CBER Clinical Review

Application Type	Original Application
STN	125518/0
CBER Received Date	July 28, 2014
PDUFA Goal Date	October 27, 2015
Division / Office	DCEPT /OCTGT
Priority Review	No
Reviewer Names	Robert Le Maura C. O'Leary Clinical Team Leader: Peter Bross
Review Completion Date / Stamped Date	October 24, 2015
Supervisory Concurrence	Ke Liu Wilson W. Bryan
Applicant	Amgen, Inc.
Established Name	talimogene laherparepvec
(Proposed) Trade Name	Imlygic
Pharmacologic Class	Genetically Modified Oncolytic Viral Therapy
Formulation(s), including Adjuvants, etc.	The product is formulated in a sterile frozen liquid single-use 2.0 mL [redacted] vial. Each vial contains talimogene laherparepvec at a nominal concentration of 10^6 plaque forming units (PFU)/mL or 10^8 PFU/mL in solution for intralesional injection.
Dosage Form(s) and Route(s) of Administration	Single-use vials (10^6 and 10^8 PFU/mL); for intralesional injection into cutaneous, subcutaneous, and nodal lesions
Dosing Regimen	The initial dose is up to 4 mL of 10^6 PFU/mL followed by 4 mL of 10^8 PFU/mL administered 3 weeks later; thereafter, subsequent doses of 4 mL of 10^8 PFU/mL are administered every 2 weeks.
Indication and Intended Population(s)	Treatment of injectable regionally or distantly metastatic melanoma.
Orphan Designated	Yes

APPROVED
By Robert Le, MD, PhD at 10:07 am, Oct 26,

APPROVED
By Maura O'Leary, MD at 10:04 am, Oct 26, 2015

APPROVED
By Peter Bross at 10:10 am, Oct 26,

APPROVED
By Ke Liu at 12:44 pm, Oct 26, 2015

APPROVED
By Wilson Bryan, M.D. at 2:11 pm, Oct 26, 2015

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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	Granulocyte Macrophage Colony-Stimulating Factor
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
OBE	Office of Biostatistics and Epidemiology
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 Executive Summary

The investigational product is talimogene laherparepvec, an attenuated herpes simplex virus type 1 (HSV-1), engineered to express human granulocyte macrophage colony stimulating factor (GM-CSF) to enhance the response to tumor antigens released during virus replication.

The applicant's proposed indication is treatment of injectable regionally or distantly metastatic melanoma.

The effectiveness claim is primarily based on Study 005/05, a single multicenter, randomized, open-label, Phase 3 study to assess talimogene laherparepvec monotherapy vs. GM-CSF injections in subjects with unresectable stage IIIB, IIIC, and IV melanoma.

In Study 005/05, talimogene laherparepvec was injected into cutaneous, subcutaneous, and nodal lesions. In contrast, GM-CSF was given subcutaneously. The intent-to-treat (ITT) population included 436 subjects: 295 in the talimogene laherparepvec arm and 141 in the GM-CSF arm. The subjects were restaged at the time of enrollment; the stage IIIB or IIIC was not the stage at the initial melanoma diagnosis. Most (96%) subjects in the clinical trial had recurrent disease at entry.

The primary endpoint was durable response rate (DRR), defined as the percentage of subjects with complete response (CR) or partial response (PR) maintained continuously for at least 6 months from the time the response was first observed and initiating at any point within 12 months of starting therapy. Tumor responses were assessed under World Health Organization (WHO) response criteria, modified to allow subjects to continue therapy and be evaluated for tumor response despite the appearance of new lesions or disease progression of the existing lesions. The primary endpoint result was based on the assessment by an independent Endpoint Assessment Committee (EAC) which was blinded to subjects' treatment allocation. The secondary endpoints included overall survival (OS), 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 was no response achieved after the progression event or until death]. Study 005/05 was conducted under an FDA Special Protocol Assessment agreement (SPA) and all amendments were reviewed and concurred with under this agreement.

The results showed that subjects who received talimogene laherparepvec had an increased DRR compared with those who received GM-CSF (15.6% versus 1.4%, $p < 0.0001$) (Table 16). The results of the analysis were similar whether the DRR was assessed by the investigator, EAC, or by FDA reviewers.

A review of the clinical response assessments revealed an imbalance in early study discontinuations, with almost two thirds of the GM-CSF subjects dropping out by the third month, as compared with one third in the talimogene arm, despite the protocol requirement that all subjects remain on study through 24 weeks unless there was a medical reason for discontinuation. This imbalance could have confounded interpretation of the study results. Discrepancies between the two arms also may have occurred in

other areas, such as outcome assessment and dosing. The existence and effects of bias are difficult to confirm and quantitate, but such discrepancies raise concerns that bias in study conduct could have affected interpretation of results. However, the FDA reviewers concluded that the magnitude of the improvement in DRR was sufficiently persuasive that overall conclusions regarding the primary endpoint were not significantly affected.

OS was a key secondary endpoint. The median OS in the ITT population was 23.3 months for the talimogene laherparepvec group and 18.9 months for GM-CSF group (primary analysis hazard ratio = 0.79, p-value 0.051). Because of asymmetric study discontinuations, FDA performed sensitivity analyses of OS, imputing survival times for 10 missing subjects (3 subjects in talimogene laherparepvec arm and 7 subjects in GM-CSF arm) based on the planned analysis cut off dates. This sensitivity analysis yielded a p-value of 0.155. An updated analysis of OS including additional information on missing subjects resulted in a p-value of 0.116, a hazard ratio of 0.82 with 95% confidence interval of (0.65, 1.05). Therefore the analyses of OS did not show a statistically significant treatment effect from talimogene laherparepvec on survival in the ITT population.

Analyses of subgroups showed higher response rates and OS in the “first line” therapy subgroup and in stage IIIB and IIIC compared with distantly metastatic subgroups (Figure 9). The “first line” therapy group consisted of subjects who had received only surgery or adjuvant therapies. No treatment effect on OS or response was noted in the distantly metastatic stage IV M1b and M1c subgroups in terms of either response rates or OS.

DRR as measured in the clinical study appeared to be reasonably well correlated with OS in the ITT population and subgroups in the study 005/05, and could thereby provide a surrogate measure, reasonably likely to predict clinical benefit.

However, the DRR may not reflect direct clinical benefit for melanoma patients due to the following concerns:

- The PR component of the primary endpoint DRR is not considered a clinical benefit.[See FDA Guidance for Industry - Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (FDA, 2007)]
- Some baseline lesions may have been too small to asses accurately for response.
- There was equivocal evidence for systemic effect with the talimogene laherparepvec treatment, other than the OS advantage observed in some subgroups of stage IIIB and IIIC.
- Tumor response as a basis for approval is usually considered in the context of systemic therapies, not local therapies.

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).

Safety evaluations included tracking of adverse events in both the talimogene laherparepvec and GM-CSF treated arms in Study 005/05. The most common adverse event other than progressive disease for both groups was flu-like symptoms.

Overall, talimogene laherparepvec was well tolerated with limited Grade 3 or Grade 4 adverse events. Deaths on study were primarily attributed to progressive disease (PD).

Talimogene laherparepvec dose administration was variable, with considerable 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 and to adequately inform practitioners to ensure safe and effective use of this product.

Because talimogene laherparepvec is a live virus, there are concerns regarding viral transmission from treated subjects to others (viral shedding). The biodistribution and shedding of intralesionally administered talimogene laherparepvec are being investigated in an ongoing study (Amgen 20120324) measuring talimogene laherparepvec DNA and virus in blood, oral mucosa, urine, injection site and occlusion dressings. Available data from the initial 20 melanoma subjects who received talimogene laherparepvec intralesional injection at dose and schedule similar to that of Study 005/05 indicate that talimogene laherparepvec DNA was present in the blood in 17 (85%) subjects and in urine of four (20%) subjects during the study. Infectious talimogene laherparepvec virus was detected at the site of injection in three (15%) subjects at a single time point each, and all within the first week after the initial injection. The exterior of the occlusive dressings was positive for talimogene laherparepvec DNA in 14 (70%) during the study, although no infectious virus was detected on the exterior of the occlusive dressing.

The applicant will complete this ongoing shedding study and has proposed a pharmacovigilance plan to collect postmarketing safety data to further characterize the shedding risk.

A Joint Meeting of CBER's Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) and CDER's Oncologic Drugs Advisory Committee (ODAC) was held on April 29, 2015 in order to provide advice to FDA regarding safety, dosing, and an overall benefit-risk assessment. During the discussions, some committee members expressed an opinion that the data suggested a favorable benefit – risk profile of talimogene laherparepvec treatment in a subset of subjects with stage III disease and not in subjects with visceral disease and that the indication should be limited to unresectable stage IIIB, and IIIC. The committee voted 22 – 1 to the question, "does talimogene laherparepvec have an overall favorable benefit-risk profile to support traditional approval for the treatment of injectable, regionally or distantly metastatic melanoma. The committee member who voted "no" indicated that he did so to emphasize that he believed the data had demonstrated benefit in only a subset of melanoma subjects, not in the ITT population.

Summary:

In this BLA, the primary evidence of effectiveness was assessed from the results of a single 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 GM-CSF. Effectiveness appeared to be greater in the subjects with localized stage IIIB and IIIC subgroups. Survival appeared to be improved in the stage IIIB and IIIC subgroups in exploratory analysis but not in the overall population.

Clinical Reviewers' Recommendations on Regulatory Action:
Following review of the BLA clinical data, and considering currently available therapies for advanced melanoma, as well as the discussions at the combined CTGTAC and ODAC meeting, the clinical reviewers recommend granting Accelerated Approval (21 CFR 601.41, subpart E) for talimogene laherparepvec for local treatment of cutaneous, subcutaneous and nodal lesions in patients with unresectable, injectable, locoregionally recurrent melanoma.

Recommendation for Accelerated Approval

Subpart E (21CFR601.41) describes requirements for Accelerated Approval of biologic products for serious and life-threatening illnesses. The approval must be based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity that provides meaningful therapeutic benefit to patients over existing therapies. Clinical reviewers consider the durable response rate used in the Study 005/05 as a surrogate endpoint which is reasonably likely to predict the clinical benefit of improved overall survival in a subgroup of subjects with unresectable, injectable, locoregionally recurrent melanoma.

As shown in Table 2, ipilimumab, vemurafenib, dabrafenib and trametinib have been recently approved for locally advanced melanoma under traditional approval, representing potentially available therapies for these patients. However, study populations supporting these approvals included 66-81% stage IV1c metastatic disease. Ipilimumab approval was based on a study population with 95% distant metastatic disease. Therefore, these approved therapeutics were studied in a different population compared with the population of patients with unresectable, injectable, locoregionally recurrent melanoma that benefited from talimogene laherparepvec therapy in this BLA. Therefore, in the clinical reviewers opinion, the indication for talimogene laherparepvec that is recommended, represents an unmet medical need for which there is no currently available therapy, making Accelerated Approval pathway feasible.

Recent traditional approvals in melanoma have relied on therapeutics' robust treatment effect on OS or progression-free survival (PFS) (Table 2). However, the lack of a statistically significant OS advantage in the ITT population, and the inherent difficulties with interpreting the persuasiveness of subgroup analyses make the traditional approval pathway [21 CFR 314.126 and 21 CFR 601.25 (d) (2)] problematic for this BLA.

Specific recommendations:

- The clinical reviewers have the following specific recommendations for the indication statement of the prescribing information (labeling). The patient population of Study 005/05 included unresectable, injectable subjects; 96% of subjects had recurrent melanoma. Therefore, the clinical reviewers' recommend that indication statement of the labeling include wording "unresectable," "injectable," and "recurrent". The effectiveness appeared to be greater in subjects with localized stage IIIB and IIIC melanoma in the Study 005/05. Thus, clinical reviewers recommend that indication statement of the labeling also include wording "locoregionally recurrent melanoma". Talimogene laherparepvec has not been shown to have a systemic effect in patients with metastatic melanoma. Thus, clinical reviewers recommend that "limitation of use" be included in the labeling to state that talimogene laherparepvec has not been shown to improve overall survival or have an effect on visceral metastases.

- The clinical reviewers recommend that a confirmatory study be conducted to describe the clinical benefit (e.g., OS) of talimogene laherparepvec in the treatment of advanced melanoma subjects.

- The clinical reviewers recommend that the Shedding Study Amgen 201203241 be completed.

2 Clinical and Regulatory Background

Talimogene laherparepvec, is an attenuated replication-competent HSV-1 that can constitutively express a biologically active form of human granulocyte macrophage colony stimulating factor (GM-CSF).

The applicant's proposed indication is treatment of injectable regionally or distantly metastatic melanoma.

2.1 Disease or Health-Related Condition(s) Studied

Melanoma Overview

Melanoma is the most aggressive skin cancer. 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 (ACS, 2014). According to Surveillance, Epidemiology and End Results (SEER) data, between 2004 and 2010, approximately 84% of patients were diagnosed with localized disease, 9% with regional disease, and 4% with distant metastatic disease (Howlader N, 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.

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)

Melanoma that is localized or has spread to regional lymph nodes (stage II-stage III) may be curable with wide excision of the primary tumor and removal of any involved regional lymph nodes. Melanoma that has spread to multiple regional nodal sites or presents with in-transit/satellite lesions (Stage IIIB/C) is infrequently curable with standard therapy (Balch et al., 2009). Patients who are diagnosed with or develop metastatic disease have a median overall survival of less than one year (Howlader N, 2014). Melanoma that has spread to distant skin, nodes, or visceral organs (stage IV) is infrequently curable with standard therapy, although long-term survival is occasionally achieved by resection of metastasis. For patients with stage IV disease, 5-year survival rates are generally poor, ranging from 62% for M1a disease (skin or nodes only), to <53% for M1b disease (lung only), and 33% for M1c disease (other visceral lesions or high lactate dehydrogenase) (Balch et al., 2009) (Howard et al., 2012).

2.2 Currently Available Treatment(s)/Intervention(s) for the Proposed Indication(s)

2.2.1 Current Treatment Options for Patients with Unresectable and Recurrent Melanoma

Until 2010, 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). 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. In 2015, nivolumab in combination with ipilimumab was granted accelerated approval for the treatment of patients with BRAF V600 wild-type, unresectable or metastatic melanoma. These therapies have demonstrated improvements in durable objective response rates or PFS, 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.

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			
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)**
Opdivo (nivolumab) and Yervoy (ipilimumab)—	**2015 Accelerated Approval**	**ORR**	**60% (95% CI: 48, 71) vs. ipilimumab alone 11% (95% CI: 3, 25)**

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 Section 12, Appendices at the end of this document.

2.2.2 Primary Endpoints for Approvals

- Response Rate:
  - Proleukin (Interleukin-2) was approved in 1998 based on overall response rate (ORR). However, more recent traditional approvals in melanoma have relied on robust overall survival (OS) or progression-free survival (PFS) advantage (see Table 2).
  - Keytruda (Pembrolizumab) and Opdivo (Nivolumab) are recent examples of Accelerated Approvals for melanoma based on response rates observed in single arm studies.
- PFS:
  - Dabrafenib was approved in 2013 based on PFS.
  - Trametinib was approved in 2013 based on PFS.
- OS:
  - Ipilimumab was approved in 2011 based on OS and ORR.
  - Vemurafenib was approved in 2011 based on OS and PFS.
- Discussion of DRR as primary endpoint of Study 005/05: At the time of the Study 005/05 Special Protocol Assessment (SPA) agreement and protocol initiation, no therapies were available with a demonstrable OS advantage for melanoma. Therefore DRR was considered to be an acceptable primary study endpoint for Special Protocol Assessment. Response rates for studies of local intralesional therapies for melanoma may not be directly comparable to those reported in studies of systemic therapies for melanoma.

2.2.3 Local therapies for melanoma

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.

Local intralesional and topical therapies for metastatic melanoma are also used in clinical practice; however, none have been approved by FDA (Table 3). Intralesional therapy is thought to have potential advantages over systemic therapy, as local injection administration allows for delivery of an increased concentration of the agent and reduced systemic exposure. Some investigators have reported a so-called 'bystander effect', where uninjected distant lesions exhibited systemic tumor responses.

For patients with more extensive disease confined to a limb, treatment with amputation, isolated limb infusion (ILI) or hyperthermic isolated limb perfusion (HILP) are options (Deroose et al., 2011). The technique of isolated limb perfusion (ILP) was introduced in 1958 by Creech et al. and allows tumors in extremities to be exposed to concentrations of chemotherapy higher than can be achieved with systemic administration. However, this procedure can be associated with regional toxicity, involve a surgical procedure and are obviously not suitable for disease outside of the extremities.

Table 3. Selected Local Therapies for Melanoma

Product	Route	Number of subjects	CR	OR
IL-2 (interleukin-2)	Intratumoral	48	69	Not Reported
PV-10 (Rose Bengal)	Intratumoral	80	24	49
Melphalan	Isolated Limb Infusion	>500	40-90	64-100

(Sloot et al., 2014)

2.3 Safety and Efficacy of Pharmacologically Related Products (s)

This BLA is a first-in-class for an oncolytic virus as a treatment for a malignancy. The target for talimogene laherparepvec is melanoma. There are no known available clinical data for related products for this indication.

2.4 Regulatory History

Table 4 below summarizes major regulatory milestones in the development of talimogene laherparepvec.

Table 4. Key Regulatory Activities Related to Clinical Development

June, 2002	**First subject enrolled in BioVex Study 001-01 in the United Kingdom**
May 2005	**US IND 12412 active (sponsor BioVex)**
April 2008	**FDA Special Protocol Assessment granted for Phase 3 study 005/05**
April 2009	**First Subject enrolled in Study 005/05**
January 2011	**Fast Track designation granted**
March 2011	**Orphan drug designation granted, Sponsorship changed to Amgen,**
September 2013	**Data cutoff for Study 005/05**
October 2013	**Pre-BLA Meeting**
July 2014	**Final BLA Module 5 (clinical) submitted**
September 2014	**Standard BLA review timeline (10 months)**
November 2014	**BLA 120 Day Safety Update Submitted** **BLA major CMC amendment submitted- review clock extended by 3 months** **Breakthrough Request Denied (IND 12412)**
April 29, 2015	**FDA Advisory Committee meeting**

Source: FDA

3 Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review.

3.2 Compliance with Good Clinical Practices

The applicant provided adequate documentation that the research study conducted was in accordance with Good Clinical Practices.

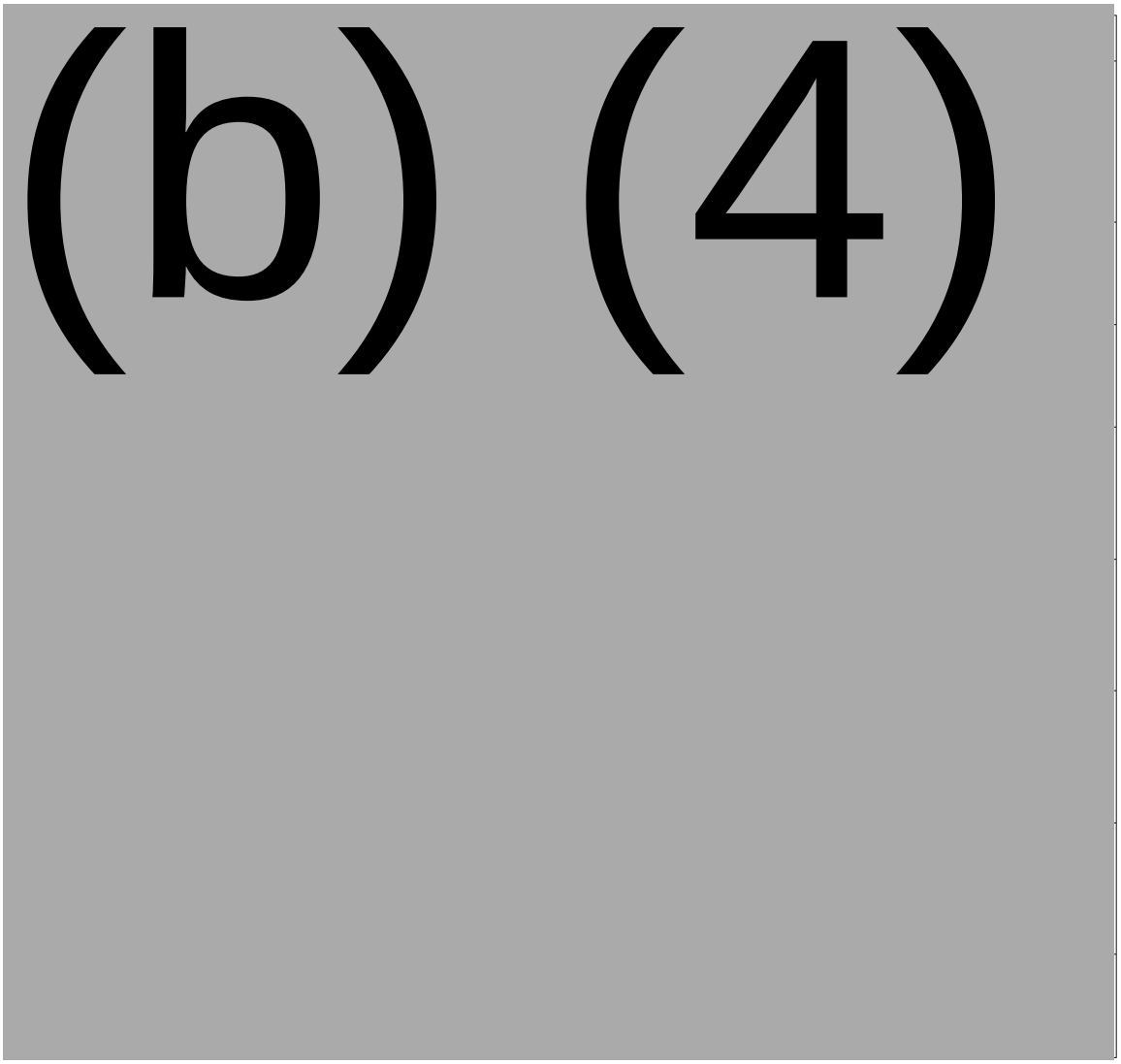
3.3 Financial Disclosures

Covered clinical study: Study 005/05, "A Randomized Phase 3 Clinical Trial to Evaluate the Efficacy and Safety of Treatment with OncoVEXGM-CSF Compared to Subcutaneously Administered GM-CSF in Melanoma Patients with Unresectable Stage IIIB, IIIC, and IV Disease"		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 310		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0 . No clinical investigators or sub-investigators who participated in Study 005/05 were full or part-time employees of BioVex or Amgen.		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0 .		
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0.		

3.4 Contract Research Organizations

Table 5 summarizes the contract research organizations participated in this study.

Table 5: Contract Research Organizations Participating in This Study



4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls

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 the Section 4.1.2 and Section 4.3.1.

4.1.1 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.

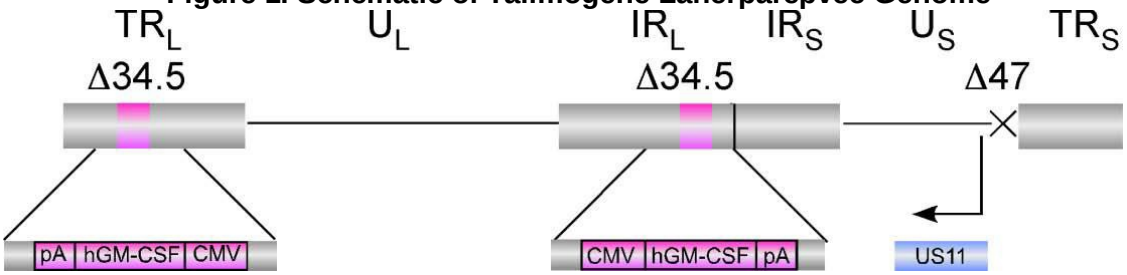
Some of these risks associated with using HSV-1 as an oncolytic viral product can be mitigated by introducing genetic mutations into viral genes associated with neurovirulence (e.g., ICP34.5) and immune response modulation (e.g., ICP47). These mutations attenuate the virus, while still preserving the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

4.1.2 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.

Pharmacologic Class:
In the BLA Submission, the applicant's proposed Pharmacologic Class was oncolytic immunotherapy. FDA reviewed the submitted information and established the Pharmacologic Class for talimogene laherparepvec. Talimogene laherparepvec is a genetically modified oncolytic viral therapy.

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 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.

4.2 Nonclinical Pharmacology/Toxicology

Intratumoral injection of the murine version (OncoVEX$^{mouseGM-CSF}$) of talimogene laherparepvec into syngeneic tumor-bearing mice resulted in reduction of tumor volume. Anti-tumor response was also observed in noninjected tumors that were distant to the injected tumor; however, this effect was notably reduced compared to the effect on the injected tumor. A T-cell-mediated immune response, measured by IFN-γ release, was observed in the mice.

Intratumoral injection of talimogene laherparepvec (i.e., the human version) into syngeneic tumor-bearing mice also resulted in reduction of tumor volume. Following injection, measurable levels of hGM-CSF were detected in the tumors, with low levels in the blood.

Following intratumoral injection of talimogene laherparepvec into mice bearing murine B cell lymphoma, viral DNA was predominantly present in the tumor, blood, and tissues likely associated with immune-mediated viral clearance (e.g., spleen). Low levels of viral DNA were detected in the brain and in highly perfused tissues; however, no abnormal histopathology findings were observed.

Systemic viral infection was observed following intratumoral injection of IMLYGIC in immunodeficient, tumor-bearing mice. Adverse findings in non-tumor tissues (e.g., gastrointestinal tract, brain) and body weight loss were also detected. These findings were consistent with the findings reported in immunocompetent or immunodeficient mice following wild-type HSV-1 infection.

No adverse effects on embryo-fetal development were observed following repeat intravenous administration of talimogene laherparepvec during organogenesis in immunocompetent pregnant mice at dose levels up to $4x10^8$ PFU/kg (approximately 60-

fold higher than the maximum clinical dose level specified in the label). Levels of talimogene laherparepvec DNA in pooled fetal blood were at or below the assay detection level. However, the relevancy of these data to humans is unclear due to study design limitations which included: 1) administration of talimogene laherparepvec expressing huGM-CSF, which is not biologically active in mice; 2) the transplacental kinetics of talimogene laherparepvec following intravenous administration in pregnant mice are not known; and 3) the significance of talimogene laherparepvec dose extrapolation from animal to human, based on body weight, is not known.

assay results indicate that talimogene laherparepvec is sensitive to acyclovir, potentially supporting use of acyclovir to mitigate adverse effects related to viral infection following administration of talimogene laherparepvec.

Genotoxicity, carcinogenicity, toxicokinetics / pharmacokinetics, safety pharmacology, and immunogenicity studies (http://www.ich.org/products/guidelines/safety/article/safety-guidelines.html) were not conducted, due to the nature of talimogene laherparepvec and the patient population evaluated in this BLA submission.

4.3 Clinical Pharmacology

4.3.1 Mechanism of Action

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.

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. The proposed therapeutic mechanism of action of talimogene laherparepvec is 2-fold. First, a direct oncolytic effect may be achieved following intralesional administration by viral replication in tumor tissue, resulting in tumor cell lysis and release of putative tumor-derived antigens. In addition, to promote the development of an anti-tumor adaptive immune response, the virally produced GM-CSF is expressed locally in order to promote the local maturation of antigen presenting cells which can take up released tumor antigens, travel to lymph nodes, and induce a systemic antitumor immune response following presentation to T-cells. This strategy may result in the destruction of injected and noninjected tumors (including micro-metastatic disease) and reduces the development of new metastases. Clinically, the intended biologic effects are delay or prevention of disease progression and relapse, and prolongation of OS.

Clinical Reviewers' Comments:
The applicant provided clinical data to support that talimogene laherparepvec induced destruction of injected as well as non-injected lesions; however information regarding systemic immune biological responses in humans was not submitted. The Study 005/05 did not collect immune response data to assess their correlation with clinical outcomes. The exact mechanism of action is not fully understood and additional studies are suggested to further elucidate the MOA and evaluate systemic effects.

4.3.2 Human Pharmacokinetics (PK)

Typical pharmacokinetic studies are not relevant for the oncolytic virus talimogene laherparepvec. Instead the pharmacology of talimogene laherparepvec is defined by the analysis of the biodistribution in the blood and urine and live virus shedding at time points post-injection. The biodistribution is discussed in Section 8.4.9.1 of this review.

4.4 Statistical

Please refer to Section 6.1.9 and Section 6.2.2 of this review and to the statistical review.

4.5 Pharmacovigilance

Talimogene laherparepvec is an oncolytic virus; therefore traditional pharmacokinetic studies to evaluate the absorption, distribution, and metabolism, elimination, and drug-drug interactions were not used. Instead, the virus was evaluated in the context of the site of intralesional injection and tumor-selective replication. The existing clinical safety database did not characterize potential talimogene laherparepvec associated herpetic infection due to the lack of definitive testing for causative infectious agent in suspected herpetic lesions. Talimogene laherparepvec associated herpetic infection in non-tumor tissue of treated patients (primary infection or reactivation/latency) and contacts (transmission/accidental exposure) will be further investigated in a prospective observational cohort study (protocol # 20130193) as a postmarketing requirement (PMR). In view of Amgen's Pharmacovigilance Plan, there are concerns regarding the ability of the proposed postmarketing study Amgen 20130193 to capture (with qPCR confirmation) cases of talimogene laherparepvec transmission to close contacts (CC)/health care providers (HCP), and cases of talimogene laherparepvec-associated symptomatic infection in the patient, should they occur, due to a multi-step lengthy process of sample collection and laboratory testing. In addition, limited talimogene laherparepvec viral shedding data makes it difficult to assess the risk of talimogene laherparepvec transmission to healthcare providers and close patient contacts. Talimogene laherparepvec viral shedding is under investigation from an ongoing single-arm clinical study (protocol # Amgen 20120324) to evaluate the biodistribution and shedding of talimogene laherparepvec in treated patients, and post-licensure, the study will be completed as a PMR."

5 Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

One Phase 3 trial supported this BLA application, a multicenter, randomized, open-label study of talimogene laherparepvec therapy compared to GM-CSF in subjects with unresectable stage IIIB, IIIC, and IV melanoma. The primary efficacy analysis for the BLA was based on the primary efficacy analysis set which includes data from Study 005/05 [n=436, intent-to-treat (ITT) population]. The supportive safety analyses set included data from the extension study protocol 005/05-E (n=30), the single-arm Phase 2 study for stage IIIC and IV melanoma (Study 002/03; n=50), and the extension protocol 002/03-E (n=3).

The clinical review focused on confirmation of the durable responses through examination of submitted case report forms (CRFs) and imaging data (including photographs) and correlation with other endpoints, such as overall survival, as well as an analysis of safety and shedding data to conduct an overall risk/benefit evaluation.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

IND 12412 eCTD documents and FDA reviews.

BLA 125518 eCTD documents, amendments 0-45, datasets, and imaging data.

Additional Imaging Data submitted in USB hard drives.

5.3 Table of Studies/Clinical Trials

The individual melanoma efficacy studies Talimogene laherparepvec are listed in Table 6:

Table 6. Description of Key Efficacy Studies in Melanoma

Study Number	Study Design	Study Population	Primary and Secondary Efficacy Endpoints	Region	Number of Subjects	Duration of Treatment
005/05	Phase 3, randomized, open-label, GM-CSF controlled	Unresectable stage IIIB, IIIC, or IV melanoma	Durable response rate[a] Overall survival Best overall response and disease burden Response onset Time to treatment failure Duration of response Response interval	US, Canada, South Africa, and UK	436 (ITT)[b]; 295 talimogene laherparepvec 141 GM-CSF	12 months (or 18 months if the subject was receiving clinical benefit)
005/05-E	Phase 3, open-label extension	Unresectable stage IIIB, IIIC, or IV melanoma	Overall response rate Durable response rate	US, Canada, South Africa, and UK	30; 27 talimogene laherparepvec 3 GM-CSF	12 additional months (or until disease progression if the subject was receiving clinical benefit)
002/03	Phase 2, open-label, single-arm	Unresectable stage IIIC or IV melanoma	Overall response rate[a] Time to tumor response Time to disease progression Overall survival	US and UK	50	Up to 47 weeks
002/03-E	Phase 2, open-label, single-arm extension	Unresectable stage IIIC or IV melanoma	Overall response rate Overall survival	US and UK	3	Up to 24 additional doses or 12 months of additional treatment, whichever was longer

[a]Primary endpoint [b]A total of 437 subjects were randomized; 1 subject who was randomized 3 times at 3 different study centers was excluded from the ITT population. Source: BLA eCTD section 2.7.3 Summary of Clinical Efficacy.

5.4 Consultations

FDA had a combined CTGTAC and ODAC meeting to discuss this BLA submission on April 29, 2015. Please refer to the Section 12.5 of this document for additional information related to Advisory Committee Meeting.

5.5 Literature Reviewed

Please also refer to the Section 2 of this document for additional literature related to melanoma. A list of references is located in Section 12.6 of this document.

6 Discussion of Individual Clinical Trials

6.1 Trial #1 (Study 005/05)

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

GM-CSF served as the comparator for the study assessing the effectiveness of talimogene laherparepvec for several reasons. Talimogene laherparepvec contains human GM-CSF gene sequences and, based on preclinical information, 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.

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

Clinical Reviewers' Comments:
The open-label design and different route of administration may have introduced bias in the study conduct and outcome assessments. GM-CSF may not have been ideal as a control since it was given subcutaneously (SQ), a different route of administration from talimogene laherparepvec that was given intralesionally. In addition the subcutaneous GM-CSF would not have controlled for mechanical effects of intralesional injection that might have ablated small lesions.

6.1.1 Design Overview

Study 005/05 was a Phase 3 multicenter, randomized, open-label study to assess talimogene laherparepvec monotherapy vs. GM-CSF in subjects with unresectable stage IIIB, IIIC, and IV melanoma. Subjects were randomized in a 2:1 allocation ratio to receive talimogene laherparepvec or GM-CSF. Randomization was stratified by known prognostic factors, including the site of first recurrence, stage of disease, presence of liver metastases, and prior nonsurgical melanoma treatment other than adjuvant therapy. Subjects with stage IV M1c disease were limited to no more than 40% of the total subjects in each treatment arm.

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 additional 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.

Primary endpoint was DRR: CR or PR rate for at least 6 months, and beginning at any point within 12 months of initiating therapy.

The objective response to treatment was evaluated by high resolution CT scanning and optionally by PET or PET/CT, high resolution ultrasonography, and clinical measurement (documented by photographs where possible) using modified World Health Organization (WHO) criteria (WHO, 1979). WHO criteria were modified for use in melanoma as discussed in Section 6.1.7 and Section 12.4 of this review. MRI scans could be used as clinically indicated. Tumors which could only be assessed by MRI were treated as non-measurable but evaluable. Representative biopsies were used to confirm the cellular composition of any residual pigmented or other masses suspected to no longer contain viable tumor where required to confirm response.

Subjects who had reached 9 months on therapy, CR, or PR as determined by the investigators were evaluated by an independent EAC. This committee reviewed blinded source documents including imaging studies, clinical measurements, histology reports, and photographs to determine response status for the purpose of efficacy analysis. The EAC's final conclusions with respect to response status were used in the primary analysis. The composition, responsibilities and functioning of the EAC are described in the Charter for that committee. (Section 6.1.8.1)

Overall survival was one of the secondary endpoints. The other secondary endpoints included overall response rate, duration of response, time to treatment failure, best response, disease burden, response onset and response interval. Exploratory endpoints included impact of response on survival, patient-reported quality of life and BRAF mutation status.

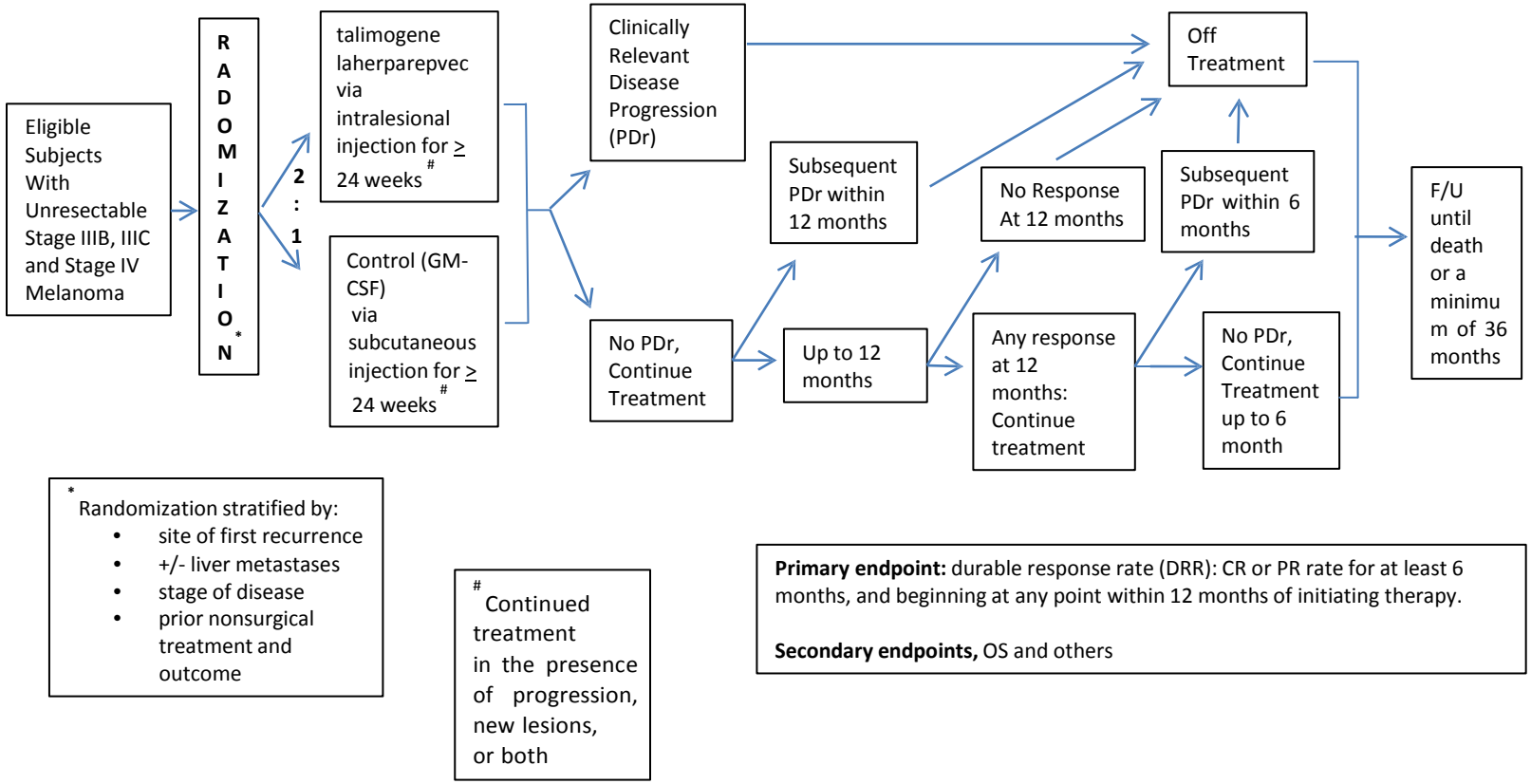
Subjects with stable disease for > 9 months were eligible for central review of tumor response; however, the results of the central review were not available to the investigator to make treatment decisions. Thus, subjects with stable disease at 12 months were also allowed to remain on treatment for up to an additional 6 months if the investigator determined that the subject was likely to continue to receive benefit from additional treatment.

Subjects were followed for response duration for at least 12 months after randomization (or, if a subject was in response at the 12-month time point, until 18 months if it was possible for them to be in response per EAC at 12 months, or disease progression, whichever was earlier).

Clinical Reviewers' Comments:

Subjects were to receive treatment until week 24 (even in the presence of disease progression, including appearance of new lesions). However, a subject could discontinue the treatment before Week 24 if the subject had a complete response, all injectable lesions disappeared, the subject developed intolerable toxicity, the investigator believed that it was in the best interest of the subject to change therapy, or the subject withdrew consent. Some of these criteria to discontinue treatment were subjective, and could have been easily influenced by investigators or subjects in this open-label trial. Early drop-outs from the GM-CSF arm resulted in imbalance in the duration of treatment and opportunities for outcome assessments. This imbalance in follow-up led to some difficulty in interpreting the study results.

Figure 2. Study Design and Follow-up



Clinical Reviewers' Comments:

1. The strengths of the study design included

a) Reasonable supporting information from early trials: the dose and regimen had been evaluated in a Phase 1 study, and the statistical assumptions and study population were based on a Phase 2 study in which 3 CR (9.6%) and 3 PR (9.6%) were reported for an ORR of 19.2% of 31 evaluable subjects.

b) Study 005/05 was randomized, controlled, stratified by prognostic factors.

c) The WHO response criteria were developed in the 1970s; partial responses were defined as a 50% reduction in the sum of the products of measurable lesions. RECIST response guidelines simplified the analysis by comparing the sums of the longest diameters of the tumors (Therasse et al., 2000). Either method was considered acceptable for regulatory purposes by FDA however the WHO criteria had been used in a previous licensing study for melanoma.

2. Weaknesses of the study design that could limit interpretation of the data included

a) The open-label study design which could lead to bias due to more study discontinuations on the GM-CSF arm.

b) The acceptability of subcutaneous GM-CSF as the control treatment. It is unclear whether GM-CSF, as administered in this study, was reasonably likely to have had any therapeutic activity.

c) The primary endpoint, rate of CR or PR lasting continuously for 6 or more months, was based on a modified WHO criteria to allow the treatment in the presence of new lesions and progression of existing lesions. Although it was agreed under an SPA in 2008, this endpoint has not been used in any prior FDA approvals.

d) The primary endpoint of response rate may not be a direct measure of clinical benefit.

e) In addition, bias could be introduced by the fact that only subjects chosen by the investigators were evaluated by the EAC for tumor response. Only data from subjects who had reached > 9 months on therapy, or CR, partial response PR as determined by the investigators were evaluated by EAC for tumor response. In an unblinded study the investigators may overestimate the response rates in the experimental arm.

6.1.2 Population

6.1.2.1 Inclusion Criteria

1. ≥ 18 years.
2. Histologically confirmed diagnosis of malignant melanoma.
3. Stage IIIB, IIIC or stage IV disease that was not surgically resectable.
4. Measurable disease defined as:
   - at least 1 melanoma lesion that could be accurately and serially measured in at least 2 dimensions and for which the greatest diameter was ≥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 had 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 had 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 >4 months from the date of randomization.
9. Provided written informed consent in accordance with all applicable regulations and followed the study procedures. Patients were capable of understanding the investigational nature, potential risks and benefits of the study.
10. Adequate organ function determined within 4 weeks prior to randomization,

6.1.2.2 Exclusion Criteria

1. Clinically active cerebral or any bone metastases. Subjects with up to 3 (neurological performance status of 0) cerebral metastases may be enrolled, provided that all lesions had been adequately treated with stereotactic radiation therapy, craniotomy, gamma-knife therapy, with no evidence of progression, and had not required steroids, for at least two months prior to randomization.
2. Greater than 3 visceral metastases (this did not include lung metastases or nodal metastases associated with visceral organs). For subjects with ≤ 3 visceral metastases, no lesion >3 cm, and liver lesions met 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 >5 years. In the case of malignancies that were diagnosed at a stage where a definitive therapy resulted in near certain cure, a disease free interval of <5 years was permissible. The Medical Monitor approved such subjects.
5. Primary ocular or mucosal melanoma.
6. Evidence of immunosuppression for any reason.
7. Baseline prolongation of QT/QTc interval (QTc interval >470 msec).
8. Open herpetic skin lesions.
9. Pregnant or breast-feeding female. Confirmation that women of child-bearing potential were not pregnant. A negative serum or urine β-human chorionic gonadotropin (β-hCG) pregnancy test result was to be obtained during the screening period.
10. Fertile males and females who were unwilling to employ adequate means of contraception (e.g., condom with spermicide, diaphragm with spermicide, birth control pills, injections, patches, or intrauterine device) during study treatment and through 30 days after the last dose of study treatment.

Clinical Reviewers' Comments:

1. *Inclusion of subjects with multiple lesions totaling 10 millimeter or larger in aggregate could allow enrollment of subjects who had only small or very small individual lesions, raising the concern regarding the feasibility of accurate injection and the accuracy in lesion assessment for response.*

2. *The Study 005/05 included subjects with distantly metastatic melanoma in the study of talimogene laherparepvec administered intralesionally. The applicant's proposed mechanism of action of talimogene laherparepvec included possible systemic antitumor immune response that could result in the destruction of injected and non-injected tumors and reduces the development of new metastases. However, the exact mechanism of action is not fully understood.*

3. *The subjects were restaged at the time of enrollment. Since 96% of subjects in the study had recurrent disease, the stage IIIB or IIIC shown here may not have been the stage at initial melanoma diagnosis. Most (96%) of subjects in the clinical trial had recurrent disease at entry. Therefore, the results of the subgroup analyses presented in this BLA for subjects with these stages may not be applicable to patients who are initially diagnosed with stage IIIB and IIIC melanoma. The study enrolled only subjects with unresectable melanoma; however, the applicant's proposed indication does not limit the patient population to individuals with unresectable melanoma.*

6.1.3 Study Treatments or Agents Mandated by the Protocol

Talimogene laherparepvec was formulated in phosphate buffered saline and a sugar stabilizer in a sterile frozen liquid single-use 2.0 mL [redacted]. Each vial contained talimogene laherparepvec at a nominal concentration of 10^{o} plaque forming units (PFU)/mL or 10^{8} PFU/mL in solution for intralesional injection into cutaneous, subcutaneous, and nodal lesions. The initial dose of talimogene laherparepvec was up to 4 mL of 10^{6} PFU/mL followed 3 weeks later by up to 4 mL of 10^{8} PFU/mL ; thereafter, subsequent doses of up to 4 mL of 10^{8} PFU/mL were administered every 2 weeks (Table 7). Each treatment cycle was defined as 28 days; however Cycle 1 was 5 weeks (second injection 3 weeks after the initial injection).

All reasonably injectable lesions [cutaneous, subcutaneous (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.

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 based on the determination shown in Table 8 below.

The control product granulocyte macrophage colony-stimulating factor (GM-CSF) was to be administered at a dose of 125 $\mu g/m^2$/day subcutaneous for 14 days, followed by a 14-day rest period. Each cycle was defined as 28 days.

Table 7. Treatment Regimens

Product	Details
talimogene laherparepvec	Intralesionally injected
Initial dose	Up to 4 mL of 10^6 plaque forming units (PFU)/mL (+/- 0.5 log),
Second dose	Up to 4 mL of 10^8 PFU/mL (+/- 0.5 log), 3 weeks later
Subsequent doses	Up to 4 mL of 10^8 PFU/mL (+/- 0.5 log), every 2 weeks
Accelerated dosing	for the progressing lesion(s) only, every 1 week
GM-CSF	125 µg/m^2/day SC for 14 days, followed by a 14-day rest period

Source: Reproduced from BLA Submission.

Clinical Reviewers' Comments:

1. *In Study 005/05, talimogene laherparepvec was injected into cutaneous, subcutaneous, and nodal lesions. Dosing Regimen for talimogene laherparepvec was complicated. The investigators decided the volume to inject based on an algorithm, frequencies of injection, and lesions to inject, leading to potential variability in the dosing regimen. In addition, there were variations in the product concentration for initial vs. subsequent doses, dose volume, and dosing schedules. Such a dosing variability could lead to considerable uncertainty in determining a safe and effective dose and schedule.*

2. *In contrast, GM-CSF, was given subcutaneously, which may not have been an optimal comparator for assessing the efficacy of intralesional talimogene. Due to lack of an intralesional injection control, it was conceivably possible that the mechanical effects of intralesional injection might have ablated small lesions that were allowed in the study, leading to a response of these lesions, not due to a treatment effect from talimogene laherparepvec.*

6.1.4 Objectives

The primary objective of the study was to achieve a statistically significant improvement in DRR, defined as the rate of CR or PR lasting continuously for 6 or more months, and initiating at any point within 12 months of starting therapy.

The secondary objectives of the study were to evaluate OS, response onset, time to treatment failure, duration of response, best response and disease burden, and response interval in subjects treated with talimogene laherparepvec or GM-CSF.

Clinical Reviewers' Comments:

As previously noted, at time of protocol initiation, no therapies were available with a demonstrable OS advantage for the study population. DRR at the time of protocol submission was considered to be an acceptable primary study endpoint. Subsequently ipilimumab for intravenous Injection was approved on the basis of a survival advantage for treatment of patients with unresectable or metastatic melanoma.

6.1.5 Directions for Use

6.1.5.1 Treatment in the Presence of New Lesions and Progressive Disease

If any injected lesion progressed, the injection frequency could have been 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.

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 below. 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 8. 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

6.1.5.2 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:
  - Complete response (disappearance of all disease)
  - All injectable tumors disappear
  - Intolerable toxicity
  - The investigator believed that it was in the best interest of the subject to stop treatment or to be given other therapy for melanoma.
  - Subject withdrew consent

  If any of the first four events listed above 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, then the subject discontinued study treatment, and no 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 above events 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 in complete 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 above events 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 subject was randomized, or until the last subject had died, whichever was earlier (Figure 2).

6.1.6 Sites and Centers

Study 005/05 was conducted at 64 centers in the United States, Canada, South Africa, and United Kingdom. A list of study centers and principal investigators is provided in the BLA submission.

CBER conducted Bioresearch Monitoring Inspections at four clinical study sites that enrolled subjects in support of this BLA, based upon numbers of subjects enrolled, previous inspectional history, numbers and types of adverse events, numbers and types of protocol deviations, and geographic location. The inspected sites represented approximately 13% of the 437 total randomized subjects. Bioresearch Monitoring inspections at the four clinical sites did not reveal substantive problems that impact the data submitted in the BLA.

In 2012, prior to the BLA submission, a BIMO inspection for the IND 12412 Study 005/05 was conducted at Site 066, in response to a complaint regarding the clinical investigator's alleged mismanagement of the study, failure to adhere to Good Clinical Practices, and the lack of data integrity in Study 005/05. The inspection identified significant problems at this site that could potentially impact the data submitted to the BLA. These problems included, but were not limited to, failure to protect the rights of the subjects, failure to follow the study protocol, and failure to maintain adequate records. This site contributed 25 subjects to the ITT analysis set. Only one subject among these 25 subjects was reported to be a durable responder. FDA determined that this subject should not qualify as a durable responder due to too many missed visits. Excluding this site from the ITT analysis set does not lead to material change of the conclusions on the DRR and OS endpoints. For example, the OS primary analysis excluding this site has a p-value of 0.056, compared to 0.051 with the ITT set. Therefore, the review team decided to include the results from the 25 subjects at Site 066 in the ITT analysis, but excluding the durable responder reported by the applicant.

6.1.7 Surveillance/Monitoring

Response Assessments by Investigators:

Efficacy was to be based on physical measurement of the tumor, photographs of superficial lesions, ultrasonography of nodal masses (or other soft tissue masses), representative biopsy of residual pigmented areas or other residual masses suspected to no longer contain tumor, and imaging studies.

Disease assessments were to be performed at the beginning of each treatment cycle, and assessed in accordance with modified World Health Organization (WHO) criteria [WHO handbook for reporting results of cancer treatment. Geneva (Switzerland) (WHO, 1979)] using two-dimensional measurements. All objective responses were to be confirmed on 2 separate measurements no less than 1 week apart.

All measurable lesions were to be assessed by the same method used at baseline, as far as possible (e.g., if the character of a tumor changes such that it was no longer measurable by CT, it may be measured by ultrasound if more appropriate).

After two cycles of therapy, a thorough assessment of the clinical response status in both treatment groups was done, particularly to determine if any evidence of biological activity of treatment could be observed. In particular, signs of tumor shrinkage, flattening, necrosis, erythema, or inflammation in individual or multiple tumors, and any signs of vitiligo were noted, together with other prospectively defined response parameters as described in this protocol. This was because, after two cycles of therapy subjects who left the study for any reason would be deemed evaluable for efficacy as part of the per protocol (PP) population, and it was thus important to determine whether there was any evidence of drug activity at that time.

CT scans of the chest, abdomen, and pelvis and all other areas where disease was noted at screening or baseline, sites where disease subsequently appeared (e.g. upper or lower extremities, neck), and ultrasonograms of nodal or other soft tissue masses where required to assess disease should be performed every 12 weeks from the start of therapy. If a response was suspected to have initiated since the last visit based on clinical assessment, CT scans and any other confirmatory procedures were to be performed within one week. Magnetic resonance imaging of the brain was to be performed every 16 weeks (or at any time when in the judgment of the investigator the subjects displayed signs or symptoms of CNS disease progression). For subjects who reached 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 was to be performed and representative biopsies taken from residual masses, as far as was clinically justified and feasible, to aid in determining their status.

If subjects developed central nervous system PD (PDcns), they were allowed to remain on study provided CNS lesions were treated with stereotactic radiotherapy (SRS), Gamma-Knife, or craniotomy. Subjects could continue to receive study drug following SRS while receiving dexamethasone or a similar corticosteroid (i.e., no more than 1.5 mg dexamethasone). If higher doses of dexamethasone were used, study drug should be held until that dose level was reached during the period of steroid tapering.

Measurability was categorized in the WHO Handbook. Measurability was defined as 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. An individual lesion measure was therefore provided by the product of a tumor's longest diameter and the diameter perpendicular to that. The overall measurable tumor burden was determined by the sum of these products for all measurable lesions.

6.1.7.1 Patient Assessments

Subjects were to undergo the assessment procedures to evaluate melanoma tumor status, described in Table 9 with the frequencies shown in Table 10.

6.1.7.2 Lesion Definition

Lesions were divided 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.

6.1.7.3 Lesion Assessments

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

Table 9. Subject Lesion Assessment Modalities

	Details
	Clinical measurements were to be 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
	Whole body (i.e., including the head and both upper and lower extremities in addition to chest, abdomen and pelvis) scans should have been 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 have been 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 of nodal or other soft tissue masses could be performed at baseline as clinically indicated. Ultrasonograms 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 could be used for soft tissue lesions which were not effectively imaged by 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 have been performed and representative biopsies taken from residual masses, as far as was clinically feasible, to aid in determining status.
	Brain MRIs were required at screening for all subjects. MRI of the brain should have been 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 10. 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 (Chest/Abdomen/Pelvis) and CT of any other areas where disease was noted at baseline or where disease 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

6.1.7.4 Measurable Lesions

a. For lesions present at baseline: tumor burden for all measurable lesions were 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 were calculated and compared with the tumor burden at baseline, according to the assessment criteria described below.

b. 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 was measured at the three different times when each lesion had first appeared.

c. Response Criteria for lesion assessment (World Health Organization Criteria):
   i. Complete Response (CR):
      a. Tumor burden for lesions present at baseline decreased by 100%, and
      b. Tumor burden for new lesions decreased by 100%
   ii. Partial Response (PR)
      a. Tumor burden for lesions present at baseline decreased by 50%, and
      b. Tumor burden for all new lesions decreased by 50%.

   iii. Stable Disease (SD): Neither sufficient overall tumor shrinkage to qualify for response (PR or CR) nor sufficient tumor increase to qualify for PD.
   iv. Progressive Disease (PD): A greater than 25% increase in the sum of the products of the perpendicular diameters of all measurable tumors since baseline, or the unequivocal appearance of a new tumor since the last response assessment time point.

d. 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.

e. Clinically relevant progressive disease (PDr): PD that was 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 was warranted.

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

6.1.7.5 Non-measurable Lesions

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

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

6.1.7.6 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 as shown in Table 11 below.

Overall response evaluation was performed by the investigators at the beginning of each treatment cycle or subsequent to study withdrawal according to Table 11 below.

Table 11. 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.

Lesion response was categorized as CR, PR, Stable disease (SD) or progressive disease (PD) according to modified WHO tumor response criteria using bi-dimensional measurements.

Clinical Reviewers' 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. Thus, overall melanoma response evaluation was performed based on integrated assessments of all measurable lesions, including those present at baseline, any new lesions that developed during treatment, and non-measurable but evaluable lesions. The DRR endpoint was agreed under the SPA.

6.1.8 Endpoints and Criteria for Study Success

6.1.8.1 Primary Endpoint: DRR

The primary endpoint was DRR, defined as the percentage of subjects with CR or PR maintained continuously for at least 6 months from the time the response was first observed and initiating at any point within 12 months of starting therapy. Subjects were assessed for response by the investigators and those subjects who had CR, PR, or stable disease > 9 months as determined by the investigators were subsequently to be evaluated by the EAC for tumor response.

Criteria for Study Success:
The primary analysis of DRR and all response based endpoints occurred when no further subjects had the possibility of meeting the criteria for durable response, or all subjects reached 18 months from first dose (whichever is the earlier). The primary analysis of DRR was a two-sided unadjusted Fisher's exact test. Study success was defined as the test being statistically significant at the 0.0488 level. A significance level of 0.0488 was used because of plans for interim analysis (IA).

Assessment Algorithm by EAC:
Primary efficacy endpoint data were reviewed by a committee consisting of board certified oncologists that had experience treating subjects with melanoma, and were blinded to treatment assignment. Two reviewers performed an independent assessment of response status at each visit for subjects triggered for EAC review in both treatment arms (i.e., subjects for whom a CR or PR was recorded by the investigator or who reached 9 months on study without a response having been recorded). The EAC was responsible for determining whether subjects were in response (CR or PR) defined by WHO criteria (i.e., as per Study 005/05) at each response assessment time point. If there was disagreement between reviewers as to whether a subject was in response, whether the response was a CR or PR, and/or the date of response, a third independent EAC member, the adjudicator, provided the final determination of the results. All measurable lesions were to be evaluated, and the EAC reviewed all available data in making their assessments, including physical measurements of the tumor, photographs of superficial lesions, ultrasonography of nodal masses (or other soft tissue masses), representative biopsies of residual pigmented areas or other residual masses suspected to no longer contain tumor, and imaging studies.

The primary endpoint results were based on the EAC's decisions. Subjects without an EAC assessment were considered non-responders in the ITT analysis. The data reviewed by the EAC included information up to 18 months after the first dose of investigational product for each subject, which included data from the extension protocol (Study 005/05-E) for some subjects. For the primary analysis, only data from the parent Study 005/05 were included; a sensitivity analysis was conducted including all available EAC assessments. For all analyses, only tumor response assessments and individual tumor measurements prior to the first subsequent anti-cancer therapy were included in the analysis.

Information Used for EAC Review

The EAC received the following information for each subject for whom review was required:

1.Blinded clinical listings will contain the following data:

a. Prior non-surgical management
b. Medical history of cancer
c. ECOG performance status
d. Prior surgery related to cancer
e. Subsequent cancer therapy
f. Biopsy of residual lesions including histology
g. Benign lesion data
h. Conversion of disease to suitable for surgical resection
i. Concurrent Medical Procedures

2. Histology reports

3. Blinded, central radiology listings

The listing of the bi-dimensional tumor measurements for all tumors per visit as determined by relevant imaging modalities by WCC and recorded in WorldPro on the IR eCRF for each visit.

4. Blinded, central photography listings

The listing of the bi-dimensional measurements of all tumors visible on photographs as assessed by the blinded dermatologist for each visit and recorded in WorldPro on the photography eCRF.

5. Suggestions as to which of the tumors assessed by each modality may be duplicates of each other (i.e. are present on more than one modality) to be confirmed by the EAC.

6. Prior Assessments

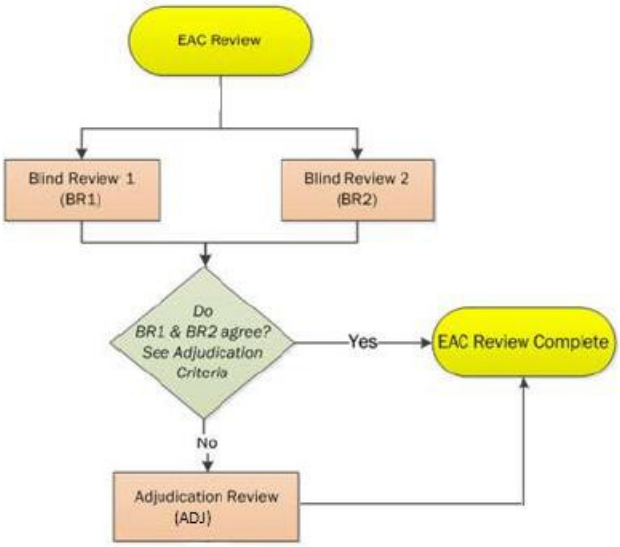
a. EAC reviewers were to have access to all relevant scans, photographs and clinical measurements taken by the site for the subject whose data was being reviewed.
b. If a prior batch review was adjudicated, only the CRFs from the adjudicator would be available for review.
c. Otherwise, if a prior batch review (BR) was not adjudicated, the data from BR1 CRFs would be made available for review
d. All assessments of new tumors and measurement changes from Baseline would use the information recorded on the available prior CRFs as a reference.

When residual tumors were biopsied, it was at the discretion of the EAC if these and all tumors for which they were representative (i.e. which appeared similar by radiology, photography or clinical assessment) were included. If tumors were resected and concluded not to contain viable tumor tissue (by histology or judged by the EAC), the resected tumor measurements would be measured as (0.00 x 0.00) on the resected visit but remained in the sum of bi-dimensional measurements at baseline or when they first appeared. On the other hand, if resected tumors were judged to contain viable tumor tissue or histology was not performed to indicate that a resected lesion was tumor free, the lesion would be removed from the sum of bi-dimensional measurements at baseline or when they first appeared, at the resected visit and at all subsequent visits as well.

EAC Review Process

The EAC members were consisted of up to three oncologists. The reviewers should review all data provided, up to and including that visit.
All data as specified above for each subject visit requiring review should be provided to each EAC primary reviewer (i.e. blinded reviewer BR1 and BR2) for independent assessment of response status at that visit. See Figure 3 below.

Figure 3. EAC Review Workflow



Source: Original BLA 125518-Clinical Study Report: 005/05 EAC Charter, Page 47.

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 to be 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.

Investigators performed the initial overall melanoma response evaluation for all subjects but only sent to the EAC information for subjects who had reached 9 months on treatment or subjects who had CR, or PR. The EAC then independently chose the measurable or non-measurable lesions for assessment of response that could differ from the lesions chosen by the investigators.

Clinical Reviewers' Comments:

1. *The EAC performed lesion response and overall melanoma response evaluation according to the schema described above. 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*.

2. *As per the applicant, the purpose of using an EAC to review the primary endpoint was to minimize the potential for bias for the open-label study. However, the EAC only reviewed a subset of subjects' results. The investigators determined which subjects' results were reviewed by EAC. This may have introduced bias.*

6.1.8.2 Secondary Endpoint: OS

OS 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.

6.1.8.3 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.

6.1.9 Statistical Considerations & Statistical Analysis Plan

The primary analysis of the primary endpoint, DRR, was performed using the ITT analysis set, which was to consist of all subjects who were randomized to study treatment. A 2-sided unadjusted Fisher exact test was used to determine whether talimogene laherparepvec improved DRR relative to GM-CSF. Overall survival as a secondary endpoint was tested only if DRR was found to be statistically significant. Overall survival, response onset, time to treatment failure, duration of response, and response interval were estimated according to the Kaplan-Meier method and compared using a log-rank test. Best response and disease burden were summarized by treatment arm, and best tumor reduction was compared using a [redacted] test. Descriptive statistics were provided for all safety endpoints.

Randomization:

Subjects were randomized 2:1 to talimogene laherparepvec or GM-CSF, stratified by

a. Site of first recurrence (3 levels): in transit or distant skin, lymph node, visceral.
b. Presence of liver metastases (2 levels): no, yes.
c. Stage of disease (3 levels): IIIB/C, IVM1a or IVM1b, IVM1c.

d. Prior treatment and time to recurrence (3 levels):
   i. No prior nonsurgical melanoma treatment other than adjuvant therapy,
   ii. Prior nonsurgical melanoma treatment other than adjuvant therapy and recurrence less than 1 year from primary diagnosis,
   iii. Prior nonsurgical melanoma treatment other than adjuvant therapy and recurrence more than 1 year from primary diagnosis.

Sample Size:
The applicant planned to randomize 430 subjects, to yield 360 evaluable subjects at 2:1 ratio in the talimogene laherparepvec versus the GM-CSF 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% (GM-CSF), 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.

Data Monitoring Committees:

An independent Data Monitoring Committee (DMC), composed of multidisciplinary experts external to Amgen, was responsible for reviewing the progress of the study at regular intervals to ensure patient safety and study integrity. The chairman of the DMC monitored serious adverse events on a regular basis. Three interim analyses were to be scheduled to compare the incidence of adverse events between treatment arms, including deaths. In the event that unanticipated safety concerns or efficacy advantages of talimogene laherparepvec emerged as a result of the data review, the DMC could recommend suspending or reducing accrual to the study, as well as assigning prior or future control subjects to talimogene laherparepvec.

Analysis of 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.

Analysis of OS:

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

a. 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.
b. 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.
c. 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.

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 GM-CSF arm). The alpha for this IA was set to a 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 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 a 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 spending 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.

6.2 Results

Study Period: 29 April 2009 (date first subject enrolled) to 21 December 2013 (data cutoff date); no subjects were still receiving treatment as of the cutoff date for this BLA submission. Subjects in whom treatment beyond the maximum number of doses allowed in Study 005/05 was warranted if the investigator decided to extend the protocol treatment (005/05-E).

6.2.1 Study Population and Disposition

6.2.1.1 Populations Enrolled/Analyzed

Demographics

Baseline demographics for the ITT population are summarized in Table 12.
There were 295 subjects enrolled in the talimogene laherparepvec arm, and 141 subjects enrolled in the GM-CSF arm. 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 GM-CSF arms and were similar across the ITT

population, first-line therapy population, second-line population, and the per-protocol population. Most subjects (96%) 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 12.

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.

Table 12. Demographic Characteristics

	Talimogene laherparepvec (n = 295)	GM-CSF (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 IIIC IV M1a IV M1b IV M1c	 22 (8%) 66 (22%) 75 (25%) 64 (22%) 67 (23%)	 12 (9%) 31 (22%) 43 (31%) 26 (18%) 29 (21%)
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.

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 GM-CSF group who had prior surgery before enrollment to the study (Table 13).

Table 13. Summary of Prior Therapies

CATEGORY Subcategory	Talimogene laherparepvec n = 295 (%)	GM-CSF 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.

Clinical Reviewers' Comments:

1. The Baseline demographics were generally balanced between the talimogene laherparepvec and GM-CSF arms.

2. BRAF status was unknown for two thirds of the subjects in both arms. However, in the current practice, therapy for melanoma patients is usually guided by BRAF status. Therefore, the results may not be applicable to the current clinical practice.

6.2.1.2 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 GM-CSF 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 GM-CSF).

As of the primary analysis cutoff date, all ITT subjects had discontinued from study treatment. Table 14 lists the reasons for discontinuation of study treatment. The most common reason was progressive disease (Table 14).

Table 14. Subject Disposition

	Talimogene laherparepvec n = 295 (%)	**GM-CSF 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 - Reasons		
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 and applicant's response on 3-17-2015]

Table 14 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 GM-CSF arm than in the talimogene laherparepvec arm, at 9.9% versus 1.4%. These 14 subjects in the GM-CSF arm and 4 subjects in the talimogene laherparepvec arm were designated as non-responders and not assessed for tumor response.

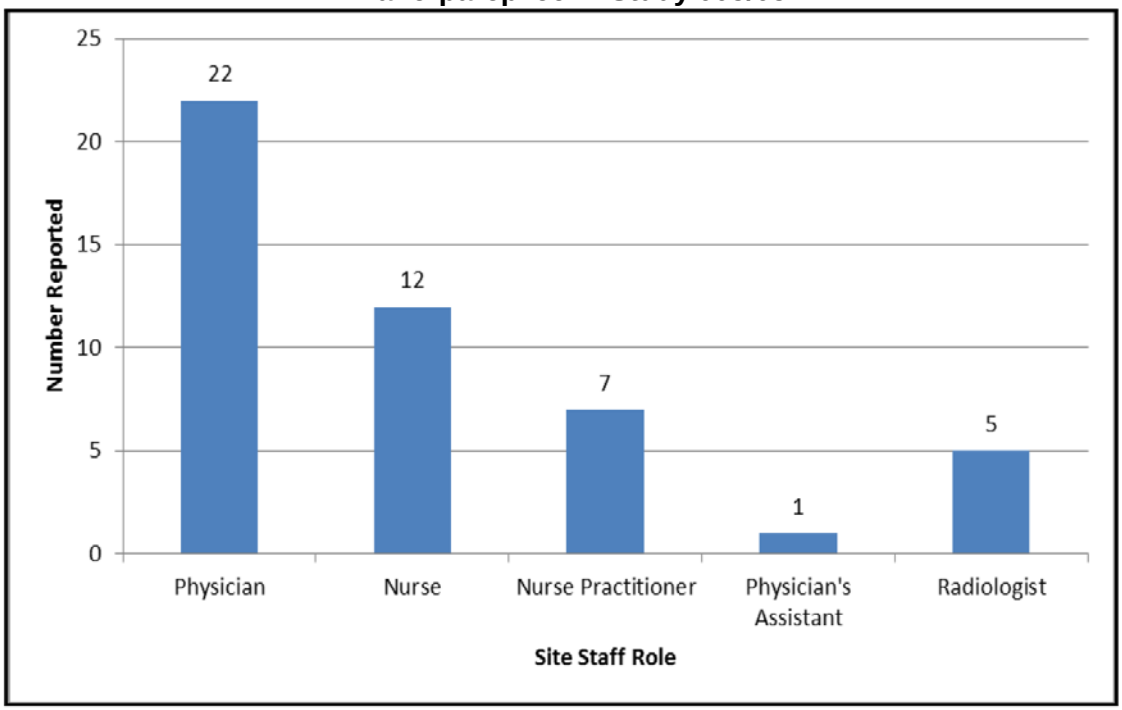
Clinical Reviewers' Comments:
The fact that more subjects did not receive the GM-CSF treatment may be due to the open-label trial design and may have biased the results to favor the talimogene arm, in terms of assessment. One subject who was randomized 3 times at 3 different study centers was excluded from the ITT population. Four (1.4%) subjects in the talimogene arm never received talimogene, and 14 (9.9%) subjects in the GM-CSF arm never received GM-CSF.

6.2.1.3 Injections of Talimogene Laherparepvec

The injections of talimogene laherparepvec were done by physicians, surgeons, physician assistants, nurses or nurse practitioner under the direction of the principal investigator in accordance with local standards. Injections of talimogene laherparepvec were performed with or without ultrasound guidance. Administration using CT guidance was not allowed in this protocol. Ultrasound was used to measure lesions in approximately 9% of subjects. Radiologists could also assist with performing injection under ultrasound guidance.

Figure 4 below provides the available information from 32 sites in the US regarding who performed the injections of talimogene laherparepvec in study 005/05. This information is based upon delegation of authority logs found in the site master file. Information from 15 US sites that enrolled at least one subject was either not available or was not reported.

Figure 4. Health Care Provider That Performed the Injections of Talimogene Laherparepvec in Study 005/05



*US = United States (32 sites)
Source: BLA submission eCTD.

6.2.1.4 Study Conduct

Regarding Study Conduct, the BLA applicant submitted information about eligibility violations for 7 subjects in the GM-CSF arm and 26 subjects in the talimogene laherparepvec arm.

The applicant also submitted information about protocol deviations including missing more than one clinical assessment in 5 subjects on talimogene laherparepvec arm; and protocol deviations about missing scans or prohibited meds.

FDA analysis showed that 9 subjects on the talimogene laherparepvec arm and 4 subjects on the GM-CSF arm missed more than 1 sequential response assessments.

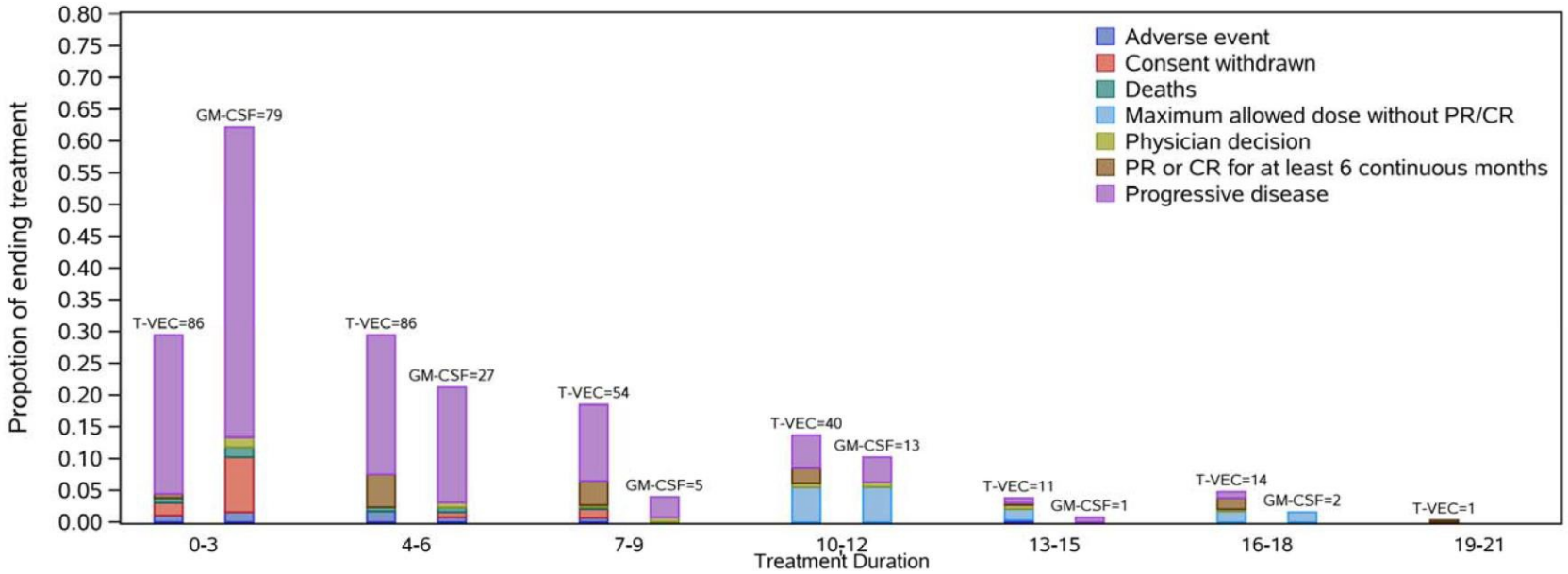
Protocol Deviations

Most protocol deviations were about eligibility violations and missing scans. Eligibility violations were reported for 26 subjects in the talimogene laherparepvec arm and seven subjects in the GM-CSF 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 GM-CSF arm. FDA analysis showed that nine subjects in the talimogene laherparepvec arm and four subjects in the GM-CSF arm were missing more than 1 sequential response assessment. FDA analysis of protocol deviations found that they had a minor effect on the study results.

Study Discontinuations

Figure 5 summarizes end of treatment reasons by treatment duration. FDA review found that there were more subjects in the GM-CSF arm who stopped treatment at or before 3-month follow up time-point, than those in the talimogene laherparepvec arm. This imbalance in study discontinuations in the 2 arms could have created bias in terms of assessment of responses to favor the talimogene laherparepvec treated subjects.

Figure 5. End of Treatment Reason by Treatment Duration



Source: Original BLA eCTD ISS (Integrated Summary of Safety).

Table 15 illustrates the marked difference in study discontinuations in the first three months when the talimogene laherparepvec arm was compared to the GM-CSF. At 6 months, the drop-out rate increased in the talimogene laherparepvec arm and by 9 months the rates were equivalent.

Table 15. 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%)
GM-CSF	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).

If a subject withdrew from treatment before clinically relevant disease progression (PDr) after Week 24, he or she should have returned for the End of Treatment (EOT)/Early Termination visit and then undergone long-term follow-up every 3 months to assess survival until End of Study (EOS; 36 months after the date the last subject enrolled was randomized, or until the last subject died, whichever was earlier). However, the protocol did not have clear provisions for tumor response assessment after discontinuation of study treatments if discontinuation occurred before Week 24. Therefore, the comparatively much higher percentage of subjects in the GM-CSF arm who discontinued study treatment by Week 24, suggests that GM-CSF subjects may have been assessed for tumor response for a shorter time than talimogene laherparepvec subjects. For example, eight (5.7%) of the GM-CSF group subjects, but none of the talimogene laherparepvec group subjects, had their last tumor assessment within the first 28 days.

Clinical Reviewers' Comments:
This differential follow-up may have influenced the study results for the primary endpoint, and may have also influenced the study safety results in favor of talimogene laherparepvec.

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." However, Table 15 illustrates the marked difference in study discontinuations in the first three months when the talimogene laherparepvec arm was compared to the GM-CSF. At 6 months, the drop-out rate increased in the talimogene laherparepvec arm and by 9 months the rates were equivalent.

Table 15 lists, in 3-month increments, the number of subjects who discontinued study treatment. There were more GM-CSF 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, which would favor the talimogene laherparepvec arm.

6.2.1.5 Surgical Interventions During Study

Two subjects in the talimogene laherparepvec arm received surgical treatment for melanoma during the course of the study, which rendered both subjects to have a complete response.

6.2.2 Efficacy Analyses

The primary efficacy analysis for the BLA is based on the ITT population primary efficacy analysis set which includes data from Study 005/05 (n=436, ITT population).

6.2.2.1 Analyses of Primary Endpoint

6.2.2.1.1 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 GM-CSF arm subjects. For this endpoint, the minimum follow-up time, calculated from the date of the last randomization to the data cutoff date, was 17.1 months.

The investigators identified 56 durable responders in the talimogene laherparepvec arm and two in the GM-CSF arm; the EAC identified 51 durable responders, 48 in the talimogene laherparepvec arm and three in the GM-CSF 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 GM-CSF 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 GM-CSF 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 16 below. Please note that although the Table 16 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 who EAC assessed as durable responders. FDA disagreed with the EAC assessment of 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 (Table 16).

Table 16. Determinations of DRR by Investigators, EAC, and FDA

	Talimogene laherparepvec, N (%)	GM-CSF 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 from BLA submission]
[#]EAC reviewed 19 subjects in GM-CSF 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

A higher DRR in talimogene laherparepvec arm was also observed when using the per-protocol population, a sensitivity analysis based on all available EAC data prior to first anticancer therapy, or evaluations from the investigator.

Comparison of DRR Evaluation by EAC to DRR Evaluation by Investigator:

Investigator bias in this open-label study may have influenced the primary endpoint evaluation. Although the primary endpoint results were based on EAC evaluation and the EAC was blinded to treatment assignment, 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 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 17. 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 17, 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 14 subjects assessed by EAC as non-durable responders and seven subjects as durable responders, compared with the investigator assessments. Investigators assessed a total of seven additional subjects as DR's as compared with the EAC.

Clinical Reviewers' Comments:

1. *The results suggest possible bias in the investigator assessment of DR's in this open-label study, since twice as many subjects were down-graded than up-graded by the EAC. However, the magnitude of the observed treatment effect on the primary endpoint makes it unlikely that the overall study conclusions would have been affected by these issues.*

2. *Some lesions that were reported to have a complete or partial response appear to be too small (0.3 cm^2 for example) for reliable measurement.*

3. *Despite these discrepancies, the FDA review confirmed that the difference in durable response rate was statistically significant, favoring the talimogene laherparepvec arm.*

6.2.2.1.2 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 18 and Table 19.

Table 18. Distribution of Subjects according to Baseline Size of the Largest Baseline Measurable Lesions Recorded by Investigators in the ITT Population

	Talimogene laherparepvec			GM-CSF		
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 18. 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%). On the other hand, 45.7% of the DRs in the talimogene laherparepvec arm had at least one lesion that was greater than 2 cm^2.

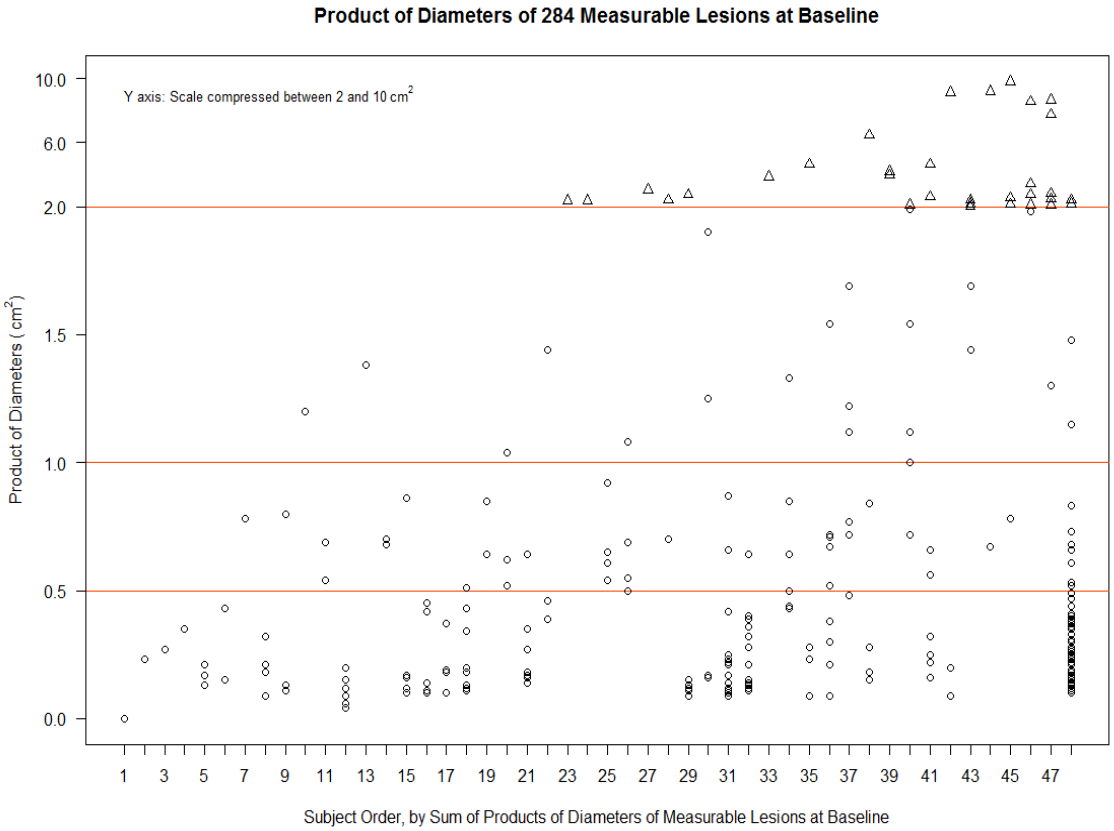
Table 19. Distribution of Baseline Measurable Lesions According to Baseline Size of the Largest Baseline Lesions

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 19 above summarizes the EAC-reported baseline size of all 284 baseline measurable lesions in the 48 DRs. There were more subjects whose largest lesions were small (< 1 cm^2) using the EAC data (43.7%,(Table 19) than using the investigator data (30.4%) as seen in Table 18. 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 EAC reviewed the same information that was submitted by the investigators.

Figure 6. Baseline Size of All Measurable Lesions in the 48 FDA Durable Responders



[Source: FDA analysis]

Figure 6 above 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 6, 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.

Clinical Reviewers' Comments:
This result suggests that subjects with smaller lesions may be more likely to respond while subjects who had larger lesions were less likely to respond to talimogene. The predominance of responders with only very small baseline lesions also raises concern regarding errors and inaccuracies in response assessment for lesions with these small sizes.

6.2.2.2 Analyses of Secondary Endpoints

6.2.2.2.1 Secondary Endpoint: OS

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). The primary analysis of OS was to occur at 290 deaths. 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 GM-CSF 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 GM-CSF arm, respectively. 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 GM-CSF 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 planned analysis cut-off date (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 by Day 16 and one censored on Day 86. The potentially informative censoring distributed disproportionately in the GM-CSF arm (7/141, 5%), compared to the talimogene laherparepvec arm (3/295, 1%). For the seven subjects in the GM-CSF 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. 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 was unknown.

Due to the concerns of informative censoring in the OS analysis performed by the applicant, FDA conducted a sensitivity analysis that imputed the planned data cut-off date (DCO) as the censoring times for the four GM-CSF subjects confirmed alive by the applicant after the DCO and counted an additional talimogene subject who died before DCO as a known event. The remaining five subjects without an update were censored at the ACOD. This *post hoc* sensitivity analysis showed a p-value of 0.116, a hazard ratio of 0.82 with 95% CI of (0.65, 1.05). The median OS is 22.9 months (19.6, 29.7) in the talimogene laherparepvec arm and 19.0 months (16.2, 24.3) in the GM-CSF arm. Thus, FDA concluded that there was no convincing statistically significant difference in overall survival between the treatment arms in the ITT population.

6.2.2.2.2 Additional Secondary and Exploratory Endpoints

Complete Responders

The applicant reported 33 subjects with a best response of complete response (CR), 32 in the talimogene laherparepvec arm and 1 in the GM-CSF arm (Table 20).

Table 20. Best Tumor Response EAC Analysis

	talimogene laherparepvec	GM-CSF	
N (%)	295	141	
DRR	**48 (16.3%)**	**3(2.1%)**	**P< 0.0001**
ORR	78(26.4%)	8(5.7%)	P< 0.0001
CR	32 (10.8%)	1 (0.7%)	P< 0.0001

Source: BLA datasets

The EAC determined that there were 24 subjects who had durable CRs, and all these subjects (8.1% of ITT subjects) were in the talimogene laherparepvec arm. However, FDA reviewers cannot confirm one subject (ID# 066017) who had a durable response determined by the EAC, and cannot confirm other 4 subjects' durable complete responses determined by the EAC. The reasons for FDA determination are listed in the Table 21. Thus, as per FDA review, 19 subjects (6.4% of ITT subjects in the talimogene laherparepvec arm) were considered as durable CRs. Fourteen of these 19 had restaged stage IIIB/IIIC melanoma at enrollment (4.7% of ITT 295 subjects in the talimogene laherparepvec arm; or 10.6% of 131 subjects who had Stage IIIb/c melanoma at enrollment in the talimogene laherparepvec arm).

No subject in the GM-CSF arm had durable CR based on reviewing the EAC CRFs.

Table 21. Durable Complete Responses Not Confirmed Based on FDA Review

Subject ID	Treatment arm	Any surgical resection prior to durable CR determination?	FDA review comments
002016	talimogene aherparepvec		PR: investigator CRFs showing not CR in assessment visits
005021	talimogene aherparepvec		PR: had residual tumor esion at cycles 2-12, not CR.
021002	talimogene aherparepvec	With surgery before CR: resection of L1(-), L2 (+)	PR: had surgical resection of the lesions in cycle 12, with positive tumor for L2.
065004	talimogene aherparepvec		PR: had CR for only 4 cycles.
066017	talimogene aherparepvec		CR for only 2 cycles, missing many assessments visits. We cannot locate photographs for lesions L1 and L2 at F/U visits.

Source: FDA review analysis.

Durable complete response (DCR) was not pre-defined endpoint in the protocol, but may be considered to be a clinical benefit or predict a clinical benefit. However, talimogene laherparepvec treatment did not have an overall survival benefit and FDA has concerns that the lesions in some of subjects were very small (see below), clinical reviewers do not believe that the DCR observed in Study 005/05 represents a clinical benefit. Instead, it may predict a clinical benefit.

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.

6.2.2.3 Subpopulation Analyses

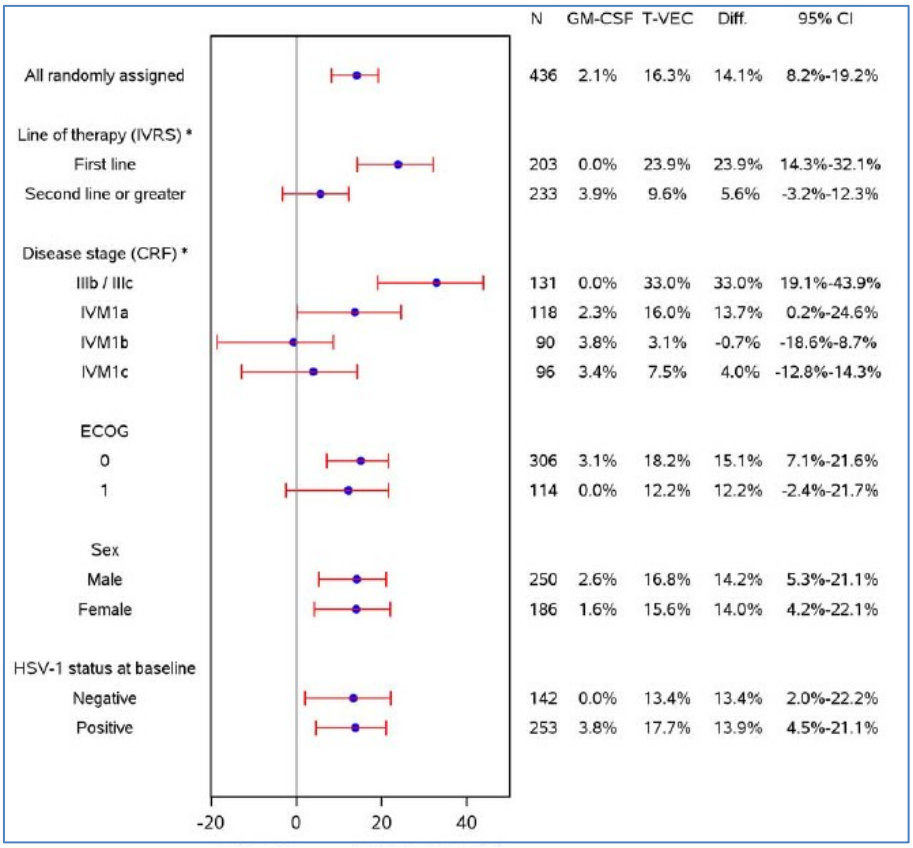
The treatment effect of talimogene laherparepvec on durable response and OS was heterogeneous across subgroups based on the stratification factors and key covariates.

In exploratory analyses, the magnitude of the estimated treatment effect on durable response and OS was greater (i.e., nominal $p \leq 0.05$, not adjusted for multiplicity) in the following subgroups, including subjects with stage IIIB/C and IV M1a disease, subjects who received talimogene laherparepvec as first-line therapy, and others (complete discussion of the subgroup results is provided in the 005/05 Supplemental CSR and 005/05 Narrative Summary). The results suggest that estimated treatment effects favored talimogene laherparepvec, and there were no statistically significant differences in the direction of the treatment effect between subgroups for any covariate.

6.2.2.3.1 Subgroup Analysis of DRR

Results for DRR by randomization factors and other covariates, including tumor stage and previous treatment history, are shown in Figure 7 below. The red color bars were Durable Response Rate (DRR) percentage difference between talimogene laherparepvec and GM-CSF.

Figure 7. Durable Response Rate per EAC Key Stratification Factors and Covariates



Source: Reproduced from BLA Submission.

T-VEC: talimogene laherparepvec; IVRS: Interactive Voice Response System

For these subgroup analyses, the "first line" therapy group consists of those subjects who had received only surgery or adjuvant therapies.

The applicant and FDA have explored consistency of DRR effects in subgroups. Subgroups formed by age (< 65 vs. ≥ 65), HSV-1 status (negative vs. positive), or sex (male vs. female) demonstrate treatment effects of similar magnitude in both study arms.

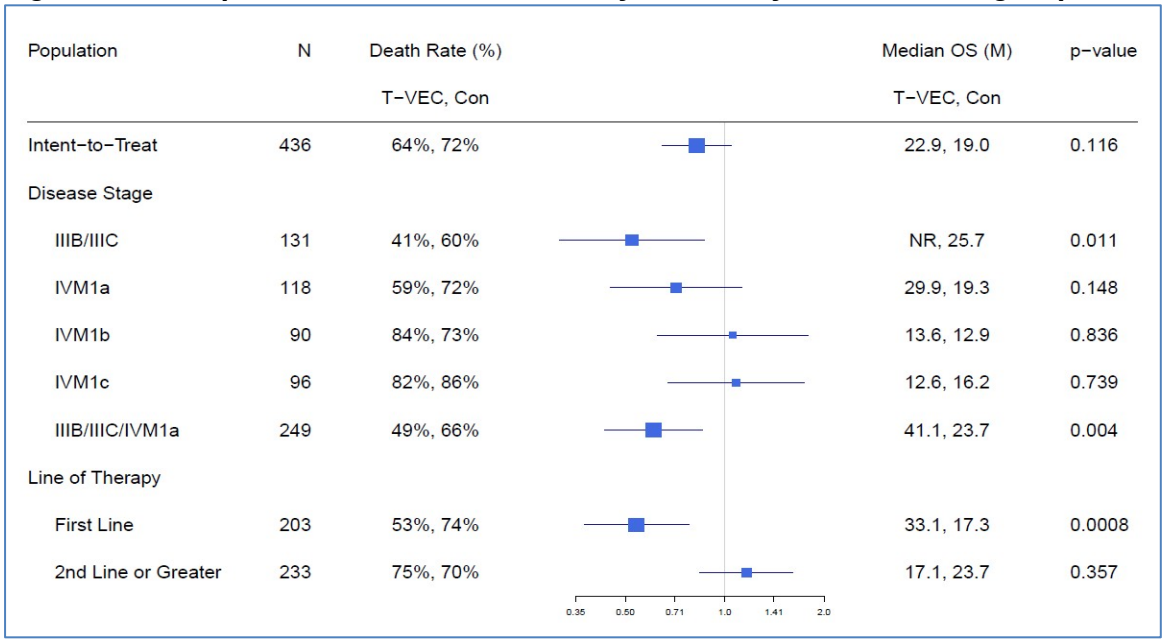
Clinical Reviewers' Comment:
1. These analyses suggest that talimogene may have had a greater treatment effect on the durable response rate in subgroups with localized disease (stage III), less advanced disease and subjects in the first line treatment group.

2. There were not enough non-White subjects to do a meaningful analysis by race.

6.2.2.3.2 Subgroup Analysis of OS

Figure 8 below shows the FDA's updated overall survival and subgroup analyses, incorporating new information obtained by the applicant on the 5 subjects who were censored due to non-administrative reasons. (See previous discussion).

Figure 8. FDA Updated Overall Survival Analyses, in Key Covariate Subgroups



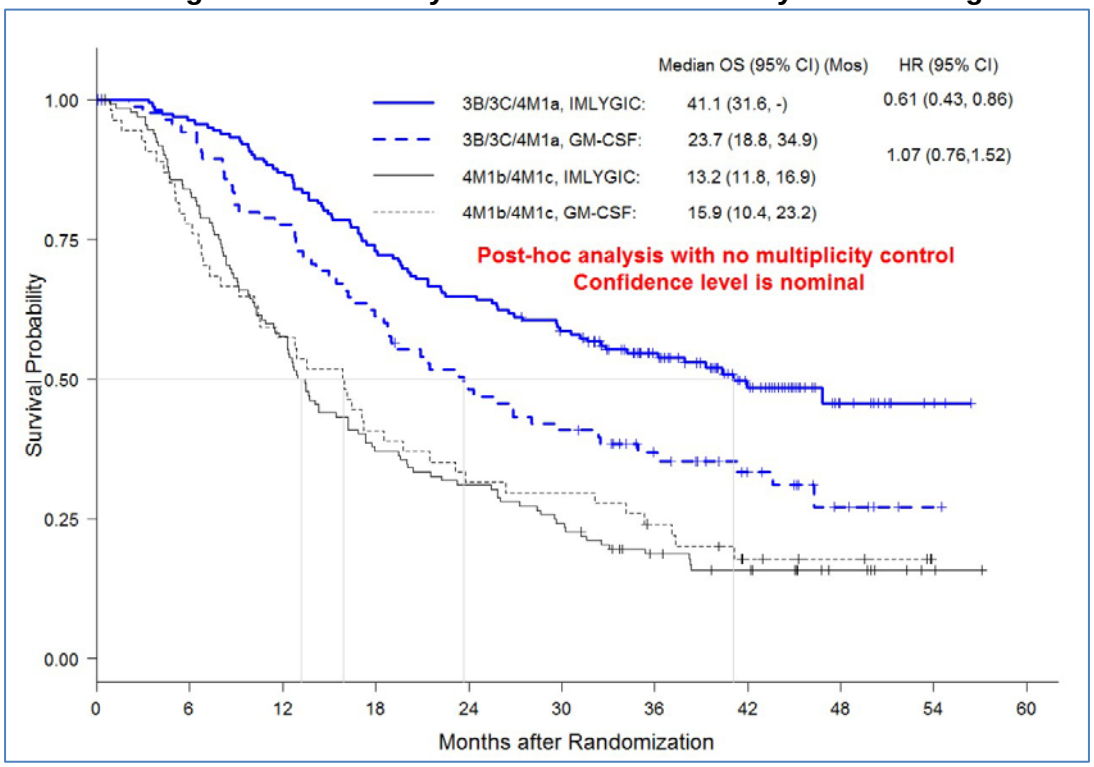
Source: FDA analysis

Clinical Reviewers' Comment:
There is an absence of a statistically significant treatment effect on overall survival in the ITT population in the above updated analysis. However, the updated subgroup analyses suggest that talimogene may have a greater treatment effect on the overall survival in subgroups with less advanced disease, stage IIIB/IIIC locoregionally recurrent melanoma, and a trend towards increased treatment effect in the IVM1a subgroup, compared with the IVM1b, 1c subgroup.

In addition, although deriving definitive conclusions from retrospective subgroup analyses is always problematic, the applicant's Kaplan-Meier analysis of OS suggests a treatment effect in the subgroup of subjects with localized disease. The subgroup of 131 subjects represents about a third of the total population. This group appears to drive the treatment effect on OS in the ITT population. The two arms were generally balanced in this subgroup. The median OS in the GM-CSF group was about 2 years, whereas the median OS was not reached in the treatment group. Therefore it appears that treatment with talimogene may predict a clinical benefit in the subgroup of subjects with earlier stage disease.

The smaller subgroup of 118 subjects with stage IVM1a also appeared to show improved overall response rate and a trend towards improved survival. The combined stage III and IVM1a subjects included over half the total study population (N=249/436, 57%). An exploratory FDA Kaplan Meier subgroup analysis of this combined sub population is reproduced in Figure 9 below.

Figure 9. FDA Analysis of Overall Survival by Disease Stage



Source: FDA statistical reviewer

6.2.2.3.3 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. The applicant claimed that these examples may support that talimogene laherparepvec 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.

Clinical Reviewers' Comment:
The Study 005/05 did not collect immune response data to assess a correlation with clinical outcomes. Some lesions reported as uninjected appeared to be too small for reliable assessment. In addition, it is difficult to determine which lesions were never injected. Therefore, the evidence that talimogene had a systemic effect on distant metastatic lesions was limited and difficult to quantitate. No survival advantage was observed in ITT population, there was no definitive evidence for a systemic effect on distant metastatic disease with talimogene laherparepvec treatment.

6.2.2.3.4 Correlation of DRR with OS

The applicant performed two types of exploratory analyses to explore the association between durable response and OS among subjects randomized to each treatment arm. In a landmark analysis, subjects in the talimogene laherparepvec arm who were still alive at 12 and 18 months, and who had achieved a durable response before these landmarks per EAC, had improved OS relative to those who were still alive at 12 and 18 months but had not achieved a durable response. When achievement of durable response was analyzed as a time-dependent covariate, the OS hazard ratio was 0.09 (95% CI: 0.03, 0.29), indicating that achieving a durable response was associated with a 91% decrease in the risk of death.

Clinical Reviewers' Comments:
We note that while an association between response / durable response and improved OS was observed, no conclusion can be made because response/durable response may act as a marker for subjects with a favorable prognosis.

6.2.2.3.5 Assessment of Tumor Responses and Surgical Resection

A total of 33 subjects in the talimogene laherparepvec arm underwent 35 surgical procedures for melanoma resection (005/05 Narrative Summary). A total of 21 (60%) melanoma resections were palliative, one of which contributed to a best response of PR per investigator assessment in one subject. The remaining 14 procedures were non-palliative, three of which contributed to a best response of CR or PR per investigator assessment in two subjects. Thus, some subjects did appear to benefit from surgery after talimogene laherparepvec administration; however, surgery did not contribute substantially to the overall response outcomes observed in this study (Table 22).

Table 22. Subject Incidence of Melanoma-related Resections: Talimogene Laherparepvec Subjects

	n (%)
Melanoma-related resections [a]	33 (100.0)
Palliative [a]	20 (60.6)
Non-palliative [a]	13 (39.4)
Pathological CR at time of surgery [a]	4 (12.1)
No evidence of disease after surgery [a]	9 (27.3)
Surgeries contributed [a] to the best response of CR or PR [b]	3 (9.1)
Palliative	1 (3.0)
Non-palliative	2 (6.1)

[a] Based on medical review.
[b] Response per investigator assessment.
T-VEC=Talimogene Laherparepvec.
Resection and tumor response data are from primary analysis data for durable response endpoint snapshot date on 3/13/2013.

Source: Original BLA eCTD Study 005/05 Narrative summary.. T-VEC: talimogene laherparepvec

6.2.2.3.6 Assessment of Subsequent Use of Any Anti-Cancer Therapy

Subsequent use of any anti-cancer therapy after permanent discontinuation of investigational product:

The most common forms of subsequent anti-cancer therapy (first and additional) were immunotherapy (198 subjects; 45.4%) and chemotherapy / targeted agents (151 subjects; 34.6%).

Among the four melanoma therapies of interest during this study, ipilimumab was the most frequently used, followed by vemurafenib (Table 23). Median time to first use of ipilimumab and vemurafenib was approximately 1 month later in the talimogene laherparepvec arm compared to the GM-CSF arm. Subjects receiving dabrafenib did so nearly 6 months later in the talimogene laherparepvec arm compared to the GM-CSF arm, but this should be interpreted with caution due to a small sample size. No difference could be calculated for trametinib because no subjects in the GM-CSF arm received this treatment.

Table 23. Summary of Subsequent Anti-Cancer Therapy: Subject Incidence and Median Time to First Use

	Subject Incidence		
	GM-CSF N = 141 n (%)	Talimogene laherparepvec N = 295 n (%)	Total N = 436 n (%)
Overall	60 (42.6)	116 (39.3)	176 (40.4)
Ipilimumab	49 (34.8)	106 (35.9)	155 (35.6)
Vemurafenib	21 (14.9)	26 (8.8)	47 (10.8)
Dabrafenib	2 (1.4)	7 (2.4)	9 (2.1)
Trametinib	0 (0.0)	3 (1.0)	3 (0.7)
	Median Time to First Use (months)		
			Difference
Overall	6.9	8.9	2.0
Ipilimumab	7.4	8.6	1.2
Vemurafenib	13.6	14.6	1.0
Dabrafenib	7.1	12.8	5.7
Trametinib	NE	18.0	NE

GM-CSF = granulocyte macrophage colony-stimulating factor.NE = not estimable
Source: Modified from *Table 14-8.2.1*

The first and additional cancer therapies received by subjects in the ITT population are also summarized for subjects receiving investigational product as first-line therapy, or second-line therapy or greater within each treatment arm. Regardless of treatment group, the use of any subsequent anti-cancer therapy was comparable (i.e., an absolute difference in incidence of ≤ 5%) between lines of therapy.

Use of the four melanoma therapies of interest was also summarized by stage of disease and line of therapy. Results by line of therapy were qualitatively similar to the full ITT population, but conclusions based on disease stage are difficult to draw due to small sample sizes.

Clinical Reviewers' Comment:
There is a theoretical possibility that a large imbalance in effective subsequent therapies could confound interpretation of overall survival results. In Study 005/05, use of subsequent anti-cancer therapies appeared to be generally balanced between treatment arms in terms of percentages of the ITT study population. Thus, subsequent therapies did not significantly confound interpretation of overall survival results in the treatment arms.

6.2.2.3.7 Patient-reported Outcomes - Quality of Life

The quality of life was assessed by the FACT-BRM questionnaire. Subjects were required to complete the questionnaire on Day 1 of each treatment cycle and at the EOT visit before they underwent any treatment-related study procedures including administration of investigational product. The treatment estimated for the 4 subscales (physical well-being, social/family well-being, emotional well-being, functional well-being), 2 treatment-specific subscales (additional concerns -physical and additional concerns – mental), overall FACT-BRM score (sum of scores for all 6 subscales), and

the trial outcome index (TOI; sum of scores for physical well-being, functional well-being, and 2 treatment-specific subscales).

The treatment estimate (95% CI) of the average change on TOI across all time points was -2.43 (-3.98, -0.87); p = 0.002 in favor of GM-CSF arm. However, these data are limited by the low completion of questionnaires in the GM-CSF group compared with the talimogene laherparepvec group during the study.

This lower completion rate is likely reflective of the increased number of earlier withdrawals in the GM-CSF group compared to the talimogene laherparepvec group. Although subjects in both groups were expected to continue treatment during the first 24 weeks despite any progression of disease, subjects receiving an investigational therapy like talimogene laherparepvec may be more willing to remain in the study.

Clinical Reviewers' Comment*: A difference in TOI was observed in favor of GM-CSF. However, the trial was not blinded to adequately assess the Quality of Life and the result was confounded by missing data. Thus the quality of life results submitted by the applicant were not interpretable.*

6.2.3 Safety Analyses

Results described below are based on the analysis from the Primary Melanoma Safety Analysis Set derived from Study 005/05: 419 subjects from Study 005/05 who received at least one dose of talimogene laherparepvec or GM-CSF. Integrated safety analysis is presented in Section 8.

6.2.3.1 Methods

Adverse events were solicited during visits to clinic, from diary cards given to the subjects, and subject outcome questionnaires. The adverse events were then recorded on the subject's electronic case report forms from the beginning of therapy until 30 days after the last dose of talimogene laherparepvec or until resolution of the adverse event. Adverse events were graded per the National Cancer Institute's CTCAE (version 3.0). The data in the BLA were also coded using preferred terms per MedDRA version 15.1.The following were included:

- Any suspected adverse medication reactions
- Apparently unrelated illnesses, including the worsening of a pre-existing illness, or injury
- Abnormalities in physiological testing or physical examination (findings that required clinical intervention or further investigation beyond ordering a repeat [confirmatory] test).
- Laboratory abnormalities that required clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they were associated with an already reported clinical event. Laboratory abnormalities associated with a clinical event (e.g., elevated liver enzymes in a patient with jaundice) were described under Comments on the report of the clinical event rather than listed as a separate adverse event.

Studies 005/05, 005/05E formed the basis Protocols for the Primary Melanoma Safety Analysis Set: The following assessments were used to assess safety by the applicant

and the in the FDA analysis. Table 24 includes the required studies as well as their timing during the course of the study. Adverse events were recorded and graded per CTCAE 3.0. The BLA submission used MedDRA coding for preferred terms.

Table 24. Schedule of Required Evaluation for the Study 005/05

Trial Period	Screening	Treatment (Tx)Period			End of Tx/Early Term
Assessments	Days -28 to -1	Day 1 Cycle 1	Subsequent Injections (Per 28 Day Cycle		30 Days post last injection
			Day 1	Day 15	
Informed Consent	X				
Medical History	X				
TNM Staging	X				
ECG	X				
Physical Exam	X				X
Symptom Directed Physical Exam		X	X		
Vital Signs	X	X	X	X	X
ECOG Performance Status	X	X	X		X
QoL		X	X		X
Photography		X	X		X
B-hCG	X				

All subjects were evaluated periodically including physical examinations and symptomatic physical exams, cardiac evaluations, vital signs and quality of life. Data collected included:

- *Hematology:* at screening and Day 1 of each cycle, red blood cell count (RBC), white blood cell count (WBC), differential of WBC count, and platelet count
- *Clinical Chemistry:* total bilirubin, serum creatinine, glucose, sodium, potassium, chloride, alkaline phosphatase, total protein, ALT/SGPT, AST/SGOT, phosphate, magnesium, lactic dehydrogenase (LDH), albumin, calcium
- *Coagulation* (at screening only): PT (or INR), PTT
- *Urinalysis* (screening only): pH, glucose, protein, specific gravity
- *Additional tests relevant to the safety review:*
  - *HSV-1 Antibody Level:* at screening for all subjects and for talimogene laherparepvec subjects only on Day 1 of Cycles 3 and 6.
- *Clinical Measurements:* skin lesions at screening, Day 1 of each Cycle, and end of therapy visit. May include ultrasound/CT evaluation
- *CT, PET, Ultrasounds, and PET/CT scans*: whole body at screening, 12 weeks, and every 12 weeks thereafter
- *Brain MRI*: at screening and every 16 weeks

Adverse event reporting: Day 1 Cycle 1 through 30 days after administration of the last

dose of study treatment. AEs was reported in the follow-up phase (>30 days post last dose of study drug) if they were deemed to be related to study drug. All deaths, including any death that occurred during the follow-up period, were reported whether or not considered causally related to the study drug.

6.2.3.2 Definitions

Treatment-emergent adverse event (TEAE): 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.

Serious adverse event (SAE): 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.

6.2.3.3 TEAEs

A total of 290 subjects (99.3%) exposed to talimogene laherparepvec had at least one TEAE (grades 1-5) (Table 25). Of the TEAEs, 93 subjects (31.9%) experienced Grade 3 and 13 subjects (4.5%) experienced Grade 4 adverse events in the talimogene laherparepvec arm. One hundred eight- six subjects (63.7%) on the talimogene laherparepvec arm experienced Grade 1 or Grade 2 TEAEs. Overall, 75 subjects (25.9%) experienced TEAEs that were considered serious in the talimogene laherparepvec arm.

Table 25. Summary of Treatment-Emergent Adverse Events Study 005/05

	Talimogene laherparepvec n =292 (%)	**GM-CSF GM-CSF n =127 (%)**
TEAEs	**290 (99.3%)**	**126 (99.2%)**
Grade 3	**93 (31.9%)**	**25 (19.7%)**
Grade 4	**13 (4.5%)**	**4 (3.2%)**
Serious TEAEs	**75 (25.9%)**	**17 (13.4%)**
Deaths within 30 days of last study treatment	**12 (4.1%)**	**2 (1.6%)**
Discontinuation due to TEAEs	**30 (10.3%)**	**8 (6.3%)**

[Source: SAE Subject Detail /AE detail tox grade 005_05_pa_dr; FDA Analysis from dataset]

For the talimogene laherparepvec group, the most common adverse events were fatigue, chills, pyrexia, and nausea (Table 26). These specific events were typical manifestations of a flu-like illness, which was the next most common adverse event. The adverse events for GM-CSF were consistent with its known safety profile. Flu-like symptoms were common in both arms, but more frequent in the talimogene laherparepvec arm. These adverse events are listed below with the exception of progressive disease.

The incidence of Grade 3 or above adverse events was higher in the talimogene laherparepvec arm as compared to the GM-CSF arm. Overall the incidence of Grade 3 adverse events for talimogene laherparepvec was 31.9%, Grade 4 was 4.5%, and serious adverse events was 25.9% (Table 25).

Cellulitis was not a common adverse event but a common serious adverse event (Table 26, Table 28). Cellulitis was reported in 5.8 % (n=17) of the talimogene laherparepvec subjects and 1.6% (n=2) in the GM-CSF arm. The incidence of injection site erythema and pruritus was higher on the GM-CSF arm,

Table 26. Most Frequent Adverse Events per MedDRA SOC in Study 005/05

		Talimogene laherparepvec N= 292 (%)	GM-CSF N=127 (%)
General Disorders and Administrative Site Conditions			
	Fatigue	147 (50.3%)	46 (36.2%)
	Chills	142 (48.6%)	11 (8.7%)
	Pyrexia	125 (42.8 %)	11 (8.7%)
	Influenza-like Illness	89 (30.5%)	19 (15%)
	Injection site pain	81 (27.7%)	8 (6.3%)
Gastrointestinal Disorders			
	Nausea	104 (35.6%)	25 (19.7%)
	Vomiting	62 (21.2 %)	12 (9.5%)
	Diarrhea	55 (18.8%)	14 (11.0%)
	Constipation	34 (11.6%)	8 (6.3%)
	Abdominal Pain	26 (8.9%)	3 (2.4%)
Musculoskeletal and Connective Tissue Disorders			
	Myalgia	51 (17.5 %)	7 (5.5%)
	Arthralgia	50 (17.1 %)	11 (8.7%)
	Extremity Pain	48 (16.4%)	12 (9.5%)
Skin and Sub-Cutaneous Disorders			
	Pruritis	28 (9.6%)	19 (15.0%)
	Rash	26 (8.9%)	10 (7.9%)
	Hyperhidrosis	23 (7.9%)	9 (7.1%)
Infections and Infestations			
	Upper Respiratory	29 (9.9%)	8 (6.3%)
	Cellulitis	17 (5.8%)	2 (1.6%)
	Oral Herpes	14 (4.8%)	2 (1.6%)
Nervous System Disorders			
	Headache	55 (18.8 %)	12 (9.5%)
	Dizziness	28 (9.6 %)	4 (3.2%)

[Source: 005_05_pa_dr AEs Common SOC and Common Pref Term Trt+FU, FDA review of the datasets]

Clinical Reviewers' Comment: *The clinical picture for the common adverse events seen with talimogene laherparepvec was consistent with the systemic effects of a mild viral illness which would be expected with the attenuated herpes product. The results for the category of skin-related disorders was consistent with the actual number of doses given since even with shortened treatment duration, the GM-CSF subjects received 14 versus 2 injections per cycle for the talimogene laherparepvec subjects*.

6.2.3.4 Deaths

Table 27. Deaths on Study 005/05 (Primary Melanoma Analysis Set)

Treatment	Subject	Treatment Start Date	Treatment End Date (day)	Death Date (Treatment Date)	MedDRA Term	End of Study Reason
GM-CSF	00505-002004				Disease Progression	Death
GM-CSF	00505-035024			)	Dyspnea	Death
Talimogene laherparepvec	00505-005018			)	Respiratory Failure	Death
Talimogene laherparepvec	00505-009018				Disease Progression	Death
Talimogene laherparepvec	00505-015005				Disease Progression	Death
Talimogene laherparepvec	00505-020009				Myocardial Infarction	Death
Talimogene laherparepvec	00505-035002				Disease Progression	Death
Talimogene laherparepvec	00505-035018				Cardiac Arrest	Death
Talimogene laherparepvec	00505-045001				Death (CSR= Disease Progression)	Death
Talimogene laherparepvec	00505-062011				Sepsis	Death
Talimogene laherparepvec	00505-067002		)		Respiratory Failure	Death
Talimogene laherparepvec	00505-106005				Metastases to the Central Nervous System	Death
Talimogene laherparepvec	00505-106009				Disease Progression	Death
Talimogene laherparepvec	00505-109002				Disease Progression	Death

[Source: FDA Review, BLA 125518]

In Study 005/05 (Table 27) and its expanded access 005/05E, a total of 12 deaths occurred within 30 days of the last dose of talimogene laherparepvec treatment. The two deaths in the GM-CSF arm occurred within 30 days of the last dose of GM-CSF. Progressive disease was the cause of death in nine subjects who received talimogene laherparepvec and two subjects who received GM-CSF. The remaining three deaths after talimogene laherparepvec treatment were due to myocardial infarction, cardiac arrest, and sepsis, respectively. The deaths after talimogene laherparepvec treatment occurred from Days 24 to 648 after initiation of therapy. The deaths in the GM-CSF arm occurred on Days(b) (6) 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 GM-CSF arm died while on therapy or in follow-up. Review of narratives for the deaths indicated that the deaths were primarily due to progressive disease, aged related complications and not due to talimogene laherparepvec or GM-CSF.

Clinical Reviewers' Comments: *The causes of death not due to progressive disease (PD) were consistent with a population with a mean age of 63 and known medical morbidities.*

6.2.3.5 Nonfatal Serious Adverse Events

Treatment-emergent serious adverse events occurred in 75/290 subjects (25.9%) in the talimogene laherparepvec arm and 17/126 subjects (13.4%) in the GM-CSF arm. The most common treatment-emergent serious adverse events were disease progression and cellulitis. Table 28 lists treatment-emergent serious adverse events at an incidence of greater than or equal to 1% (excluding disease progression).

Table 28. Treatment-Emergent Serious Adverse Events for Talimogene Laherparepvec in Study 005/05 except Disease Recurrence

Treatment-Emergent Serious Adverse Events	Talimogene laherparepvec n*=290	GM-CSF n*=126
Treatment-emergent serious adverse events	**75 (25.9%)**	**17 (13.4%)**
Cellulitis	**7 (2.4%)**	**1 (0.8%)**
Respiratory Failure	**6 (2.1%)**	**2 (1.6%)**
Pyrexia	**5 (1.7%)**	**0**
Tumor Pain	**4 (1.4%)**	**0**
Cerebral Hemorrhage	**3 (1.0%)**	**0**
Deep Vein Thrombosis	**3 (1.0%)**	**0**
Gastrointestinal Hemorrhage	**3 (1.0%)**	**0**
Infected neoplasm	**3 (1.0%)**	**0**
Pleural Effusion	**3 (1.0%)**	**0**

*subjects [Source: 005_05_pa_dr AEs-Serious Pref Term Trt+FU, FDA Analysis from dataset]

Cellulitis at the site of the injection of talimogene laherparepvec was an important adverse event. In the clinical studies, impaired healing at the injection site was reported. Talimogene laherparepvec may increase the risk of impaired healing in patients with underlying risk factors (e.g., previous radiation at the injection site or lesions in poorly vascularized areas).

In addition to the serious adverse events noted above, there were individual important serious adverse events. Some examples are:

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). This patient had an amputation of a lower extremity 6 months after talimogene laherparepvec injection due to an infected non-healing wound. This wound area had been treated with surgery and radiation prior to talimogene laherparepvec treatment and had previous wound complications.

Clinical Reviewers' Comments:
Cellulitis was reported in seven subjects (2.4%) as a severe adverse event with talimogene laherparepvec given intralesionally. One subject required an amputation 6 months off therapy due to a non-healing wound infection. Overall the incidence of cellulitis was low in Study 005/05. However, in this population treated with talimogene laherparepvec intralesionally, there was an increased risk for poor healing, damaged tissues, and local increased infection risk due to the likelihood that previous therapies (surgery, radiation) or the melanoma lesions may have already affected the tissue at the treatment site. Therefore, if talimogene laherparepvec is to be approved, these risks need to be described in the product labeling so that healthcare professionals are familiar with these risks.

6.2.3.6 Adverse Events of Special Interest (AESI)

Adverse events of special interest were identified by the applicant based on the mechanism of action and preclinical or emerging clinical data (Table 29). These include flu-like symptoms, injection site reactions, hypersensitivity, cellulitis, herpes simplex-1 infections, and vitiligo.

Table 29. Adverse Events of Interest by Category (Study 005/05)

Adverse Events of Special Interest	Talimogene laherparepvec n*= 292 (%)	GM-CSF 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 at injection site	**17 (5.8%)**	**2 (1.6%)**
Herpes simplex -1 infection	**16 (5.5%)**	**2 (1.6%)**
Vitiligo	**15 (5.1%)**	**2 (1.6%)**

*subjects
[Source: Applicant's Statistical Analysis Plan]

Details of these AESI in Study 005/05 are described below:

Flu-like Symptoms:

- Consistent with treatment with a live oncolytic viral vaccine.

Injection Site Reactions:

- Higher incidence in the GM-CSF arm (Table 29)
- In the talimogene laherparepvec arm, the most common adverse event in this category was injection site pain 27.7% versus 6.3% in the GM-CSF arm.
- 3 serious events related to pain
- In GM-CSF arm, the most common events were erythema 26.1% and pruritis 16.5%
- Impaired Wound Healing at Injection Site:
  - Described in preferred terms of wound complication (1.4%), wound secretion (1.4%), and wound infection (1%) in the talimogene laherparepvec arm.
  - Impaired wound healing may be a potential risk to talimogene laherparepvec therapy as noted above with the report of an amputation due to complications in the region of previous injections.

Herpes Simplex Virus Infections

- Oral herpes was 4.8% in the talimogene laherparepvec arm versus 1.6% in the GM-CSF arm (Table 29)
- 14 subjects reported oral herpes, 6/14 were seronegative at baseline.
- Could not confirm herpes viral type due to lack of confirmatory testing.
- Study 002/03 in the Supportive Analysis Set had 3 reports of oral herpes.

Hypersensitivity:

- Higher incidence in the GM-CSF arm 19.7% versus 18.2% for talimogene laherparepvec.
- Rash was frequently reported preferred term. 7.9% in GM-CSF arm and 8.9% in the talimogene laherparepvec arm (Table 26)
- No serious reactions in either arm
- Two serious event in the talimogene laherparepvec arm were found:
  - Asthma
  - Bronchial reactivity after upper respiratory infection

.

Cellulitis

- In the talimogene laherparepvec arm of Study 005/05, 17 subjects (5.8%) developed cellulitis; seven of these events (2.4%) were categorized as serious, requiring hospitalization. Only two subjects in the GM-CSF arm had low grade cellulitis.
- One subject in the talimogene laherparepvec arm developed associated streptococcal glomerulonephritis.

Vitiligo:

- Talimogene laherparepvec arm: 15, (5.1%) and GM-CSF: two (1.6%) . No serious vitiligo reported in either arm.

Other Events.

- Opportunistic Infection

- talimogene laherparepvec arm: blastomycosis in an endemic area in a 65 year old white male (069010) with a history of autoimmune disease

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 a history of hematuria, papillary necrosis, and acute renal failure, singular kidney, hypertension and diabetes.
  - Acute renal failure/glomerulonephritis developed in a 57 year-old white male and 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).
  - Vasculitis developed in a 41 year-old white female on Day 259 of therapy.
  - Exacerbation of psoriasis in a 73 year-old white male
  - Hypothyroidism (Grade 2) developed in a 60 year-old white male on Day 77.
- Three subjects in the GM-CSF arm had auto-immune events: an exacerbation of rheumatoid arthritis, alopecia, and a rash, respectively.

6.2.3.7 Other Neoplastic Events:

Talimogene laherparepvec arm:

- 57 year-old male with metastatic squamous cell carcinoma after 18 cycles of talimogene laherparepvec and 987 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 transitional developed 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.
- A plasmacytoma was reported in proximity to the injection site after administration of talimogene laherparepvec in a patient with smoldering multiple myeloma.

Two subjects in the GM-CSF arm developed three malignancies: An 81 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 by the applicant of adverse events, serious adverse events, and discontinuation of treatment for talimogene laherparepvec versus GM-CSF did not show

a higher safety risk in the talimogene laherparepvec arm by age, race, gender, region, or disease stage.

Clinical Reviewers' Comment:
The adverse event of flu-like symptoms was 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 was difficult to categorize since the documentation of the infectious agent was not available. In general, talimogene laherparepvec subjects were followed longer due to a lower drop-out rate. Hyper-sensitivity reactions were almost equal in both groups. Injection site reactions were higher in the GM-CSF arm. The malignancies other than melanoma that developed while subjects were on the Study 005/05 were related to prior existing conditions and known risk factors. The risks and benefits of talimogene laherparepvec should be considered before treatment in patients with multiple myeloma or in whom a plasmacytoma develops during treatment. While there were two episodes of glomerulonephritis developed in Study 005/05, an FDA review of the combined safety databases did not identify any additional cases.

6.2.3.8 Clinical Test Results

Minimum Critical Toxicities:
Minimum critical toxicities measured organ toxicity with laboratory testing, radiologic evaluations, and clinical monitoring. This analysis was conducted using the Supportive Melanoma Analysis Set (n=342) as detailed in Section 8, the Integrated safety analysis. The critical adverse events analyzed were drug-induced liver injury, hepatotoxicity, nephrotoxicity, bone marrow toxicity, and QT prolongation and other ECG abnormalities. No critical toxicities associated with talimogene laherparepvec were identified. Analysis of the Program-Wide Analysis Set (talimogene laherparepvec for any disease indication), again did not identify toxicities specific to the talimogene laherparepvec arm as detailed above and in the FDA integrated safety analysis. There were no Grade 3 or 4 laboratory values from baseline of Grade 0 to 1 for bilirubin, alkaline phosphatase, ALT, and AST.

6.2.3.9 Study Discontinuations due to AEs

Thirty subjects (10.3%) in the talimogene laherparepvec arm and 8 subjects (6.3%) in the GM-GSF arm experienced adverse events leading to discontinuation of study treatment. The most common adverse events (AEs) leading to treatment discontinuation were disease progression (PD) when reported as an adverse event.

- Seven in the talimogene laherparepvec arm due to PD
- Two in the GM-CSF arm due to PD

In addition, 10 (7.9%) subjects in the GM-CSF and 39 (13.4%) subjects in the talimogene laherparepvec arms had treatment delayed. Half of the delays in both arms were due to serious adverse events. Deaths occurred and are described in Table 27. Events that were not related to progression included:

- Seven subjects in the talimogene laherparepvec arm discontinued study treatment due to TEAEs per the local investigator.
- 22 additional subjects in the talimogene laherparepvec arm discontinued therapy.

- One event of cellulitis and one event of herpetic keratitis were noted as causative for discontinuation in the talimogene laherparepvec arm discontinued therapy per the investigator.

- Additional events such as cardiac and respiratory disorders were also identified

Table 30. AEs in the Talimogene Laherparepvec Arm That Resulted in Discontinuation of Therapy (Study 005/05)

AEs not related to PD in the talimogene laherparepvec arm (n)	Discontinued Therapy (n)
cellulitis (1)	**Tumor hemorrhage (1)**
herpetic keratitis (1) [history of wild-type herpes simplex virus]	**Cerebral hemorrhage (1)**
Sepsis (1)	**Respiratory Disorders (4)**
General (3)	**Rash (1)**
Metabolism and nutrition disorders (2)	**Deep Vein Thrombosis (1)**
Musculoskeletal pain and weakness (3)	**Vomiting (1)**
Spinal stenosis (1)	**Cardiac (1)**
Glomerulonephritis (1)	

[Source: BLA Submission]

6.2.3.10 Long Term Follow-up of Talimogene laherparepvec Subjects
Monitoring included clinical assessments per standard of care. Participation was voluntary. Clinical data (CT scans, laboratory evaluations) were not submitted. However, serious adverse events were submitted to the database with supportive clinical data if appropriate.

In particular, the sponsor monitored and asked investigators to report herpes-related infections (e.g., orofacial infections, ocular herpes, herpes simplex, encephalitis, herpetic lesion at injection site).

Clinical Reviewers' Comment:
As long-term follow-up (LTFU) information becomes available, this data will complement the data obtained from the planned pharmacovigilance study. However, the participation in this voluntary LTFU study is low; therefore the amount of data to be obtained may be limited.

6.2.3.11 Safety Summary for Study 005/05

In general, the safety profile for Study 005/05 indicated that talimogene laherparepvec had no unexpected risks. The events reported were consistent with the use of a live oncolytic virus which was directly injected into tumors. Adverse events were primarily low grade. Most common were flu-like symptoms that improved over time. Cellulitis was more common in the talimogene laherparepvec arm that could contribute to serious consequences including amputation.

Overall, results of the subgroup analyses for the analysis of adverse events and serious adverse events for talimogene laherparepvec relative to GM-CSF did not indicate an altered safety profile of talimogene laherparepvec by age, sex, race, region, or disease stage. (See Section 9)

There is a concern that the risk to close family contacts and medical personnel from the talimogene laherparepvec, a modified HSV-1 live virus, was not adequately assessed from the safety data submitted. This risk will be addressed by post-marketing pharmacovigilance testing if talimogene laherparepvec is approved. Please refer to the review for this BLA by The Office of Biostatistics and Epidemiology (OBE) for a discussion and resolution of these issues.

7 Integrated Overview of Efficacy

7.1 Indication #1

The applicant's proposed indication is treatment of injectable regionally or distantly metastatic melanoma.

7.1.1 Methods of Integration

There was one pivotal Phase 3 trial for the BLA application as described in Section 6.The primary evidence of efficacy for the BLA was based on the primary efficacy analysis set which includes data from Study 005/05 (n=436, ITT population). This was a Phase 3, randomized, open-label study of talimogene laherparepvec therapy compared with GM-CSF in subjects with unresectable stage IIIB, IIIC, and IV melanoma.

The supportive efficacy analysis set included data from the extension study protocol Study 005/05-E (n=30), the single-arm Phase 2 study for Stage IIIC and IV melanoma (Study 002/03; n=50), and the extension protocol Study 002/03-E (n=3).

7.1.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics are discussed in Section 6.2.1.1.

7.1.3 Subject Disposition

Subject Disposition is discussed in Section 6.2.1.2.

7.1.4 Analysis of Primary Endpoint(s)

Analyses of Primary Endpoint is discussed in Section 6.2.2.1.

7.1.5 Analysis of Secondary Endpoint(s)

Analyses of Secondary Endpoints are discussed in Section 6.2.2.2.

The assessment of overall survival could have provided additional evidence of both a systemic effect and a clinically meaningful benefit. However, there was no overall survival benefit in the ITT population (p=0.051, from primary analysis). In addition, an updated overall survival incorporating the survival statuses of 10 subjects who had informative censoring revealed a p value of 0.116, supporting the primary analysis that there was no overall survival difference in the ITT population. However, the exploratory analysis of OS in certain subgroups, specifically the stage III and first line

subjects, suggested that talimogene laherparepvec may have some benefit on survival in these subgroups as described above.

7.1.6 Other Endpoints

Additional Secondary and Exploratory Endpoints are discussed in Section 6.2.2.2.

Exploratory Patient-reported Outcomes analyses are discussed in Section 6.2.2.2.

7.1.7 Subpopulations

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.

Additional subgroup analyses for race, sex, and age are discussed in Section 6.2.2.3.

7.1.8 Persistence of Efficacy

Applicant reported that, among the 78 objective responders in the talimogene laherparepvec arm, the median duration of response (and 95% CI) per EAC has not been reached. At the last tumor assessment, 56 subjects (71.8%) were still in response. Among the 8 objective responders in the GM-CSF arm, the median duration of response (and 95% CI) per EAC was 2.8 (1.2, NE) months. At the last tumor assessment, 4 subjects (50%) were still in response.

7.1.9 Product-Product Interactions

Since talimogene laherparepvec is sensitive to acyclovir, use of this or similar antiviral agents would presumably render the product inactive. The sponsor has initiated ongoing studies of the use of talimogene laherparepvec with immune modulating checkpoint inhibitors including Ipilimumab and pembrolizumab for the treatment of melanoma and other malignancies.

7.1.10 Additional Efficacy Analyses

Supportive studies

An open-label extension study for Study 005/05, Study 005/05-E (n=30) evaluated the safety and efficacy of extended treatment with talimogene laherparepvec therapy for subjects who were determined to be able to potentially benefit from treatment continuation beyond what was allowed in Study 005/05. Among talimogene laherparepvec-treated subjects, two of them who had a best response of stable disease in Study 005/05 and three subjects who had a best response of PR in Study 005/05 achieved a best response of CR in the extension Study 005/05-E.

In Study 002/03, a single-arm trial in 50 subjects with stage IIIC or stage IV melanoma, talimogene laherparepvec was administered intralesionally up to 24 doses. Of the 50 subjects enrolled, 14 (28%) achieved a response - 8 (16%) were CRs. Three subjects received additional treatment with talimogene laherparepvec in an optional extension study, in which one additional CR was observed resulting in a combined overall response rate of 30%. Of the 15 responses that occurred eight were still ongoing at end of Year 1 and two were ongoing at the end of Year 2.

These results appear to support the efficacy results of Study 005/05.

7.1.11 Issues of efficacy Review

7.1.11.1 Study Design

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.

7.1.11.2 Patient Population

Since Study 005/05 was initiated, several therapies (ipilimumab, vemurafenib, dabrafenib, trametinib, pembrolizumab and nivolumab) 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. 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 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.

7.1.11.3 Primary Endpoint analysis

The study assessment of 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. 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. In addition, the majority of the baseline measurable lesions in these 48 DRs were small to very small with measurements of 0.04 cm2 to 0.5 cm^2 (64.8% of all lesions). 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.

7.1.11.4 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. 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, 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, although there is a scientific rationale 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.

7.1.11.5 Subject Disposition

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. In contrast, 14 (9.9% of subjects randomized to the GM-CSF arm never received the drug, and 106 (75.1%) of subjects in the GM-CSF arm withdrew from the study before the protocol-specified 24 weeks. Subject or investigator bias regarding the relative benefit of talimogene laherparepvec and the GM-CSF 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 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. As seen in Table 17, 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.

7.1.11.6 Dosing Issue

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.

7.1.12 Efficacy Conclusions

In this BLA, the primary evidence of effectiveness was assessed from the results of a single 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 GM-CSF. Effectiveness appeared to be greater in the subjects with localized stage IIIB and IIIC subgroups. There was no overall survival difference between the treatment arms in the ITT population. However, an exploratory subgroup analysis suggests that overall survival may be better in the stage IIIB and IIIC patients who received talimogene laherparepvec.

8 *Integrated Overview of Safety*

8.1 Safety Assessment Methods

The applicant submitted summary statistics for treatment duration, average dose, and cumulative dose, number of doses, cumulative volume, and average volume for all subjects who received at least one dose of talimogene laherparepvec in both melanoma studies (Supportive Melanoma Analysis Set). Overall subject exposure to talimogene laherparepvec was submitted for all studies (Program-wide Analysis Set). Please see Sections 8.2.1, 8.2.2, including the number of subjects receiving at least one dose of talimogene laherparepvec and the number of subjects receiving talimogene laherparepvec by duration of exposure (0 to <6 months, 6 to <12 months, 12 to <18 months, and ≥ 18 months).

Table 31. Schedule of Required Evaluations for Study 002/03

	Pre-screen	Screen	Day 1 Pre 0	0 (day 1)	0 + 1h	0 + 4h	0 + 6h	Day 2 + 24h	Day 3 + 48h	Sub-Sequent injections	One-week Follow-up (post first Injection)	Final Visit (30 days post last dose)	Follow-up (every 3 Months)
Histopathology	X												
Clinical Assessment		X										X	
ECOG		X	X							X		X	
Hematology-Chemistry		X	X						X	X		X	
CT		X								X Q 12 weeks			
ECG		X											
Antinuclear Antibody		X								X q 12 weeks			
Injection				X						X			
Ab to HSV1		X								X q 6 weeks			
PCR vector Blood and Urine			X		X	X	X	X	X				
Medical AE													
Vital signs		X		X	X	X	X	X	X				
Survival			X	X	X	X	X	X	X	X	X	X	X

Screening occurred within 2 weeks of the first dose of talimogene laherparepvec. Treatment regimen for 002/03 (E) was similar to Study 005/05 (E) for talimogene laherparepvec. The total number of doses (up to eight doses were given) was less than the number given with Study 005/05. In addition, accelerated dosing was not utilized in Study 002/03.

Assessment for safety in Study 002/03:

Clinical laboratory testing*:* similar to Study 005/05 as described above in Table 24.

Adverse event*:* graded per CTCAE 3 and submitted in the BLA with MedDRA classification system.

The safety profile for Study 002/03 was similar to Study 005/05 for safety issues concerning the talimogene laherparepvec arm of Study 005/05. Dosing was the same but exposure was less due to a shorter planned treatment.

Shedding data collection for Study 002/03:

- *Polymerase Chain Reaction (PCR) for vector in blood and urine:* pre-dose and 1.4.6 hours post dose, day 2- 24 hours post dose, and day 3- 48 hours post dose. *Antibodies to vector in blood:* HSV1 antibody by [redacted] at screening, 3, 6, 9,12,15,18, 21, and 24 weeks, and the final visit (Note: These tests were not validated: see Section 8.4.9.
- *Viral Screening:* swabs from exterior of the occlusive dressing and the injected tumor.

Studies 001/01, 001/01, 004/04, 005/04, and 006/09 along with the above studies constituted the Program -Wide Analysis Set. The final clinical study reports were included in the submission on 7.25.14. FDA reviewed safety information provided for these studies to assess adverse events of special interest, immune related events, and deaths.

Safety information was assessed through the database and the summaries in the clinical study reports.

8.2 Safety Databases

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Safety Databases are described in Table 32.
Studies 005/05, 005/05E formed the basis Protocols for the Primary Melanoma Safety Analysis Set: The assessments that were used to assess safety by the applicant and the in the FDA analysis of Study 005/05 are in Table 24. Adverse events were recorded and graded per CTCAE 3.0. The BLA submission used MedDRA coding for preferred terms.
Studies 002/03, 002/03 E (expanded access) and 005/05, 005/05E (expanded access) formed the Supportive Melanoma Analysis Set. Table 32.

Primary Melanoma Safety Analysis Set: Study 005/05 with extension study (E)
Supportive Melanoma Analysis Set: Study 002/03 (E) + Study 005/05 (E)
Program-Wide Analysis Set: Study 005/05 (E), Study 002/03 (E) + Study 001/01, Study 004/04, Study 005/04, Study 006/09.

Table 32. Talimogene Laherparepvec in All Safety Analysis Sets

	Primary Melanoma Safety Analysis Set N=419 (GM-CSF and talimogene laherparepvec)		**Supportive Melanoma Analysis Set N=342**	**Program-Wide Analysis Set N=408**	**Comments**
Studies	GM-CSF N=127	Talimogene laherparepvec N=292	Talimogene laherparepvec only	Talimogene laherparepvec only	
005/05	X	X	X	X	melanoma
005/05E	X	X	X	X	melanoma
002/03			X	X	melanoma
002/03E			X	X	melanoma
001/01				X	First in human, multiple diagnosis
004/04				X	Squamous cell carcinoma of the head and neck
005/04				X	Pancreatic Cancer
006/09				X	Squamous cell carcinoma of the head and neck
009/07					Registry for LTFU for other talimogene laherparepvec studies.

Clinical Reviewers' Comments:
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 those 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.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Exposure to Talimogene laherparepvec (Table 33, Table 34, below):

- Primary Melanoma Analysis Set (Study 005/05):
  - Median treatment with talimogene laherparepvec was 23 weeks (range 0.1-78.9 weeks and 10 weeks (0.6 – 72 weeks) in the GM-CSF arm.
  - Includes adverse event data on 127 who received GM-CSF alone as comparison to talimogene laherparepvec.
  - The cut- off for new data for the Primary Analysis Data Set for Study 005/05 was:
    - 005/05: March 5, 2014
    - 005/05-E: June 2, 2014

- Supportive Melanoma Analysis Set (005/05[E] plus 002/03[E]) of 342 (372 were enrolled but only 342 received at least one dose of talimogene laherparepvec) received talimogene laherparepvec for:
  - < 6 months: 206 subjects
  - 6- < 12 months: 94 subjects
  - 12-< 18 months: 22 subjects, and
  - ≥ 18 months: 20 subjects.
  - Median duration was 22.1 weeks (0.1-132.1 weeks)

In the Primary Melanoma Safety Analysis Set, baseline demographics were generally balanced between the talimogene laherparepvec and GM-CSF arms (Table 12). Full demographic and baseline characteristics for 005/05 are described in Section 6.2.1.1 of the review. In the Supportive Melanoma Analysis Set, age and race were generally consistent across the talimogene laherparepvec studies.

Table 33. Exposure of Subjects to Talimogene Laherparepvec Over the Duration of the Study(ies)

	≥ 1 dose	0 - < 6 months	6 – < 12 months	12 - < 18 months	18 months and longer
Overall total exposure (Program-Wide Data Set)	**408**	**269**	**96**	**23**	**20**
Melanoma Studies Supportive Melanoma Data Set	**342**	**206**	**94**	**22**	**20**
Non-Melanoma Studies	**66**	**63**	**2**	**1**	**0**

[Source: BLA Submission]

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. In 005/05, 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 GM-CSF arm. (Table 34)

Table 34. Treatment Duration Study 005/05 Safety Analysis

	Talimogene laherparepvec	GM-CSF
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 in Study 005/05. 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.

Accelerated therapy (Section 6.1.5.1) in the talimogene laherparepvec arm occurred in 82 of the 292 evaluated in the primary safety analysis set (Table 35**)**. Accelerated dosing was defined as subjects who received 2 consecutive doses of talimogene laherparepvec less than 9 days apart. The accelerated talimogene laherparepvec dosing could be given once weekly for four doses if there were lesions that progressed after previous injection and this could be repeated up to 3 times. Therefore, subjects who received accelerated dosing had a higher overall exposure to talimogene laherparepvec. Accelerated dosing was restricted to the talimogene laherparepvec arm of the study 005/05. Accelerated dosing was not included in the single arm melanoma study 002/03.

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 35). Subjects who received accelerated dosing had a higher overall exposure to talimogene laherparepvec.

Clinical Reviewers' Comment: *The accelerated dosing provided safety data for higher dosing (weekly) in 82 subjects. In general, the safety profile did not change with the accelerated schedule. Accelerated dosing was as well tolerated as standard dosing despite weekly exposure to talimogene laherparepvec.*

Table 35. Dosing for Talimogene Laherparepvec after Initial Does (Study 005/05)

	Talimogene Laherparepvec (Accelerated Dosing) N=82	Talimogene Laherparepvec (no Accelerated Dosing) N=210	Total Talimogene Laherparepvec N=292
Average dose post cycle 1 day 1 (10^8 pfu)			
Subjects	82	208	290
Mean (10^8 pfu)	3.21	2.68	2.83
SD (10^8 pfu)	1.03	1.25	1.21
Median (10^8 pfu)	3.74	2.94	3.33
Min, Max (10^8 pfu)	0.5, 4.0	0.3, 4.4	0.3, 4.4
Average Volume post cycle 1 day 1 (ml)			
Mean	3.21	2.69	2.84
SD	1.03	1.25	1.22
Median	3.74	2.94	3.33
Min, Max	0.5,4.0	0.3, 4.4	0.3, 4.4

[Source: BLA Submission] * After initial dose, two subjects had dropped out.

Table 36. Dosing for GM-CSF

		GM-CSF
Subjects		127
Daily prescribed dose (µg)		
	Mean	245.58
	SD	49.01
	Median	247.50
	Min, Max	125.0, 515.0
Dose Reductions n (%)		
	One	6 (5%)
Number of Doses		
	Mean	60.46
	SD	54.78
	Median	42.00
	Min, Max	4.0, 252.0

[Source: BLA Submission]

The shorter treatment duration in the GM-CSF group was primarily due to a higher rate of discontinuations within the first 3 months of study treatment in that group (79 of 127 subjects [62.2%]) compared with the talimogene laherparepvec group (86 of 292 subjects [29.5%]). The discontinuations were attributed to progressive disease, adverse events (Section 6.2.1.2 and Section 6.2.3.9) and withdrawn consents. These occurred despite the protocol stipulation that subjects continue on therapy even with evidence of PD.

Dosing for talimogene laherparepvec and GM-CSF is described in Section 6.1.5.

Exposure to GM-CSF was less than that to talimogene laherparepvec. The method of administration also was different, with talimogene laherparepvec given directly into the tumor lesions and GM-CSF subcutaneously into normal tissue. The differences in the method of administration were considered in the evaluation of safety reports of adverse events. In general, the review focuses on the adverse events for talimogene laherparepvec. The issues for talimogene laherparepvec included the local effect of the talimogene laherparepvec (wound healing, cellulitis) and systemic effects (flu-like illness, new herpetic lesions).

8.2.3 Dose Modifications

The dose schedule for the talimogene laherparepvec allowed for variability dependent on lesion size, lesion number, and investigator choice. For the 10^8 PFU doses in the talimogene laherparepvec arm, the mean dose was 2.68 x 10^8 PFU with a mean volume of 2.69 ml when the non-accelerated dosing regimen was given and increased to 3.21 x 10^8 PFU with a volume of 3.21 ml in the accelerated dosing group (
Table 35). In the FDA review of the durable responders, in general, few subjects were given the maximum volume of 4 ml of 10^8 PFU. This was mainly due to small lesion size in many of the durable responders. Small lesion size translated into non-injectable lesions or clusters of small lesions that were dosed together and still due to size were given a small volume.

Clinical Reviewers' Comment: *Lesion size is an issue with the dosing instructions. In particular, small clusters of lesions which when the applicant queried investigators, were often treated in aggregate. See Section 6.2.2.1.*

Discontinuations for Adverse Events**:** See Section 6.2.3.9

8.2.4 Categorization of Adverse Events

This is discussed in Section 6.2.3.2.

8.3 Safety Results

8.3.1 Deaths
Deaths on study 005/05 are listed in Table 27. The main cause of death in both the talimogene laherparepvec and the GM-CSF arms was disease progression with the exception of three subjects on the talimogene laherparepvec arm who died of myocardial infraction, cardiac arrest, and sepsis respectively. Deaths on Studies 001/01, 002/03, 005/05 were also related to their primary disease or medically debilitated state from their advanced cancers.

Clinical Reviewers' Comment:
The primary cause of death across all studies is disease progression. The other causes of death were related to the debilitated medical status of the subjects or advanced age (Section 6.2.3.4).

8.3.2 Nonfatal Serious Adverse Events

Serious adverse events in Supportive Melanoma Analysis Set were consistent with the Primary group (See Table 28, Section 6.2.3.5).

8.3.3 Study Discontinuations

See Section 6.2.3.9

8.3.4 Common Adverse Events
Please see Section 6.2.3.3 and Table 26.

In the Primary Melanoma Analysis Set (005/05), the incidence of all treatment emergent adverse events was 99.3% for the talimogene laherparepvec group and 99.3% for the GM-CSF group. See Section 6.2.3.3

In the Supportive Melanoma Analysis Set the results for common adverse events were similar to those in 005/05 (Section 6.2.3.3.)

8.3.5 Clinical Test Results
There were no clinically relevant differences in laboratory values between the talimogene laherparepvec and GM-CSF treatment arms. No Grade 3 or 4 adverse events were noted if the baseline Grade was 0 or 1 for bilirubin, alkaline phosphatase, ALT, and AST were noted in the Primary Analysis Set (Section 6.2.3.8). This was also true of the Supportive Melanoma Analysis Set.

With respect to HSV-1 studies for the Program-Wide Analysis Set, 63.4% were positive at study entry.

- Study 001/01: All sero-negative subjects converted to positive within 3 weeks of the first dose of talimogene laherparepvec
- Study 002/03: No subjects were sero-negative after the first dose of 10^6 PFU/ml of talimogene laherparepvec.
- Study 004/04: All but 2 subjects converted to seropositive after two doses and all were seropositive by the end of the study.
- Study 005/04: All were seropositive after the first dose.
- Study 005/05: 59.9% seropositive at baseline. Of the 98 negative subjects in the talimogene laherparepvec arm, post treatment results are available for 85. Seventy- seven became positive by cycle 3. Tests on the remaining seronegative subjects revealed that 3 remained negative at cycle 3 and 5 at cycle 5. Symptoms such as pyrexia, chills, and influenza like illness were more prominent in the seronegative group.

Clinical Reviewers' Comment:
This is consistent with exposure to a live virus vaccine and the known incidence of herpes simplex in the general adult population.

8.3.6 Systemic Adverse Events
Vital signs were stable in the Primary Melanoma Analysis Set and Supportive Melanoma Set. Deterioration of clinical status was primarily due to disease progression.

8.3.7 Local Reactogenicity
See Section 6.2.3.3.

8.4 Additional Safety Evaluations

8.4.1 Dose Dependency for Adverse Events
None.

Clinical Reviewers' Comment:
In the absence of knowing the dose of talimogene laherparepvec that was injected into each lesion, it is not possible to assess dose dependency.

8.4.2 Time Dependency for Adverse Events

With the exception of more pronounced pyrexia, chills, and influenza like illness in the HSV-1 seronegative subjects who received talimogene laherparepvec, there were no time dependent adverse events for talimogene laherparepvec. For the comparison of GM-CSF and talimogene laherparepvec, there was as previously noted a shorter treatment time for those in the GM-CSF arm due to early discontinuation of therapy due to disease progression.

8.4.3 Product-Demographic Interaction

Please see Section 9.1.

Clinical Reviewers' Comment:
The subject population was older with a mean age of 63 (14 year SD). Few younger subjects were included.

8.4.4 Product-Disease Interactions

No analysis of safety was conducted by stage of disease. Please see Section 9.1.

8.4.5 Product-Product Interactions
There were no product-product interactions.

8.4.6 Human Carcinogenicity
There were second malignancies reported but did not appear to be associated with talimogene laherparepvec. See Section 6.2.3.7

8.4.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound
There was no information on overdose. There is no concern about abuse potential.

8.4.8 Immunogenicity (Safety)
Autoimmune reactions were reported such as glomerulonephritis but no definite association was established with the treatment with talimogene laherparepvec. No immune studies were done in Study 005/05 to correlate an immune response to treatment with talimogene laherparepvec.

8.4.9 Person-to-Person Transmission, Shedding

Talimogene laherparepvec is an oncolytic virus; therefore traditional pharmacokinetic studies to evaluate the absorption, distribution, and metabolism, elimination, and drug-drug interactions were not used. Instead, the applicant evaluated the virus in the context of the site of intralesional injection and tumor-selective replication. These evaluations included the assessment of viral clearance through:

- Analysis of the biodistribution in blood and urine
- Shedding of infectious virus from the surface of injected tumors and the exterior of occlusive dressing at specific time-points post-injection.
- Blood and urine were analyzed with quantitative polymerase chain reaction (qPCR) assays which detected talimogene laherparepvec viral DNA as non-infectious fragments or potentially infectious intact genomes.
- Shedding of infectious virus was analyzed by plaque assays of collection swabs.

In Studies 001/01, 002/03, 004/04 and 005/04, the biodistribution of talimogene laherparepvec in humans was evaluated. In addition, there was some information collected on the 005/05 study. All the initial evaluations of viral biodistribution were done with non-validated assays.

Recently, to further delineate the biodistribution and shedding profile an additional study was initiated (Amgen 20120324) which is an on-going single-arm study of Stage IIIB to Stage IV M1a melanoma. Thirty to 40 subjects are to be enrolled. Biodistribution is evaluated with blood and urine samples utilizing qPCR. Shedding is further tested with swabs of the exterior of occlusive dressings, injected lesions, oral mucosa, genital mucosa, and new lesions suspected to be of herpetic origin by qPCR. Initial analysis with qPCR if positive, is followed with additional studies to determine if the virus was infectious. There is also a data collection at the end of treatment to assess potential asymptomatic shedding. In close contacts such as family and health care workers, qPCR of suspected lesions will be done to look for talimogene laherparepvec. FDA has received an update in the 120 day safety report of 20/60 planned subjects on this study.

8.4.9.1 Overview of Biodistribution and Vital Shedding

Table 37. Overview of Biodistribution and Viral Shedding, Data Obtained in Each Clinical Study of Talimogene Laherparepvec

Study Number	qPCR assay for talimogene laherparepvec DNA in blood and urine	Plaque assay for detection of infectious virus from swabs	Reactive Swabs (oozing lesions, dressings)
001/01	X	X	X
002/03 (Melanoma)	X	X	X
004/04		X	X
005/04	X		
005/05 (Melanoma)			X

Viral Shedding:

- Measured by swabs of the surface of injected tumors and the exterior dressings.

- Of note, the plaques assay did not distinguish between wild type (WT) HSV-1 and talimogene laherparepvec.
- No testing for virus at site of GM-CSF injections
- Swabs done after all injections on 001/01 and 004/04 and after the first injection in Study 002/03.
- Reactive swabs were collected in Studies 001/01, 002/03, 004/04, and 005/05 from herpes labialis or other non-injected lesions that arose and were suspected to be herpetic in origin.
- Herpes testing methods were not validated.

Study 001/01:

- Most comprehensive early study.
- N= 27.
- Subjects had multiple tumor diagnoses
- Part 1: received single doses of 10^6, 10^7, and 10^8 PFU/ml in separate dose cohorts
- Part 2: received one dose of 10^6 PFU/ml, followed by 2 doses of either 10^7 or 10^9 PFU/ml.
- Blood and urine samples were collected for up to 7 weeks in part 1 and 14 weeks in part 2.
- Collection times were designed to include any signs of viral replication in the first 48 to 72 hours after a dose.
- Results:
  - 3% positive in blood and urine in part 1, 48 hours after dose
  - 5% positive in part 2, 48 hours after dose and transiently (up to 1 week) in blood.
  - Viral DNA was not detected in the urine samples in part 2 (multiple doses)
  - Four swabs positive for talimogene laherparepvec by qPCR.

Study 002/03:

- Shedding studies started before the results from Study 001/01 were available N=28, diagnosis: melanoma Stage IIIC or Stage IV, shedding results consistent with 001/01.
- Only one of 28 samples tested positive for talimogene laherparepvec virus by swabbing.
- Due to limited data from 001/01 and lack of positive swabs, no benefit to further blood and urine testing was cited as the reason to discontinue shedding studies for this trial.

Studies 004/04 and 005/04

- Similar pattern of biodistribution to 001/01 and 002/03.
- N= 3 of 17 had swabs for virus on 004/04.
- Disease: 004/04: squamous cell carcinoma of the head and neck (SCCHN); 005/04: pancreatic cancer.
- Measured viral DNA in tumor biopsies which confirmed preclinical studies that talimogene laherparepvec remains at the site of injection and this is where the viral replication occurs and not in the blood. It also explained the lower levels of viral DNA in the blood and urine samples noted above.

Clinical Reviewers' Comment:
The methods used to detect the talimogene laherparepvec in the above studies were not validated. Therefore, while these results provide a framework for future shedding studies, FDA recommended to the sponsor that they conduct a more comprehensive shedding study based on these preliminary studies. The ongoing shedding study (Amgen 20120324) as well as the planned pharmacovigilance trial (postmarketing study) will assess shedding and general risks that may be associated with the shedding of the virus.

8.4.9.2 Accidental Exposure to Talimogene laherparepvec

Accidental Exposure from Subjects who received talimogene laherparepvec to family members and health care providers:

In the Study 005/05 there was intermittent surveillance of family members and health care providers.

- Accidental exposure was reported in 5 health care workers
- One developed a herpetic infection at the site of a needle stick which resolved with therapy with acyclovir. A second needle stick was treated immediately.
- One HCP experienced exposure to their eye which was treated with anti-viral ophthalmic ointment without sequelae.
- Questionnaires to close contacts and HCPs did not produce evidence of significant risk.
    - Family Surveillance Questionnaire: family, caregivers, or other household contacts. To be completed at the beginning of each cycle (monthly) of talimogene laherparepvec and at the time of signs or symptoms of a herpetic infection.
    - Healthcare Staff Questionnaire: Monthly, to include healthcare staff and covered the preparation, handling, and/or administering of the talimogene laherparepvec.
- Results:
    - Family Surveillance Questionnaire:
        - 177 of the expected 226 subjects participated with an actual completion rate of 49-55%.
        - 11 subjects identified cohabitants that had signs and symptoms that may be related to the subject's participation in the clinical trial
        - Two subjects indicated that they had a health care provider who had signs and symptoms that may be related to the subject's treatment
        - Two subjects indicated that they had contact who had signs and symptoms
        - Healthcare Staff Questionnaires:
            - 51 of 64 sites for 005/05 participated
            - 82 questionnaires total were returned from 36 sites with a completion rate of 14%.

Clinical Reviewers' Comment:
There was limited participation with the questionnaires. In the health care contact group with very limited compliance (14%), there was one confirmed herpetic lesion after a

needle puncture although there was no confirmation that it was talimogene laherparepvec. The lesion responded to acyclovir and subsequent exposure with immediate treatment in the same individual did not result in a second infection. In the household contact Group where there was an approximate compliance of 50%, there were no major concerns raised by the survey results. Overall, with limited data, there is no significant risk identified. Post-marketing surveillance will need to address at risk contacts and confirm this conclusion. In addition, labelling and patient information will need to clearly define the possible risk and appropriate clinical step for exposed individual if talimogene laherparepvec is to be approved.

8.4.9.3 On-going Shedding Study and Postmarketing Pharmacovigilance Plan

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

The trial design and preliminary shedding information for talimogene laherparepvec from the ongoing shedding protocol (Amgen 20120324) are described in Table 38 and Table 39. The trial design for the proposed postmarketing study (Protocol #20130193) is described in Table 40 and summarized below.

8.4.9.4 Shedding Protocol (Amgen 20120324)

Table 38. 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 Study 005/05

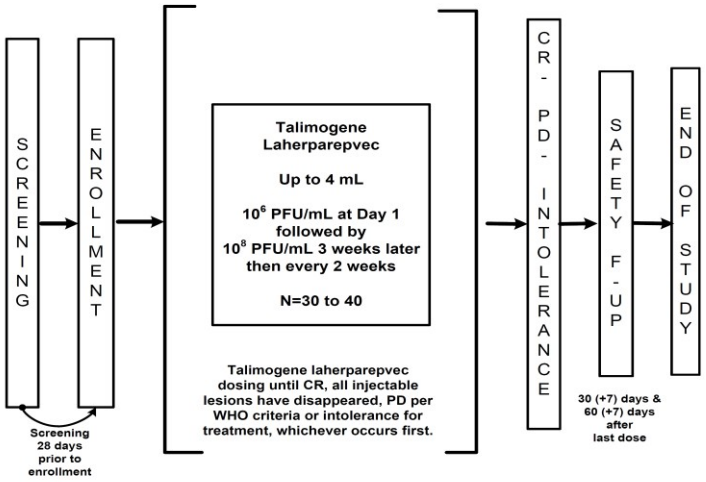
Dose	Talimogene laherparepvec is administered by intralesional injection into injectable cutaneous, subcutaneous, and nodal lesions at an initial dose of up to 4 ml of 10^6 PFU/mL followed by a dose of up to 4 ml of 10^8 PFU/mL 21 days after the initial dose and every 14 (± 3) days thereafter.
Treatment Plan	
Sample Analyses	Samples will be analyzed according to the sampling plan described in Table 49.
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 39. Sampling Plan for Amgen Protocol 201203241[1]

Blood[2]/Urine qPCR	Occlusive Dressing/injection site swabs[3]: qPCR and TCID50[4]	Oral mucosal swab: qPCR and TCID50	Unscheduled 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 talimogene laherparepvec administered to lesions below the waist.** **Other unscheduled sampling for whatever reason.**
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**	
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** **Day +30, 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.

8.4.9.5 Summary of preliminary results[1] from the shedding study: Amgen 20120324

Talimogene laherparepvec viral DNA levels in various tissues and secretions were determined using a quantitative polymerase chain reaction (qPCR) assay. Infectious talimogene laherparepvec at the injection sites and at some potential herpetic lesions was also quantified using viral infectivity assays.

The biodistribution and shedding of intralesionally administered talimogene laherparepvec is being investigated in an ongoing study measuring talimogene laherparepvec DNA and virus in blood, oral mucosa, urine, injection site, and occlusive dressings. In the initial 20 subjects with melanoma who received talimogene laherparepvec intralesional injection at a dose and schedule similar to that of Study 005/05 *(*Table 38*,* Table 39*).* Available data indicate that talimogene laherparepvec DNA was present in the blood in 17 (85%) subjects and in urine of 4 (20%) subjects during the study. The peak levels of talimogene laherparepvec DNA in the urine were detected on the day of treatment. Infectious talimogene laherparepvec virus was detected at the site of injection in 3 (15%) subjects at a single time point each, and all within the first week after the initial injection. The exterior of the occlusive dressings was positive for talimogene laherparepvec DNA in 14 (70%) subjects during the study; however, no infectious virus was detected on the exterior of the occlusive dressing. The number of subjects with measurable levels of talimogene laherparepvec DNA on the exterior of occlusive dressings declined over time with no measurable DNA by the third treatment in 13 subjects tested.

Clinical Reviewers' Comment:
This study is incomplete but the testing so far suggests that there is a low risk to the general population from the shedding of viral particles of talimogene laherparepvec. The presence of live virus in blood and urine is not being evaluated in the current shedding study due to assay difficulties. However, the presence of viral DNA is being evaluated.

8.4.9.6 Pharmacovigilance Plan
In order to monitor and evaluate transmission of talimogene laherparepvec to HCPs and close contacts, the applicant has proposed a postmarketing study.

Table 40. Proposed Postmarketing Study (Amgen 20130193)

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
Study duration	5 years
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 by qPCR, occurring more than 30 days after ending use of talimogene laherparepvec, i.e., symptomatic reactivation in subject • Case counts of close contacts and HCPs with product-positive herpetic lesion "occurring during the treatment period of subject." • Adverse Drug Reactions, Serious Adverse Drug Reactions (Adverse Drug Reactions (ADRS) listed in Appendix 3 of the PV review). • Data on demographics, disease characteristics, and treatment use • Overall survival will be estimated with Kaplan-Meier method with the time to death being calculated from the date of study enrolment. Subjects will be censored who are alive or lost to follow-up.
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) • Spontaneous reporting and unsolicited follow-up Multi-step process of sample collection: Individual reports suspected herpetic infection to Amgen and visits HCP; Amgen sends questionnaire to HCP, reviews HCP's response to questionnaire and provide a list of "acceptable swabs" for sample collection. HCP determines if qPCR testing is required for 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.
Statistical Plan	Estimate two measures of product-positive herpetic lesions: o incidence rate of herpetic lesions: number of events/ subject-years o incidence proportion of subjects with herpetic lesions: number of subjects who have an event/number of enrolled subjects According to the sponsor, the sample size of 920 subjects is powered to have an 80% probability of detecting a true event rate of 1 per 1000 subject-years; "a criterion met with 1600 subject-years of observation. If zero primary endpoints occur, the precision at the 95% confidence level for the incidence rate is 0 to 2.3 events per 1000 subject-years and for the incidence proportion is 0 to 0.4% of

	subjects."
	Study Status: planned PMR study 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.

Clinical Reviewers' Comments:
It is unclear how the determination of which lesions would need qPCR testing. In addition, the onus would be on the primary HCP to 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.

In addition to routine pharmacovigilance and adverse event reporting in accordance with 21 CFR 600.80, the following actions are recommended:

Expanded adverse experience reporting (in addition to complying with the requirements under 21 CFR 600.80) to FAERS for 3 years following product licensure of all reports of herpetic infection in patients and contacts, with Talimogene qPCR results when available, submitted as 30-day (monthly) reports if not previously filed as 15-day reports.

After review of the existing safety and shedding data, it was decided that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the

FDCA will not be sufficient to identify "unexpected serious risk when available data indicates the potential for a serious risk" for talimogene laherparepvec associated herpetic infection of non-tumor tissue in patients (primary infection/latency and reactivation) and contacts (transmission/accidental exposure). Furthermore, the new FDA pharmacovigilance system under Section 505(k)(3) of the FDCA would not be sufficient to identify this serious risk. Therefore, based on appropriate scientific data, when talimogene laherparepvec is approved, it has determined that Amgen is required, under Section 505(o) of the FDCA (amended by FDAAA, Title IX, Section 901), to conduct two PMR studies (see above: Completion of the ongoing Shedding Study, Amgen 201203241 and Amgen 20130193). The PMR studies were concurred by CBER FDAAA SWG on June 25, 2015. The timeline for Amgen 201203241 is listed in Table 40.

Clinical Reviewers' Comment:
Per the Office of Biostatistics and Epidemiology (OBE) the available clinical trial safety data did not suggest a safety concern that would require a Risk Evaluation and Mitigation Strategy (REMS) to ensure that benefits of Talimogene outweigh its risks. If any future safety concerns are identified, FDA may recommend further modifications of the above listed pharmacovigilance activities. However, due to the first in class product, it was decided to issue a Medication Guide for patients.

8.5 Safety Conclusions

Clinical Reviewers' Comment:
There appears to be minimal risk to treatment with talimogene laherparepvec based on the safety profile in the Safety Data Sets. In general, it was well tolerated. The most common cause of any adverse event was progressive disease. The serious adverse events reported were again associated primarily with progression. Other serious events included cellulitis and the symptoms associated with an influenza-like clinical picture which is consistent with therapy with an oncolytic virus. There is a consistency of data results from the Primary melanoma Analysis Set to the Program-Wide Analysis Set. Updated shedding information in a study specifically designed to observe shedding throughout the treatment program is consistent with preliminary shedding data on the Phase 1 and Phase 2 studies. The one documented health care exposure was due to a needle stick and responded to acyclovir therapy. Additional close contact exposure related infections will need to be monitored in the future for response to available anti-herpes viral therapy.

The shedding data to date on close household contacts and medical personnel is incomplete. The initial exploratory shedding studies lacked a validated assay. The Amgen 20120324 trial is ongoing. With the limited data from the latter study as well as exploratory shedding data from the earlier trials in the Program-Wide Safety Data Set, it appears that there is no evidence of increased risk with the attenuated product as compared to experience with wild type Herpes Type 1 infections. Further evaluation of at risk subjects, close contacts, and medical personnel will be done with the completion of the current shedding study as well as the planned postmarketing trial. The latter has issues with the planned collection of data on subjects with presumed herpes infections as noted above.

9 Additional Clinical Issues

9.1 Special Populations

There are limited data on the use of talimogene laherparepvec in special populations. Subgroup analyses of adverse events, serious adverse events, and discontinuations due to adverse events were conducted for the following pre-specified intrinsic factors collected at baseline: age (< 65 years vs ≥ 65 years, < 75 years vs ≥ 75 years), sex (male vs female), race (white vs non-white), region (US vs other countries), ECOG performance status (0 vs 1), disease stage (Stage IIIB/C, Stage IV M1a, Stage IV M1b, Stage IV M1c), and HSV-1 serostatus (positive vs negative).

Overall, results of the subgroup analyses for the analysis of adverse events and serious adverse events for talimogene laherparepvec relative to GM-CSF in Study 005/05 did not indicate an altered safety profile of talimogene laherparepvec by age, sex, race, region, or disease stage. The “non-white” subgroup for race comprised < 2% of subjects (n = 8) in the analysis set, and the “other countries” subgroup for region each comprised < 15% of subjects (n = 54) in the analysis set; these small sample sizes should be considered in the interpretation of these data.

9.1.1 Human Reproduction and Pregnancy Data

There are no data on human use of talimogene laherparepvec in pregnant women. In murine studies, there were:

- No talimogene laherparepvec related mortality or maternal signs of clinical issues
- A decrease in body weight in moms
- No talimogene laherparepvec-related effects on litters
- No increase in fetal deaths or complications
- No increase in visceral, external, or skeletal malformations.
- Negligible transfer of viral DNA from murine mother to fetus.

There is no data on the use or exposure to talimogene laherparepvec in the pregnant female and newborns (breastfed infants). There were limited pre-clinical data in murine models submitted with the BLA.

Overall, limited safety data was provided for subpopulations. One may extrapolate from known HSV-1 data for maternal-fetal transmission risk and breastfeeding neonates but talimogene laherparepvec is an attenuated product. The murine data on pregnant mice was limited but indicated that perhaps the risk is low. This information was relevant to our lack of complete shedding profile and our ability to provide a risk assessment for an acquired infection. For most cases, the infected individual could be treated with anti-virals but in the context of pregnancy, there may be an increased risk to the fetus.

9.1.2 Human HSV-1 Data (not attenuated)

- 25-65% of women in the United States have genital infection with HSV-1 or HSV -2 associated with a neonatal HSV infection rate of 8-60 per 100,000 live births (Corey and Wald, 2009).

- HSV infection of the neonate occurs during transit through the birth canal with 5% occurring in utero and these are most often associated with systemic infection in the mother (Straface et al., 2012). One-third of newly diagnosed genital infections are due to HSV-1 so the risk is low. However newly infected women during pregnancy carry the highest risk of viral transmission due to lack of passive immunity.
- Highest intrauterine infection is the first 20 weeks.

Clinical Reviewers' Comment:

There are known statistics to establish risk of herpes infection in utero and at birth dependent on the history of genital herpes in the mother (Baker, 2007). There is no data for the attenuated talimogene laherparepvec virus. The murine model did not identify issues but this may not be reflective of what occurs with human infection. Therefore, the use of talimogene laherparepvec is contraindicated in pregnant females. In addition, pregnant health care workers and close contacts will need to be protected with appropriate safety precautions. In particular, they should have no contact with the injections sites or dressings.

9.1.3 Use During Lactation

There are no data on the use of this product in subjects who were breast feeding.

9.1.4 Pediatric Use and PREA Considerations

The sponsor requested Orphan designation for the indicated population of Stage IIIB, IIIC and IV melanoma and it was granted on March 14, 2011. Therefore, the product is exempt from PREA regulations. No pediatric data were presented in the application.

9.1.5 Immunocompromised Patients

There was no human data submitted on immunocompromised subjects. . In Study 005/05 studies, immune-mediated events, including glomerulonephritis, vasculitis, pneumonitis, worsening psoriasis, and vitiligo were reported in subjects treated with talimogene laherparepvec.

Clinical Reviewers' Comment:

*Therefore**,** talimogene laherparepvec is contraindicated in patients with underlying autoimmune disease. In patients who develop immune-mediated events, therapy with talimogene laherparepvec should be discontinued..*

9.1.6 Geriatric Use

The median and mean age of the talimogene laherparepvec subjects treated on Study 005/05 was 63 years. Analyses for subjects in Study 005/05 > 65 and ≤ 65 as well as > 75 and ≤ 75 were done. The product was well tolerated but the number of subjects exposed was limited.

Clinical Reviewers' Comments:

- *There is no data on the use or exposure to talimogene laherparepvec in the pregnant female, immunocompromised subject, and newborns (breastfed infants). There was limited pre-clinical data in murine models with the BLA submission. The shedding data to date on close household contacts and*

medical personnel is incomplete. The initial exploratory shedding studies lacked a validated assay. The ongoing Amgen 20120324 trial to describe the shedding patterns for talimogene laherparepvec is ongoing. However, with the limited data available, it appears that there is no increased risk with the attenuated product. Further evaluation of at risk subjects, close contacts, and medical personnel will be done with the completion of the current shedding study as well as the planned postmarketing trial.

- *Overall, there were limited safety data provided for subpopulations. One may extrapolate from known HSV-1 data for maternal-fetal transmission risk, risks to immunocompromised subjects, and breastfeeding neonates but talimogene laherparepvec is an attenuated product. The murine data on pregnant mice are limited but indicate that perhaps the risk is lower. This information also is relevant to our lack of complete shedding profile and a risk assessment of an acquired infection. If there was transmission of talimogene laherparepvec, in most cases, the infected individual could be treated with anti-virals but in the context of pregnancy, there may also be an increased risk to the fetus.*

10 Clinical Review Conclusions

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 GM-CSF (15.6% vs. 1.4%; $p < 0.0001$). The unadjusted relative risk was 7.6 (95% CI 2.4, 24.1), with a p-value of 0.0001."
Although the review of study shows evidence of potential bias in study design, conduct, and results, the difference in the durable response rate appears to be sufficiently robust so that the overall conclusions are unlikely to be affected by bias.

The key secondary endpoint of overall survival in the ITT population was not statistically significant with a p value of 0.051 at the time of the final analysis. An updated analysis of survival data by the FDA including information on missing subjects had a p value of 0.116. Therefore, there was no survival advantage from talimogene laherparepvec treatment in the ITT population. In addition, there was no clear evidence of systemic anti-tumor activity. However, in a subgroup of subjects with re-staged Stage IIIB, IIIC and IV1Ma, talimogene laherparepvec treatment appeared to have a longer overall survival and DRR compared with subcutaneously administered GM-CSF. However in the absence of a significant difference in the ITT population, this observation is considered to be exploratory. There was no difference between treatment arms in either DRR or OS in subjects with visceral metastasis.

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. There is no data on the use of talimogene laherparepvec in pregnancy or immune compromised patients. Therefore, the recommendation is that these patients not receive talimogene

laherparepvec. The applicant has proposed a pharmacovigilance plan to collect postmarketing safety data which proposes a complicated and difficult plan to obtain information on those most at risk for infection with talimogene laherparepvec. The applicant has agreed to complete the ongoing shedding study and initiate a pharmacovigilance study as reviewed by the OBE. Additional information will be collected on close contacts and possible herpes infections that may be secondary to the talimogene laherparepvec.

11 Risk-Benefit Considerations and Recommendations

11.1 Risk-Benefit Considerations

As stated above, the risk of talimogene laherparepvec appears to be reasonable, considering the risks associated with recently approved systemic agents for advanced or metastatic melanoma. These risks include severe immune reactions such as colitis, pneumonitis, and other medical morbidities, while the safety profile for talimogene laherparepvec is tolerable, although a fair comparison was not possible due to the lack of information from a head to head comparison.

Benefit from talimogene laherparepvec appears to be tumor shrinkage, either partial response or complete disappearance of cutaneous, subcutaneous, and nodal lesions. This tumor shrinkage benefit has to be considered in the following contexts:

1) There are other therapies for advanced melanoma approved based on the prolongation of overall survival (see Appendix Section 12).

2) This benefit of tumor shrinkage in the locoregional recurrence of cutaneous, subcutaneous, or nodal melanoma lesions did not support the following indication that the applicant is seeking: injectable regionally or distantly metastatic melanoma. Clinical reviewers have considerable concerns regarding this proposed indication. It is too broad and allows use of talimogene laherparepvec in subjects with resectable lesions who are otherwise eligible for curative surgical resection. The patient population of Study 005/05 included only unresectable subjects and most of them had recurrent disease.

3) Study discontinuations: Administration of talimogene laherparepvec 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, this variability in dosing raises concern whether there is sufficient information to ensure the safe use of talimogene laherparepvec for the labeling.

11.2 Risk-Benefit Summary and Assessment

Thus, talimogene laherparepvec appears to have a favorable benefit to risk profile in patients who had recurrence of cutaneous, subcutaneous, or nodal melanoma lesions. However, as stated in Section 11.1, this favorable benefit was mainly manifested as tumor shrinkage rather than improvement in overall survival.

11.3 Discussion of Regulatory Options

Given that this BLA has demonstrated a favorable benefit risk profile of talimogene laherparepvec, clinical reviewers recommend BLA approval.

The available regulatory pathways for approval include:

1. **Traditional approval** for talimogene laherparepvec [21 CFR 314.126 and 21 CFR 601. 125 (d) (2)]. Although Study 005/05 achieved its primary objective of demonstrating a treatment effect on the primary endpoint of DRR, there is absence of a clear benefit on OS in the ITT population. Recent traditional approvals for the treatment of melanoma have been based on improvements in OS or PFS. The lack of a statistically significant OS advantage in the ITT population makes a recommendation for traditional approval problematic.

   Durable **complete** responses (DCRs) have been used in support of traditional approval for other therapies such as IL-2 in metastatic melanoma. However, the small number (19) of subjects had DCR after talimogene laherparepvec and many of them had small to very small baseline lesions, making it very difficult to believe that these DCRs could present a clinical benefit without overall survival advantage (see below for further discussion). In addition, recent traditional approvals in melanoma have been based on OS and PFS benefits.

   The benefit of tumor shrinkage (increased ORR) appeared to be reasonably well correlated with OS in the ITT population and subgroups in the Study 005/05, and could thereby provide a surrogate measure, reasonably likely to predict clinical benefit. However, the DRR may not reflect a clinical benefit for melanoma patients due to the following concerns:

   - The partial response (PR) component of primary endpoint DRR is not considered a clinical benefit.(See FDA Guidance for Industry - Clinical Trial Endpoints the Approval of Cancer Drugs and Biologics Guidance for Industry Clinical Trail Endpoints the Approval of Cancer Drugs and Biologics) (FDA, 2007).
   - Some baseline lesions may have been too small to assess accurately for response.
   - There was equivocal evidence for systemic effect with talimogene laherparepvec treatment.
   - Tumor response as a basis for licensure is usually considered in the context of systemic therapies, not local therapies.

2. **Accelerated Approval** under Subpart E (21CFR601.41),

Subpart E (21CFR601.41), describes Accelerated Approval of biologic products for serious and life-threatening illnesses based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity that provides meaningful therapeutic benefit to patients over existing therapies. Accelerated approval is “subject to the requirement that the applicant study the biologic product further, to verify and describe its clinical benefit, where there is uncertainty as to the

relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome."

The clinical reviewers recommend Accelerated Approval for talimogene laherparepvec for local treatment of cutaneous, subcutaneous and nodal lesions in patients with unresectable, injectable, locoregionally recurrent melanoma, rather than regular "traditional" approval, based upon the following considerations:

- There is uncertainty as to the relation of DRR and ultimate outcomes of clinical benefit, including OS in the ITT population, since the talimogene laherparepvec has not demonstrated an OS advantage.
- Analysis of subgroups showed a higher response rates and a trend in OS prolongation in the stage III subgroups compared with distantly metastatic subgroups. There was "no-effect" on response rates and OS in the stage IV M1b and M1c subgroups. The subjects were restaged at the time of enrollment; the stage IIIB or IIIC was not the stage at the initial melanoma diagnosis. Therefore, the results of the subgroup analyses presented in this BLA for patients with these stages may not be applicable to or relevant for patients who are initially diagnosed with stage IIIB and IIIC melanoma.

Therefore, clinical reviewers opine that the durable response rate (DRR) may be considered as a surrogate endpoint that is reasonably likely to predict clinical benefit such as overall survival in patients with unresectable, injectable, locoregionally recurrent melanoma.

11.4 Advisory committee meeting

A Joint Meeting of CBER's CTGTAC and CDER's ODAC was held on April 29, 2015, to discuss the issues FDA identified during its review for this BLA. After discussions and deliberations, the committee was asked to vote on the following question:

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

Vote: Yes = 22 No = 1 Abstain = 0

- Some committee members who voted "yes" to the question stated that the bulk of the data suggests a favorable benefit – risk profile and that the drug represents an important new tool for oncologists, particularly in a subset of patients with non-visceral disease.

- Some committee members who voted "yes" qualified their vote by recommending that the approval be limited to only unresectable Stage III and earlier metastatic patients; other committee members wanted no limitations on the approval, citing reimbursement issues, physician autonomy, and possible benefits from combination therapy.

- Some committee member stated that “There was very little evidence that patients who had visceral metastases or patients who had large lesions, large skin lesions, actually received any benefit. …I think there is an argument that could be made for an accelerated approval to basically get more data, another clinical trial, in the context of contemporary treatments for advanced melanoma… I would recommend that there be strong labeling discouraging physicians from using it in situations where there is substantial metastatic disease.”

The committee member who voted “no” indicated that he did so to avoid giving blanket approval to a drug that had demonstrated benefit in only a subset of melanoma patients (Stages IIIB, IIIC, and IVM1a).

11.5 Resolution of Review Issues

Clinical reviewers considered review issues discussed in this review regarding both efficacy and safety of this BLA. These issues have been resolved as described below:

a. Patient Population

Because the majority of subjects of Study 005/05 had local regional recurrent melanoma after initial surgery and because the study has not demonstrated a systemic effect including an OS benefit and the treatment effect was associated with a local tumor shrinkage, the indication statement in the packaging insert should read: talimogene laherparepvec is indicated for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery. In addition, the packaging insert should state that talimogene laherparepvec has not been shown to improve overall survival or have an effect on visceral metastases. Therefore, the issue of patient population is resolved.

b. Dosing

To alleviate the concerns regarding the variability in the dosing of talimogene laherparepvec and ensure a safe and effective use, the clinical reviewers recommend that the packaging insert contain clear instructions on the dose calculation, algorithm for injection as well schedules and situations for re-treatment. This dosing variability issue is resolved.

c. Potential risk of viral transmission

Clinical reviewers recommend that the applicant complete the on-going shedding study (Study 20120324) and conduct the postmarketing study (Study 20130193) to characterize the long-term safety in treated patients and the risk of herpetic illness among patients, close contacts, and healthcare providers. Furthermore, the applicant has established a dedicated phone line so that the healthcare professionals and consumers could report issues related to the potential transmissions. In addition, the clinical reviewers recommend that contraindication section of the package insert contraindicate the use of talimogene laherparepvec in pregnant women and individuals who are immunocompromised. Therefore, the clinical reviewers consider that these

measures considerably mitigate the concern of the potential risk of viral transmission, albeit cannot completely resolve it at the time of approval.

11.6 Recommendations on Regulatory Action

The clinical reviewers recommend that FDA grant Accelerated Approval (21 CFR 601.41) subpart E) for talimogene laherparepvec for the local treatment of cutaneous, subcutaneous and nodal lesions in patients with melanoma recurrent after initial surgery.

Postmarketing studies are discussed in Section 11.8 below.

11.7 Labeling Review and Recommendation

Below are review comments and specific recommendations for each particular section of prescribing information.

1 INDICATIONS AND USAGE

Refer to Section 11.5.a.

Refer to Section 11.5.b.

14 CLINICAL STUDIES

Study 005/05 did not demonstrate that talimogene laherparepvec conferred an OS benefit, we recommend that this section include the following description regarding overall survival: There was no statistically significant difference in overall survival (OS) between the talimogene laherparepvec and the GM-CSF arms. The median OS in the overall study population was 22.9 months in the talimogene laherparepvec arm and 19.0 months in the GM-CSF arm (p = 0.116).

11.8 Recommendations for Postmarketing Actions

a. A confirmatory study to describe the clinical benefit of talimogene laherparepvec in the treatment of advanced melanoma subjects, in a combination study of talimogene laherparepvec with other agent, using OS as primary endpoint.
b. 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

12 Appendices

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/guidanc

es/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

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 was 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 was 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

12.3.2.1 Nivolumab Monotherapy

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.

12.3.2.2 Nivolumab and Ipilimumab Combination

On September 30, 2015, a combination of nivolumab and ipilimumab received an accelerated approval from FDA for the treatment of patients with BRAF V600 wild-type unresectable or metastatic melanoma. The approval of the combination of nivolumab and ipilimumab regimen is based on data from the study CheckMate-069, which was the first to report outcomes of the regimen in previously untreated patients with unresectable or metastatic melanoma.

Approval was based on demonstration of an increase in the objective response rate (ORR), prolonged response durations, and improvement in progression-free survival (PFS) in an international, multicenter, double-blind, randomized, two-arm, active-controlled trial in patients who were previously untreated for unresectable or metastatic, BRAF V600 wild-type melanoma.

The clinical trial randomized (2:1) 142 patients to receive nivolumab plus ipilimumab (n=95) or ipilimumab plus placebo (n=47). Randomization was stratified by BRAF V600 mutation status based on an FDA-approved test. Patients in the nivolumab plus ipilimumab arm received nivolumab 1 mg/kg and ipilimumab 3 mg/kg intravenously every 3 weeks for four doses, then nivolumab 3 mg/kg every 2 weeks until disease progression or unacceptable toxicity. Patients in the ipilimumab arm received ipilimumab 3 mg/kg and nivolumab-matched placebo intravenously every 3 weeks for four doses followed by placebo. At the time of disease progression, patients on the ipilimumab arm were offered nivolumab 3 mg/kg every 2 weeks.

Of the 109 patients with BRAF V600 wild-type melanoma, the median age was 66 years and ECOG performance score was 0 (84%) or 1 (15%). Forty-six percent had M1c disease and 20% had elevated baseline LDH.

The trial demonstrated a significant improvement in ORR. The ORR was 60% [95% confidence interval (CI): 48, 71] in the nivolumab plus ipilimumab group (n=72) and 11% [95% CI: 3, 25] in the ipilimumab group (n=37), an improvement in ORR of 49% (95% CI: 31, 61; p-value <0.001). Of the 43 patients with an objective response in the nivolumab plus ipilimumab group, 9 patients (21%) with response duration ranging from 3 to 7 months have progressed after response, died, or received subsequent therapy. The remaining 34 patients (79%) had ongoing responses at the time of final analysis; in 14 patients the duration of ongoing responses is at least 6 months but less than 9 months and in 20 patients the duration of ongoing responses is at least 9 months. In addition, there was a significant improvement in PFS for the combination group compared with the ipilimumab group [HR 0.40 (95% CI: 0.22, 0.71); p-value < 0.002] with an estimated median PFS of 8.9 and 4.7 months in the nivolumab plus ipilimumab and ipilimumab groups, respectively.

Among the 140 patients with BRAF V600 wild-type or mutation-positive melanoma who received at least one dose of nivolumab or ipilimumab, serious adverse reactions (62% vs. 39%), adverse reactions leading to permanent discontinuation (43% vs. 11%) or dose delay (47% vs. 22%), and grade 3 or 4 adverse reactions (69% vs. 43%) all occurred more frequently in patients receiving the combination (n= 94) compared with those receiving single-agent ipilimumab (n=46). The most frequent serious adverse reactions in patients receiving the combination were colitis (17%), diarrhea (9%), pyrexia (6%), and pneumonitis (5%). Additional clinically significant immune-mediated adverse reactions included pneumonitis, hepatitis, endocrinopathies, nephritis/renal dysfunction, and rash.

Common adverse reactions (greater than or equal to 20%) in patients receiving nivolumab plus ipilimumab were rash, pruritus, headache, vomiting, and colitis. The most frequent grade 3 and 4 laboratory abnormalities occurring in at least 5% of patients receiving the combination were increased ALT, increased AST, increased lipase, increased amylase, hyponatremia, and lymphopenia.

When used in combination with ipilimumab, the recommended dose and schedule is nivolumab 1 mg/kg administered as an intravenous infusion over 60 minutes, followed by ipilimumab on the same day, every 3 weeks for four doses. The recommended subsequent dose of nivolumab, as a single agent, is 3 mg/kg as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.

12.4 Response Evaluation Criteria

For assessment of objective response to cancer treatment, modified World Health Organization (WHO) criteria (WHO handbook for reporting results of cancer treatment. Geneva (Switzerland); 1979) (WHO, 1979), and the response evaluation criteria in solid tumors (RECIST) had been reported (Table 41) (Therasse et al., 2000) (Gehan and Tefft, 2000).

Table 41. Comparison of WHO and RECIST Guidelines

Characteristic	WHO	RECIST
Measurability of lesions at baseline	**1. Measurable, bidimensional (product of LD and greatest perpendicular diameter)†** 2. Nonmeasurable/evaluable (e.g., lymphangitic pulmonary metastases, abdominal masses)	**1. Measurable, unidimensional (LD only, size with conventional techniques ⩾20 mm; spiral computed tomography ⩾10 mm)** 2. Nonmeasurable: all other lesions, including small lesions. Evaluable is not recommended.
Objective response	1. Measurable disease (change in sum of products of LDs and greatest perpendicular diameters, no maximum number of lesions specified) CR: disappearance of all known disease, confirmed at ⩾4 wk **PR: ⩾50% decrease from baseline, confirmed at ⩾4 wk** **PD: ⩾25% increase of one or more lesions, or appearance of new lesions** NC: neither PR or PD criteria met 2. Nonmeasurable disease CR: disappearance of all known disease, confirmed at ⩾4 wk PR: estimated decrease of ⩾50%, confirmed at ⩾4 wk PD: estimated increase of ⩾25% in existent lesions or appearance of new lesions NC: neither PR or PD criteria met	1. Target lesions (change in sum of LDs, maximum of 5 per organ up to 10 total [more than one organ]) CR: disappearance of all target lesions, confirmed at ⩾4 wk **PR: ⩾30% decrease from baseline, confirmed at 4 wk** **PD: ⩾20% increase over smallest sum observed, or appearance of new lesions** SD: neither PR or PD criteria met 2. Nontarget lesions CR: disappearance of all target lesions and normalization of tumor markers, confirmed at ⩾4 wk PD: unequivocal progression of nontarget lesions, or appearance of new lesions Non-PD: persistence of one or more nontarget lesions and/or tumor markers above normal limits
Overall response	1. Best response recorded in measurable disease 2. NC in nonmeasurable lesions will reduce a CR in measurable lesions to an overall PR 3. NC in nonmeasurable lesions will not reduce a PR in measurable lesions	1. Best response recorded in measurable disease from treatment start to disease progression or recurrence 2. Non-PD in nontarget lesion(s) will reduce a CR in target lesion(s) to an overall PR 3. Non-PD in nontarget lesion(s) will not reduce a PR in target lesion(s)
Duration of response	1. CR From: date CR criteria first met To: date PD first noted **2. Overall response** **From: date of treatment start** **To: date PD first noted** 3. In patients who only achieve a PR, only the period of overall response should be recorded	1. Overall CR From: date CR criteria first met To: date recurrent disease first noted **2. Overall response** **From: date CR or PR criteria first met (whichever status came first)** **To: date recurrent disease or PD first noted** 3. SD From: date of treatment start To: date PD first noted

*WHO = World Health Organization, RECIST = Response Evaluation Criteria in Solid Tumors, LD = longest diameter, CR = complete response, PR = partial response, PD = progressive disease, NC = no change, SD = stable disease.
†Lesions that can only be measured unidimensionally are considered to be measurable (e.g., mediastinal adenopathy, malignant hepatomegaly).

Source: Adapted from the article (Gehan and Tefft, 2000)

In the report of prospective comparison of WHO and RECIST, 3 patients were identified as progressed disease following the WHO criteria while they were still stable disease following the RECIST, suggesting that modified WHO criteria was at least as conservative. (Therasse et al., 2000) (Therasse et al., 2005).

12.5 Advisory Committee Meeting

A Joint Meeting of CBER's CTGTAC and CDER's ODAC was held on April 29, 2015, at FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Rm. 1503), Silver Spring, Maryland.

On April 29, 2015, the joint committee met in open session to discussed talimogene laherparepvec, Amgen, Inc., BLA 125518, for the treatment of patients with injectable regionally or distantly metastatic melanoma.

Following the Open Public Hearing, the Committee addressed the following discussion topics:

Discussion Topic 1: Clinical Benefit

Study 005/05 met its primary objective by demonstrating a higher durable response rate in the talimogene laherparepvec group than in the 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.

- The committee discussed the various ways to define benefit (e.g., direct benefit to the patient, quality of life, improved surrogate markers, overall survival), the historical background behind the strategy of using localized injections into tumors, concerns with using localized injections for up to six months in patients with a progressive disease, study bias, the pros and cons for using granulocyte-macrophage colony stimulating factor (GM-CSF) as the control, survival data (including sensitivity analyses), the issue of resectable versus unresectable patients, and concerns over the potential expanded use of the drug in a patient population for whom the product would not have an acceptable balance of benefits and risks.

- Various members of the committee stated that talimogene laherparepvec appears to benefit some patients, a subset of the studied population, or a subset of the proposed indicated population. (See Discussion Topic 3)

- Some members of the committee stated that Durable Response Rate (DRR) correlated with overall survival in some subgroups.

- Some members of the committee stated that talimogene laherparepvec appeared to have an effect on non-visceral metastases, but expressed concern that the

available data do not support that talimogene laherparepvec has a systemic effect on visceral metastases.

Discussion Topic 2: Safety

In Study 005/05, the most common treatment-emergent adverse events in the talimogene laherparepvec arm were fatigue, chills, pyrexia, nausea, influenza-like illness, and injection-site pain. Serious adverse events included cellulitis at the injection-site and immune-related adverse events.

Individual members of the committee expressed the following opinions:

- The safety profile for talimogene laherparepvec appeared to be generally acceptable relative to the safety profile reported for other melanoma treatments.
- Flu-like symptoms were generally tolerable in light of the pathology that was being treated.
- Cellulitis and possible effect of viral shedding on vulnerable populations (e.g., family members, children, pregnant women, healthcare workers, and other cancer patients) were concerns. (See Discussion Topic 5)
- Many of the more serious adverse events (e.g., amputation) were generally found in patients with other complicating conditions and could not be attributed solely to the use of talimogene laherparepvec.
- Other safety concerns may come to light with widespread use of talimogene laherparepvec.

Discussion Topic 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.

- Some members of the committee indicated that talimogene laherparepvec has an overall favorable benefit-risk profile for patients with skin and lymph node diseases, lower-stage melanoma patients (e.g., Stage IIIB, Stage IIIC, Stage IVM1a), and older melanoma patients, particularly those with comorbidities.
- The committee discussed but did not reach consensus on talimogene laherparepvec's place in therapy (i.e., first-line versus second-line therapy), on its use in relation to other available melanoma therapies (e.g., BRAF signal transduction inhibitors, checkpoint inhibitors), in resectable versus unresectable patient populations, in patients with BRAF mutations, or its use in earlier stages of the disease to inhibit or slow down visceral metastases.

Discussion Topic 4: Dosing

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

- Some members of the committee expressed concern that the Applicant's dosing instructions were not clear or sufficient to inform the healthcare provider in clinical practice on the safe and effective dose and administration of talimogene laherparepvec.
- Some committee members felt that the Sponsor's "fuzzy" dosing instructions may have been intentionally vague to give investigators some clinical discretion.
- The committee discussed the possibility that, due to the possible immune response and replication of the HSV-1 virus, a lower volume of the drug may be needed to be administered per lesion. However, some committee members felt that additional studies are needed to collect supportive data.
- Some members of the committee also noted that the recommended doses (expressed as 10^6 PFU/mL) did not scale linearly with tumor volume, which may have accounted for the smaller lesions being more responsive to the drug than larger lesions.
- Some members of the committee noted that higher talimogene laherparepvec doses may not provide a better cellular immune response than lower doses of the drug, since HSV has a number of genes which have not been altered and can inhibit the immune response.

Discussion Topic 5a: Shedding Data

Viral shedding may expose healthcare providers (HCP) and close patient contacts to talimogene laherparepvec.

- Some members of the committee stated that the risk of shedding appears to be much lower with talimogene laherparepvec than with the wild type HSV-1 virus, as evidenced in analyses of blood, urine, external dressings, and oral mucosal swabs.
- Questions were raised by some members of the committee as to whether talimogene laherparepvec interacts with the latent wild type HSV in patients.
- The committee also discussed the importance of educating patients who receive talimogene laherparepvec on wearing protective gear (e.g., gloves, eyeglasses), using alcohol wipes on occlusive dressings, being wary of self-inoculations to the eye, the risk of transmission to highly compromised individuals, and the importance of collecting shedding data, especially in the context of wild-type HSV-1 infections.

Discussion Topic 5b: Pharmacovigilance

Talimogene laherparepvec is an attenuated replication-competent Herpes Simplex Virus-1 (HSV-1) that has the potential for transmission, latency, and symptomatic reactivation. However, the ongoing study provides only limited data on talimogene laherparepvec shedding, which serves as a proxy for transmission.

- Some members of the committee felt that the proposed postmarketing study protocol was an overly complicated, multistep process that relied on passive rather than active reporting of suspected herpetic infections, placing too much responsibility on the healthcare provider.
- Concerns were also raised that following the proposed protocol would delay reporting, to such an extent that lesions may be gone before they have been clinically assessed.
- Some members of the committee suggested that each healthcare provider in clinics have test kits on hand to assess patients, the patient's family members, or any other close contacts with suspected herpetic illnesses. Committee members suggested that the Applicant replace the kits periodically as they process them.

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 to support traditional approval for the treatment of injectable, regionally or distantly metastatic melanoma? In voting, please consider only whether the available evidence would support traditional approval and not Accelerated Approval.

Vote: Yes = 22 No = 1 Abstain = 0

- Some committee members who voted "yes" to the question stated that the bulk of the data suggests a favorable benefit – risk profile and that the drug represents an important new tool for oncologists, particularly in a subset of patients with non-visceral disease.
- Some committee members who voted "yes" qualified their vote by recommending that the approval be limited to only unresectable Stage III and earlier metastatic patients; other committee members wanted no limitations on the approval, citing reimbursement issues, physician autonomy, and possible benefits from combination therapy.
- Some committee member stated that "There was very little evidence that patients who had visceral metastases or patients who had large lesions, large skin lesions, actually received any benefit. …I think there is an argument that could be made for an accelerated approval to basically get

more data, another clinical trial, in the context of contemporary treatments for advanced melanoma… I would recommend that there be strong labeling discouraging physicians from using it in situations where there is substantial metastatic disease."

- The committee member who voted "no" indicated that he did so to avoid giving blanket approval to a drug that had demonstrated benefit in only a subset of melanoma patients (Stages IIIB, IIIC, and IVM1a).

12.6 References

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