) or ipilimumab naïve (Trial P006), each with co-primary endpoints of progression-free survival and overall survival.

FDA granted pembrolizumab breakthrough therapy designation for pembrolizumab for this indication in January 2013 based on preliminary evidence of clinical activity in patients with unresectable or metastatic melanoma, previously untreated with or refractory to ipilimumab.

12.3.2 Nivolumab

Nivolumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, thereby releasing PD-1 pathway-mediated inhibition of the immune response, including anti-tumor immune response.

Approval was based on objective response rate (ORR) and durability of response in the first 120 subjects who were treated with nivolumab and had a minimum 6 months follow- up from an on-going, randomized, open-label trial in which 370 subjects with unresectable or metastatic melanoma received nivolumab 3 mg/kg intravenously every 2 weeks (n=268) or investigator's choice of chemotherapy (n=102). Chemotherapy included either dacarbazine or the combination of carboplatin plus paclitaxel. Subjects were treated until disease progression or unacceptable toxicity. Subjects with unresectable or metastatic melanoma were required to have disease progression following ipilimumab, and a BRAF inhibitor if BRAF V600 mutation positive. Subjects were excluded from the trial if they had an autoimmune disease, a medical condition that required corticosteroids or immunosuppression, or a history of severe ipilimumab-related adverse reactions.

Among these 120 subjects, 65% were male, the median age was 58 years (68% less than age 65), 98% were White, and 58% and 42% had a baseline ECOG performance status of 0 or 1, respectively. Disease characteristics included BRAF V600 mutation -positive melanoma (22%), elevated lactate dehydrogenase (56%), M1c disease (76%), history of brain metastases (18%), and two or more prior therapies for advanced or metastatic disease (68%).

The major efficacy endpoints were confirmed ORR according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) and response duration. ORR was assessed by a blinded independent review committee. The ORR was 32% (95% CI: 23, 41) with four complete responses and 34 partial

responses. Five responding subjects have progressed, while the remaining 33 subjects (87%) have ongoing responses (range 2.6+ to 10+ months). Thirteen subjects have ongoing responses of 6 months or longer.

The most common (greater than or equal to 20%) adverse reaction among the 268 subjects receiving nivolumab was rash. The most frequent Grade 3 and 4 adverse drug reactions observed in 2% to less than 5% with nivolumab were abdominal pain, hyponatremia, increased aspartate aminotransferase, and increased lipase. Clinically significant immune-mediated adverse reactions included pneumonitis, colitis, hepatitis, nephritis/renal dysfunction, hypothyroidism, and hyperthyroidism.

As a condition of this Accelerated Approval, Bristol-Myers Squibb is required to conduct a multicenter, randomized trial(s) establishing the superiority of nivolumab over standard therapy in adult subjects with unresectable or metastatic melanoma to verify and describe the clinical benefit of nivolumab.

FDA granted nivolumab breakthrough therapy designation in September 2014 based on preliminary evidence of clinical activity in this patient population.