**Department of Health and Human Services**
**Food and Drug Administration**
**Center for Biologics Evaluation and Research**
**Office of Biostatistics and Epidemiology**
**Division of Epidemiology**

# Talimogene laherparepvec BLA 125518
# Pharmacovigilance Plan: Review Memorandum

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| To: | Ramjay Vatsan, PhD<br>Chair, BLA Review Committee<br>Division of Clinical Evaluation and Pharmacology / Toxicology<br>Office of Cellular, Tissue and Gene Therapies (OCTGT) |
| Through: | Christopher Jankosky, MD, MPH<br>Acting Deputy Division Director<br>Branch Chief, Pharmacovigilance Branch (PVB)<br>Division of Epidemiology (DE)<br>Office of Biostatistics and Epidemiology (OBE) |
| From: | Meghna Alimchandani, MD<br>Medical Officer, PVB, DE, OBE |
| Subject: | Pharmacovigilance Plan Review Memorandum |
| Applicant: | Amgen, Inc |
| Product: | Talimogene laherparepvec (T-VEC), Imlygic, OncoVEX$^{GM\text{-}CSF}$, Herpes Simplex Type-1 Virus-Encoded with Human Granulocyte-Macrophage Colony-Stimulating Factor (rHSV-1hGM-CSF) |
| Indication: | Amgen's proposed indication: Treatment of injectable regionally or distantly metastatic melanoma. |
| BLA Submission Date: | July 28, 2014 |
| Action Due Date: | October 27, 2015 (includes 3-month-extension due to Major Amendment). |

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# 1. INTRODUCTION

## 1.1 Objectives and Scope

Office of Biostatistics and Epidemiology, Division of Epidemiology (OBE/DE) has completed a pharmacovigilance plan review of BLA 125518 seeking US licensure of Talimogene laherparepvec; proposed trade name IMLYGIC. The purpose of this review is to identify potential safety issues that may need to be addressed through postmarketing safety surveillance, studies, or other pharmacovigilance activities, should the product be licensed. As part of a comprehensive safety evaluation, the pharmacovigilance plan (PVP) submitted by Amgen as part of the Risk Management Plan (RMP) with supporting background clinical trial information from the BLA was reviewed. Currently Talimogene is not licensed in any country and there is no postlicensure safety data.

(This memo will use T-VEC, Talimogene, Talimogene laherparepvec and IMLYGIC interchangeably.)

## 1.2 Product Description

*Product nomenclature:* T-VEC, Talimogene laherparepvec; trade names Imlygic, OncoVEX$^{GM\text{-}CSF}$, Amgen laboratory code name (b) (4) strain identifier JS1/34.5-/47-/hGM-CSF

*Product class:* This is a first-in-class product; FDA determination of product class (under consideration as of June 25, 2015) is "oncolytic virus."

*Indication*:

> Amgen's proposed indication: Treatment of injectable regionally or distantly metastatic melanoma.
>
> FDA proposed indication (under consideration as of June 24, 2015): Imlygic is an oncolytic virus indicated for the local treatment of cutaneous, subcutaneous, and nodal lesions in patients with unresectable recurrent melanoma. Imlygic has not been shown to improve overall survival or have an effect on visceral lesions.

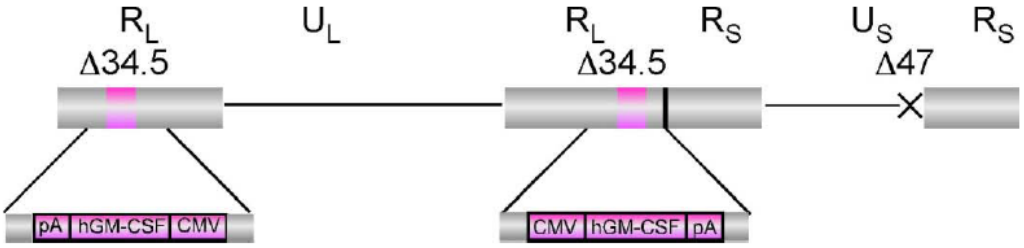
*Composition*: HSV-1 is an enveloped double-stranded (linear) DNA virus. Talimogene is derived from the newly isolated JS1 strain of HSV-1, and has been genetically modified as follows:

i. attenuated via functional deletion of genes ICP34.5 and ICP47.
ii. insertion of human granulocyte macrophage colony stimulating factor (hGM-CSF)

ICP34.5 is associated with neurovirulence. ICP47 gene leads to early expression of US11, and partially reverts the effect of ICP34.5 deletion (i.e. partially restores virulence of the virus). ICP47 gene deletion enables up-regulation of the US11 gene, resulting in increased replication in tumor cells, and also makes the virus more immunogenic. The genetic features of Talimogene make it replication competent, while permitting infected cells to present the viral and other cellular antigens, through their normal antigen presenting pathway.

Amgen's schematic diagram of Talimogene genome. (BLA 125518, module 3.2.S.1.2, page 1)

**Figure 1. Schematic Representation 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. The genome is composed of a unique long region ($U_L$) flanked by long repeats ($R_L$) and a unique short region ($U_S$) flanked by short repeats ($R_S$). 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 CMV promoter, hGM-CSF cDNA and a pA signal.

*Mechanism of Action*: A dual mechanism of action is postulated

- Direct oncolytic effect: local tumor lysis following Talimogene replication in tumor cells
- Systemic anti-tumor immune response: local GM-CSF expression and release of tumor antigens from lysed tumor cells to macrophages and other antigen presenting cells. In theory, this would lead to systemic anti-tumor cytotoxic immune response at distal tumor sites and protect against micrometastatic disease and future relapse.

Reviewer comment: The exact mechanism of action is not fully understood. There exists limited evidence of systemic effectiveness in this BLA submission.

*Route of administration*: Intralesional injection into cutaneous, subcutaneous and nodal tumor sites which are visible, palpable or detectable by ultrasound.

*Pharmaceutical form*: Talimogene will be packaged in sterile single-use vials containing 1mL preservative-free, frozen liquid at a concentration of 1 x $10^6$ PFU/mL or 1 x $10^8$ PFU/mL.

*Dosing*: The BLA is based on a single phase 3 study 005/05, in which the median duration of treatment was 23 weeks (range 0.1 – 78.9 weeks) in the Talimogene treatment arm. Amgen recommends duration of Talimogene treatment for at least 6 months, unless other treatment is required or until no injectable lesions are remaining; treatment may be reinitiated with disease progression and appearance of new lesions. The dosing schedule is as follows:

- First dose: concentration $10^6$ PFU/mL
- Second dose after 3 weeks of initial dose: concentration of $10^8$ PFU/mL
- Subsequent doses every 2 weeks: concentration of $10^8$ PFU/mL

Maximum volume of 4 mL Talimogene can be injected into one or more tumors at each visit. The volume of Talimogene to be injected into each lesion depends on the size of the lesion according to an algorithm.

## 1.3 Epidemiology and clinical manifestations of wild-type HSV-1[1,2, 3, 4, 5, 6, 7, 8, 9, 10]

It is important to note that despite genetic modifications, Talimogene has similar biologic properties to wild type HSV-1 and is capable of in vivo amplification, spread to uninfected tissue, life-long latency in neural ganglia, symptomatic reactivation, recombination with wild-type HSV-1, viral shedding from infected person, and transmission and infection of untreated persons. Talimogene remains susceptible to antiviral therapy (acyclovir).

HSV-1 is widely prevalent in the U.S. population and up to sixty-three percent of the US population has antibodies to HSV-1. Even though majority of HSV-1 related infections are mild (most common manifestations are oral ulcers), serious clinical sequelae can occur. Recurrent lips/perioral HSV-1 infection is estimated to occur in 20 - 40% of the population worldwide. Frequent recurrences of cold sores (defined as six or more episodes annually) occur in 5% - 10% of the population. Ocular HSV (conjunctivitis, keratitis, or uveitis) occurs at an incidence of 8 to 13 per 100,000 in the general population. Herpetic keratitis is the leading infectious cause of blindness in developed countries. In very rare cases, occurring at an incidence of 1 to 4 per million, wild type HSV-1 enters the central nervous system, and causes meningoencephalitis, which can be fatal. Certain vulnerable populations, such as the immunocompromised, are at higher risk of developing disseminated infection. With HSV-1 infection (primary or reactivation) in pregnant women, there exists the potential for the virus to cross the placental barrier and also a risk of transmission during birth due to exposure to maternal blood and potential viremia (animal studies data). Infections in the fetus/neonate with wild-type HSV-1 have been associated with serious clinical sequelae, multi-organ failure and death.

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| HSV-1 widely prevalent in US population | 54% - 63% population with positive serology |
| Recurrent oral herpetic lesions | 20% - 40% of population |
| *Frequen*t recurrent oral herpes | 5 – 10% |
| Ocular HSV: conjunctivitis, keratitis, uveitis | Incidence of 8 to 13 per 100,000 |
| Herpetic encephalitis | Incidence of 1 to 4 per million |

[1] Bradley H, Markowitz LE, Gibson T, McQuillan GM. Seroprevalence of herpes simplex virus types 1 and 2--United States, 1999-2010. J Infect Dis. 2014 Feb 1;209(3):325-33.
[2] Engelberg R, Carrell D, Krantz E, Corey L, Wald A. Natural history of genital herpes simplex virus type 1 infection. Sex Transm Dis. 2003 Feb;30(2):174-7.
[3] Kennedy, P.G. (2005). Viral encephalitis. Journal of neurology 252, 268-272.
[4] Kimberlin, D.W. (2007). Management of HSV encephalitis in adults and neonates: diagnosis, prognosis and treatment. Herpes : the journal of the IHMF 14, 11-16.
[5] Wald A., C.L. (2007). Persistence in the population: epidemiology, transmission. In: Arvin A, Campadelli-Fiume G, Mocarski E, et al., editors. Human Herpesviruses: Biology, Therapy, and Immunoprophylaxis. Chapter 36 (Cambridge: Cambridge University Press).
[6] Xu F, Markowitz LE, Gottlieb SL, Berman SM. Seroprevalence of herpes simplex virus types 1 and 2 in pregnant women in the United States. Am J Obstet Gynecol. 2007;196(1):43.e1-6.
[7] Young RC et al.. Incidence, recurrence, and outcomes of herpes simplex virus eye disease in Olmsted County, Minnesota, 1976-2007: the effect of oral antiviral prophylaxis. Arch Ophthalmol. 2010 Sep;128(9):1178-83
[8] Zuckerman R, Wald A; AST Infectious Diseases Community of Practice. Herpes simplex virus infections in solid organ transplant recipients. Am J Transplant. 2009 Dec;9 Suppl 4:S104-7.
[9] Rooney JF, Straus SE, Mannix ML, et al. Oral acyclovir to suppress frequently recurrent herpes labialis. A double-blind, placebo-controlled trial. Ann Intern Med. 1993 Feb 15;118(4):268-72.
[10] Klein RS. Epidemiology of herpes simplex virus type 1 infection. Accessed UpToDate; August 13, 2015. http://www.uptodate.com/contents/epidemiology-of-herpes-simplex-virus-type-1-infection

## 1.4 Disease to be treated with product: Melanoma

Melanoma of the skin is the sixth most common cancer in the United States with a rising trend (on average 1.4%) over the past 10 years in the number of new cases each year. Approximately 2.1 % of men and women will be diagnosed with melanoma of the skin at some point during their lifetime (2010-2012, SEER). In the United States, it is anticipated that there will be 73,870 new cases of melanoma in 2015 and 9,940 deaths[11]. Of those newly diagnosed with melanoma, approximately 10,000 have regional or distant (metastatic) disease (SEER, 2013), which is the indicated population for treatment with Talimogene. Cancer stage at diagnosis impacts survival. Survival by stage at diagnosis: 84% have localized disease with 98% 5-year survival; 9% have regional lymph node metastasis with 63% 5-year survival (possible niche for Talimogene therapy); 4% have distant metastasis with 16% 5-year survival.

## 1.5 Regulatory History

Key dates in the development of Talimogene are outlined below.

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| April 25, 2005 | Original submission of IND 12412 Phase I studies |
| 2007 | Phase 2 studies in the US and UK (OncoVEX$^{GM-CSF}$ 002/03, 004104, 005/04) |
| 2008 - 2009 | End of Phase II meeting for discussion for pivotal trial in melanoma |
| | Special Protocol Agreement: Pivotal Phase 3 study OncoVEX$^{GM-CSF}$ **005/05** - A Randomized Phase 3 Clinical Trial in Melanoma Patients with Unresectable Stage IIIB, IIIC and IV Disease |
| November 2010 | Fast Track designation granted for indication in melanoma |
| March 14, 2011 | HSV-1 encoded with hGM-CSF granted Orphan Drug designation by the Office of Orphan Products Development (OOPD) for treatment of Stage IIB - stage IV melanoma (Designation request # 11-3340) as requested by BioVex. Currently BioVex is a wholly owned subsidiary of Amgen Inc. |
| July 2012 | Enrollment completed for Phase 3 study 005/05 |
| August 2013 | New phase 2 Study protocol 20120324: 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." *(ongoing study).* The protocol (dated 23 Jul 2013) was originally submitted on 07 Aug 2013 (Serial 0164). |
| July 28, 2014 | Amgen completes submission of BLA 125518 seeking the initial licensure of IMLYGIC (Talimogene laherparepvec) in the United States |
| September 2014 | Amgen submits a Marketing Authorization Application (MAA) to the European Medicines Agency (EMA) for Talimogene laherparepvec |
| Aug/Sep 2014, April 2015 | Amendments to viral shedding Study protocol 20120324 |
| September 2014 | Priority review *denied*; BLA 125518 will follow a standard review PDUFA timeline. Breakthrough designation *denied*. |
| December 2014 | Major Amendment leading to 3-month-extension to review timeline |
| April 29, 2015 | Cellular, Tissue, and Gene Therapies Advisory Committee and Oncologic Drugs Advisory Committee Meeting |
| June 25, 2015 | Proposed PMR studies presented to CBER FDAAA Safety Working Group |
| July 20, 2015 | Sponsor notification regarding PMRs (telecon) |

[11] Surveillance, Epidemiology and End Results Program (SEER) of National Cancer Institute. SEER Stat Fact Sheets: Melanoma of the Skin. Available at: http://seer.cancer.gov/statfacts/html/melan.html Accessed May 7, 2015.

# 2. MATERIALS REVIEWED

Materials reviewed in support of this assessment are listed below.

| Document Reviewed | Source |
|---|---|
| United States Risk Management Plan module 1.16, Version 1, dated 25 June 2014 | Amgen BLA 125518 |
| Proposed Risk Evaluation and Mitigation Strategy (REMS) and Supporting Document | |
| Clinical Overview (module 2.5) | |
| Summary of Clinical Safety (module 2.7) | |
| Summary of Clinical Efficacy (module 2.7.3 ) | |
| Study Protocol 20120324 | |
| Study Protocol 20120139 | |
| Proposed Package Insert | |
| This BLA was the subject of the joint Cellular, Tissue, and Gene Therapies Advisory Committee and Oncologic Drugs Advisory Committee Meeting (FDA and Amgen Briefing Documents, Slide Presentations, Recommendations) | Advisory Committee, April 29, 2015 |
| Input from Clinical and Statistical reviewers | CBER staff |

# 3. CLINICAL STUDIES

## 3.1 Pivotal Phase 3 Study 005/05

The primary evidence of effectiveness of Talimogene comes from Study 005/05, described below.

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| **Study title**<br>Phase 3 study 005/05 - A Randomized Phase 3 Clinical Trial in Melanoma Patients with Unresectable Stage IIIB, IIIC and IV Disease |
| **Study design:** Phase 3, randomized, open-label, multicenter (64 centers in United States, Canada, United Kingdom and South Africa) |
| **Goal:** Efficacy and safety of Talimogene monotherapy (treatment arm) compared with GM-CSF (control) |
| **Study population:** Adults (age ≥ 18y) diagnosed as stage IIIB, IIIC, or IV malignant melanoma that was not surgically resectable, with at least one cutaneous, subcutaneous or nodal mass ≥10 mm in longest diameter or multiple lesions totaling ≥ 10 mm; ECOG status 0 or 1, life expectancy > 4 months from the date of randomization |
| **Study size:** Total n = 439. Talimogene arm, n = 296; GM-CSF arm, n = 143. |
| **Intervention**<br>Dosing with either Talimogene or control will continue unless there is a clinically relevant Progression (PDr) after 24 weeks on study.<br>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.<br>GM-CSF was administered at 125 µg/$m^2$/day subcutaneously, on a four week schedule, consisting of daily doses for 14 days, followed by a 14-day rest period. |
| **Primary Endpoint:** Durable response rate (DRR), defined as complete or partial response (CR or PR) maintained for at least 6 months beginning at any point within 12 months of initiating Talimogene. In Complete Response (CR), the lesion disappears; in Partial Response (PR) there is 50% reduction in tumor size (response measured bidimensionally as per modified WHO criteria). |

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| **Criteria for measurement of DRR:** Modified WHO criteria to measure responses; evaluations performed by local investigators and subsequently by central EAC. Multimodal assessment includes measurement of lesions, radiology (e.g., CT, MRI, PET, PET/CT), biopsy results. |
| **Key Secondary Endpoint:** Overall Survival (OS) |
| **Study duration:** Treatment 12 months, Follow-up: 36 months. Ongoing survival follow-up. |
| **Safety follow-up:** Treated up to 12 months, OS follow-up 36 months. During treatment, solicited follow-up of adverse events (AEs) at treatment visits (biweekly); questionnaires and patient diary cards. |

**Key Efficacy findings**

Single pivotal phase 3 clinical trial 005/05 met its primary efficacy endpoint demonstrating higher durable response rate (DRR) with Talimogene (N = 46; 15.6%) compared to GM-CSF control (N = 2, 1.4%). OR = 12.8, P < 0.0001. However, it was unclear whether Talimogene was also associated with improvement in overall survival (OS), a key secondary endpoint.

Further subgroup analysis of DRR by disease stage suggested the following:
- Talimogene may have a greater benefit on DRR in subgroups with less advanced disease (stage IIIB/IIIC), with the caveat that the subjects were restaged at the time of enrollment into study 005/05 and the stage IIIB or IIIC used for subgroup analysis was *not* the stage at the initial melanoma diagnosis.
Reviewer comment: The results of the subgroup analyses stratified by disease stage may not be relevant for patients who are *initially diagnosed* with stage IIIB and IIIC melanoma.
Talimogene may have a greater benefit on DRR in subjects receiving Talimogene as "first-line therapy."
Reviewer comment: For these subgroup analyses, the "first line therapy" group consists of those subjects who had received *prior* surgery or adjuvant therapies.

**FDA review concerns regarding benefit-risk profile of Talimogene**
This BLA was the subject of the joint Cellular, Tissue, and Gene Therapies and Oncologic Drugs Advisory Committee (AC) Meeting on April 29, 2015, which decided by a vote of **22 to 1**, that Talimogene had an overall favorable benefit-risk profile to support approval. FDA identified concerns regarding both the study design and the study results. The FDA Briefing Document states that "these concerns include the appropriateness of the study control; differential outcome assessments in the two arms of the study; the reliability of response assessments; the meaningfulness of the primary endpoint of durable response rate; the absence of a clear effect on overall survival; and limited evidence that the product has a systemic effect."

1. Clinical benefit of Talimogene

- *Primary endpoint*: DRR has not previously been used in oncology approvals. Small lesion size may potentially influence reliability of measurements for outcome assessment. It was difficult to determine which lesions were never injected.
- *Systemic benefit:* Study 005/05 did not collect immune response data to correlate with clinical outcomes.
- *Overall survival (Secondary endpoint):* FDA Briefing Document for AC states that "it is not clear whether Talimogene laherparepvec had a benefit on overall survival in the ITT [intent to treat] population (p=0.051, from primary analysis). In addition, absence of the survival information for

10 subjects who were censored early, potentially informatively, increases the uncertainty about the presence or magnitude of any benefit on survival. Thus the survival results are not robust, and the conduct of the study with regard to a relatively small number of subjects, potentially subject to investigator bias, could have had substantial impact on the results of the survival analysis."

2. Study design

- *Control:* Key differences with regard to using GM-CSF as a control for Talimogene include i.) GM-CSF monotherapy is not used to treat advanced melanoma; ii.) different route of administration and dosing schedule (GM-CSF administered subcutaneously, on a four week schedule, daily doses for 14 days, followed by 14-day rest period; Talimogene administered intralesionally (max volume 4mL) on a biweekly schedule) iii.) difference in treatment duration and length of follow-up (GM-CSF median duration 10 weeks due to high number of early drop-outs; Talimogene median duration 23 weeks).
- The open-label study design may have led to a higher number of early dropouts in the control arm; potential investigator bias/assessment bias could have occurred since the Endpoint Assessment Committee (EAC) did not review data from all subjects in the ITT population.
- Dosing regimen: Talimogene administration was variable, with investigator discretion in the selection of lesions to be injected, number of lesions to be injected, dose administered into each lesion, total dose administered per treatment, and frequency of injections.

3. Patient population

- In single phase 3 study 005/05, Talimogene was studied in subjects with unresectable melanoma. However, the sponsor's proposed indication omits "unresectable" and the intended target patient population for Talimogene is for a broader indication than supported by the clinical trial data. The appropriateness of this omission was discussed by members of the AC, although consensus was not reached. During the AC the sponsor indicated verbally that certain subsets of the pivotal trial patient population would derive benefit.
- FDA AC Briefing Document states "since Study 005/05 was initiated, several therapies have been approved for the treatment of melanoma, some with demonstrated improvement in overall survival," such as ipilimumab, vemurafenib, dabrafenib, trametinib, pembrolizumab, nivolumab.

4. Incomplete viral shedding data on Talimogene from an ongoing study

- Viral shedding is a proxy for transmission. Limited viral shedding data makes it difficult to assess the risk of viral transmission to healthcare providers and close patient contacts. The risk of Talimogene associated herpetic infection of non-tumor tissue in patients (primary infection/latency and reactivation) and contacts (transmission/accidental exposure) was not fully characterized in study 005/05.

## 3.2 Ongoing Phase 2 Viral Shedding Study 20120324

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| **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 |

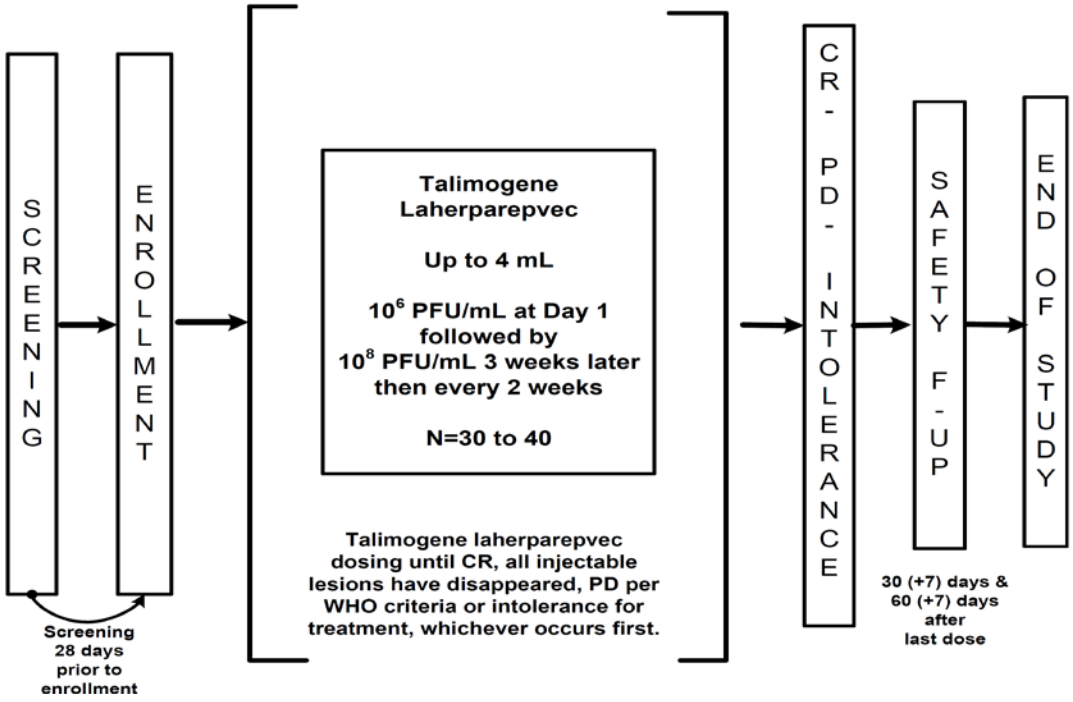
**Study population:** goal enrollment of 60 subjects with unresected, Stage IIIB to IVM1c melanoma

**Primary Objectives/ Endpoints:** To estimate the proportion of subjects with detectable Talimogene DNA in the blood and urine any time after administration of Talimogene within the first 3 treatment cycles.

**Secondary Objectives/ Endpoints:** 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.

**Study Schema**




**Outcome measures**

Talimogene qPCR of samples from: blood and urine in all subjects (primary outcome); injection site, exterior of occlusive dressing, oral mucosa, genital swabs, suspected herpetic infection in treated subjects. Protocol mandated sample collection for 3 treatment cycles and at end of treatment.

Additional assays for infective virus (TCID50).

**Study Timeline**

Study status: ongoing

Protocol originally submitted under IND 12412: August 7, 2013.

Most recent revised protocol submitted: April 6, 2015.

Number subjects enrolled: 46 subjects as of June 15, 2015.

Projected date of primary analysis data cut-off: February 8, 2016

The projected date of the final analysis data cut-off: July 27, 2016

Reviewer comment: FDA will require study 20120324 to be a PMR (concurred by CBER FDAAA SWG on June 25, 2015; Amgen notified on July 20, 2015) and milestone study dates proposed by Amgen (see Amgen response to IR dated July 31, 2015) are as follows:

Final Protocol Submission: November 2015
Study Completion: September 2016
Final Report Submission: May 2017

### 3.3 Preliminary Viral shedding data: 120 day safety update[12] and subsequent data

| Specimen | Positive samples (qPCR) | Subjects with positive samples | Max number of copies of DNA | Additional information |
|---|---|---|---|---|
| **Blood** | 66/176 samples (38%) | 11/12 subjects (92%) | 123 copies/µg DNA | Peak cycle 2; absent by cycle 4 |
| **Urine** | 2/177 samples (1%) | 2/12 subjects (17%) | 66 copies/µg DNA | only on day 1 of cycle 2 |
| **Swabs of injected lesions** | 65/158 samples (41%) | 11/12 subjects (92%) | 129,000 copies/µg DNA | Negative test for viral infectivity^ |
| **Exterior occlusive dressings** | 11/119 samples (9%) | 8/12 subjects (67%) | 579 copies/µg DNA (during the second cycle) | Negative test for viral infectivity^ |
| **Swabs of oral mucosa** | *1/49 samples (2%) | 1/12 subjects (8%) | 19 copies/µg DNA | Positive in cycle 5. Negative test for viral infectivity^ |
| **6 swabs of suspected herpetic lesions from 3 subjects** | 0 | - | - | |

**Additional information on this subject: Talimogene was injected into a tumor lesion in right middle upper chest. This subject had Talimogene qPCR positive blood samples in cycle 1 and 2 but all urine samples were negative. All swabs (9/9 swabs) of injected lesion were positive in first two treatment cycles and initial dose of cycle 3.*

^ Most of the test results for infective virus (TCID50 results) have been negative, despite the presence of Talimogene DNA (qPCR). However, as per FDA CMC reviewers, due to assay sensitivity and potential loss of virus viability, **presence of viral DNA should be taken as an indication of potentially infectious virus.**

### Overall Summary of Shedding Data[13]

Viral shedding serves as a proxy for transmission. Preliminary data from the ongoing phase 2 shedding study (protocol #20120324) in the 120-day-safety-update submission[14] (details are included in Appendix

[12] Amgen BLA 125518, Module 2.7.4, 120-day-safety-update.
(b) (4)
[13] FDA Briefing Document for BLA 125518, Joint Cellular, Tissue, and Gene Therapies Advisory Committee and Oncologic Drugs Advisory Committee Meeting on April 29, 2015
[14] Amgen BLA 125518, Module 2.7.4, 120-day-safety-update.
(b) (4)

A), while incomplete, indicate that the risk for virus transmission is as follows:

- Greatest at the injection site, for the duration of the study, **even after covering the site with occlusion dressing** (highest observed level Talimogene DNA on the occlusive dressing, was almost as high as the injection site). Talimogene DNA was detected at the injection site by qPCR on all tested days in most subjects. Infectious Talimogene was detected at the injection site in 3/20 subjects (TCID50 results) after a positive qPCR analysis.
- Blood from subjects may contain viral DNA and should be considered potentially infectious. In blood, Talimogene DNA is detectable within 1 hour of injection, but was cleared from the blood prior to the next injection in the majority of subjects.
- Low risk of transmission from the urine; risk is greatest on the day of injection. Urine was positive for Talimogene DNA, on the day of injection, in a small number of subjects.
  Reviewer comment: We do not know if virus is shed again in subsequent cycles, because samples were not collected.
- In one subject, the oral swab was positive for Talimogene DNA; subject had Talimogene injected into a lesion in the right middle upper chest.

Reviewer comments: Preliminary data from Talimogene treated subjects documents the presence of Talimogene DNA in blood, urine, body fluids (oral swab), injection site and occlusive dressing. As per FDA CMC reviewers, due to assay sensitivity and potential loss of virus viability, **presence of viral DNA should be taken as an indication of potentially infectious virus.** The potential for viral transmission from patient to contacts has not yet been fully characterized. Data from the completed study serves as the basis for documenting Talimogene viral shedding, infectivity, and the potential transmission of the virus to patient contacts – thus FDA requires this study to be a PMR. Potential Talimogene associated herpetic infection in patients or contacts (particularly in vulnerable populations such as immunocompromised or pregnant women) may lead to rare serious clinical sequelae including keratitis, encephalitis and life-threatening disseminated infection.

Additionally, in the most recent revised protocol dated April 15, 2015, the protocol synopsis updated the number of enrolled subjects to N = 50 - 60 subjects, but under section on Statistical Considerations (section 10.2 Sample Size Considerations, p. 69-70), the rationale was for the original sample size of 30 subjects. Amgen has agreed to revise the protocol to reflect updated sample size for N = 60 subjects (see Amgen response dated July 31, 2015).

# 4. CLINICAL TRIAL SAFETY DATA

## 4.1 Clinical Safety database

The primary safety analysis was based on study 005/05: total N = 419 subjects; 292 subjects in Talimogene arm and 127 subjects in GM-CSF control arm. Supplemental safety data was obtained from 116 subjects, who received Talimogene in Phase 1 and Phase 2 studies for melanoma and other solid tumors. The clinical program consists of a total of 8 studies (includes melanoma and non-melanoma studies): 001/01, 002/03, 002/03-E, 004/04, 005/04, 005/05, 005/05-E, and 006/09, in which 408

subjects received at least one dose of Imlygic (342 were melanoma subjects). [15] Ninety-six subjects received treatment for longer than 6 months. For details, please refer to Appendix B.

Reviewer comment: Of note, early studies with Talimogene for treatment of solid tumors (head and neck tumors, pancreatic tumors) differ from the patient population (melanoma) for the proposed indication for Talimogene in this BLA. The data for the Primary Safety Analysis for the BLA is based on single pivotal phase 3 randomized open-label study 005/05 (292 Talimogene subjects) conducted in a patient population comprised of subjects with unresectable stage IIIB, IIIC, and IV melanoma.

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

Reviewer comment: For evaluation of safety clinical trial data from study 005/05, it is important to note the following differences between Talimogene treatment arm and GM-CSF control arm. The difference in duration of treatment impacts the observation time/follow-up of AEs. The shorter treatment duration in the GM-CSF control arm was primarily due to a higher rate of subject drop out within the first 3 months (79 of 127 subjects [62.2%]) compared with Talimogene (86 of 292 subjects [29.5%]).

Additionally, as per discussion with the clinical review team, the safety evaluation emphasizes AEs for Talimogene which has distinct biological properties and mechanism of action. GM-CSF treatment may be interpreted as an inactive control and AEs experienced by subjects receiving GM-CSF were consistent with its known safety profile.

| | **Talimogene treatment arm** | **GM-CSF control arm** |
|---|---|---|
| **Duration of treatment** | Median duration of treatment was 23 weeks (range 0.1-78.9 weeks) | 10 weeks (0.6-72 weeks) in the control (GM-CSF) arm |
| **Dosing regimens** | Two dose levels: 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. Two dosing regimens: non-accelerated or accelerated (with disease progression) 82 of 292 subjects received accelerated dosing, and subjects who received accelerated dosing had a higher overall exposure to Talimogene. | 125 µg/$m^2$/day subcutaneously, on a four week schedule, consisting of daily doses for 14 days, followed by a 14-day rest period |

## 4.2 Adverse Events

AEs were graded as Grade 1 through 5, with Grade 5 being death. A serious AE was any untoward medical occurrence regardless of grade that resulted in death, was life-threatening, required or prolonged hospitalization, resulted in significant disability/incapacity, or was a congenital anomaly/birth defect. Treatment-emergent adverse event (TEAE) was defined as any AE that occurred after the

[15] Amgen BLA 125518, Summary of Clinical Safety, module 2.7.4 p19.

administration of the first dose of Talimogene 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. TEAEs are summarized in table below (source BLA 125518).

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

**Most frequently reported AEs with Talimogene** were fatigue, chills, pyrexia, and nausea (Table below from FDA Briefing Document for Advisory Committee). These specific events are typical manifestation of a flu-like illness, which is the next most common AE.

Reviewer Comment: Flu-like symptoms may be consistent with treatment with a viral vaccine with a proposed immunological mechanism of action.

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

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

**Serious TEAEs** occurred in 75/292 subjects (25.7%) and 17/127 subjects (13.4%) in the control arm. The most common serious TEAEs were **disease progression** or events related to disease progression. The most commonly reported treatment-related serious AE was **cellulitis**. In the Talimogene arm, a total of 18 subjects (6.2%) developed cellulitis; 7 of these events (2.4%) were categorized as serious, requiring hospitalization. One subject (055012) with streptococcal cellulitis at his injection site developed glomerulonephritis; renal biopsy was possibly consistent with an infectious origin. Treatment emergent serious AEs are summarized in table below (source BLA 125518).

Reviewer comment: Cellulitis at the injection site is an important TEAE due to the intralesional route of administration of Talimogene and its mechanism of action causing tumor lysis and necrosis. However, it is reassuring to note that the incidence of *serious* AE of cellulitis was low.

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

| | | |
|---|---|---|
| Metastatic melanoma | 3 (1.0%) | 0 (0%) |
| Pleural Effusion | 3 (1.0%) | 0 (0%) |

**Adverse Events of Special Interest:** As per Amgen, AE of special interest was identified based on the mechanism of action and preclinical or emerging clinical data (summarized in table below; source BLA 125518).

| **Adverse Events of Special Interest** | **Talimogene treatment arm** N =292 (%) | **GM-CSF control arm** N =127 (%) |
|---|---|---|
| T-E AEs of Special Interest | 275 (94.2%) | 108 (85%) |
| Flu-like symptoms | 264 (90.4) | 83 (65.4) |
| Injection site reactions | 122 (41.8) | 64 (50.4) |
| Hypersensitivity | 53 (18.2) | 25 (19.7) |
| Cellulitis injection site | 18 (6.2) | 2 (1.6) |
| Herpes simplex virus infections | 16 (5.5) | 2 (1.6) |
| Vitiligo | 15 (5.1) | 2 (1.6) |

## 4.3 Individual cases of important serious AEs

**Herpetic infection:** In Phase 3 Study 005/05, 16 subjects (5.5%) in Talimogene arm had AEs related to HSV infection, compared to 2 subjects (1.6%) in control (GM-CSF) arm; none of the subjects were qPCR tested for causative agent (Talimogene v. wild type HSV-1). Fifteen subjects had lesions of oral herpes and 1 subject developed herpetic keratitis (this subject had a past history of herpetic keratitis due to wild-type HSV-1; however additional testing to confirm wild type HSV-1 or Talimogene was not done).

Reviewer comment: The increased incidence of HSV-1 infection in the Talimogene arm compared to GM-CSF control arm is difficult to interpret since, i.) qPCR testing to characterize the infectious agent was not done; ii.) duration of treatment impacts the observation time/follow-up of AEs and Talimogene subjects were followed longer due to a lower drop-out rate. Potential Talimogene associated herpetic infection in patients or contacts (particularly in immunocompromised individuals or pregnant women) may lead to rare serious clinical sequelae including encephalitis, keratitis, and life-threatening disseminated infection. Talimogene associated herpetic infection in non-tumor tissue of treated patients (primary infection or reactivation/latency of Talimogene or wild-type HSV-1) are important potential risks that have not been characterized due to lack of follow-up qPCR Talimogene testing in the phase 3 study. A required postmarketing study (PMR) is planned to assess the incidence of Talimogene positive herpetic infection in Talimogene treated patients, characterize herpetic infections, and collect data on herpetic manifestations in immunocompromised hosts, and transmission to close contacts and HCPs.

**Immune-Mediated AEs (auto-immune):** 6 subjects in Talimogene arm and 3 subjects in GM-CSF control arm had immune-mediated AEs; individual cases are further described below.

Talimogene arm: N = 6 subjects

- Glomerulonephritis (403007): 49 year old man, with past history of only one kidney, exposure to contrast dye and analgesics, hypertension, diabetes developed hematuria, papillary necrosis, and acute renal failure after one year on study. Talimogene was discontinued; possibly related.
- Acute renal failure/glomerulonephritis (055012) in 57 year old man. Renal biopsy showed immune complex glomerular injury possibly due to post-infectious etiology. History of streptococcal cellulitis at injection site that was treated with Augmentin. Past history of partial nephrectomy for renal cell carcinoma. Amgen considered case to be possibly related to Talimogene.
- Pneumonitis (037008) in 65-year-old man with history of ulcerative colitis and on therapy with anti-TNFα therapy and mesalamine which was considered causative. He developed interstitial fibrosis 3 months after start of Talimogene treatment. Talimogene was continued until he developed progressive disease.
- Vasculitis (005030) in 41-year-old-woman (developed on day 259 of Talimogene treatment). She was treated with prednisone and delayed Talimogene for one dose. Considered possibly related per investigator.
- Psoriasis (003007) in 73-year-old man ; diagnosis was made prior to enrollment on study. He was treated with retinol while on study.
- Hypothyroidism (72002) in 60-year-old man (grade 2 on day 77 of Talimogene treatment). Limited clinical information. Considered to be unrelated to Talimogene.

GM-CSF control arm: N = 3 subjects
exacerbation of rheumatoid arthritis (66005); alopecia (14008) and rash (20005)

**Plasmacytoma:** 1 subject in Talimogene arm, with a prior history of pre-existing (smoldering) multiple myeloma developed plasmacytoma near the injection site of a scalp tumor, after 9 cycles of Talimogene treatment. Talimogene was subsequently discontinued. The plasmacytoma was thought to be a secondary plasmacytoma which developed at the injection site due to recruitment of plasma cells in response to Talimogene injections, and the case was considered “possibly related” to Talimogene treatment.

**Poor wound healing** (Case ID 003009): an 84 year-old woman (a durable responder). This is a serious adverse event reported in the Talimogene arm. Prior to the study, she had a history of melanoma lesions in the left foot, peripheral vascular disease, radiation, surgery to the region, and a non-healing wound. During the study treatment, she was injected in the left foot as a site of disease recurrence. Six months after the last dose of therapy (preceded by 3 months of unsuccessful medical interventions) the subject underwent a below-the-knee amputation for a non-healing, infected wound in the left foot. The intratumoral Talimogene injections may have contributed to the event.

Flu-like illness (Case ID 5005): In an 86 year-old man in the Talimogene arm; there was one serious AE categorized as flu-like illness that required hospitalization.

Obstructive airway disorder (Case ID 003017): Serious obstructive airway disorder required emergency tracheostomy in a 41 year-old woman with a laryngeal mass of unclear etiology (no evidence of melanoma or herpetic infection on biopsies). She received Talimogene to treat a recurrent right supraclavicular mass. Of note, 6 weeks prior to Talimogene therapy, she was treated with high-dose interleukin-2, and sustained acute respiratory failure with subsequent intubation.

Other Neoplastic Events (excluding melanoma progression): 7 subjects in Talimogene arm and 2 subjects in GM-CSF control arm had other neoplasms; individual cases are further described below.

7 subjects in Talimogene arm:

- 57 year old (045007) man with metastatic squamous cell carcinoma post 18 cycles of Talimogene; diagnosis 987 days post last dose.
- 73 year old woman (031001), who was a former smoker, with adenocarcinoma of the lung at the time of enrollment to study.
- 80 year old man (045019) with a history of smoking, had transitional cell carcinoma of the bladder.
- 89 year old man (020009), who was a former smoker, with transitional cell bladder carcinoma that developed 3 months into Talimogene therapy.
- 81 year old man (003006) with prior history of prostate cancer, recurred on day 237/681 days of Talimogene therapy.
- 67 year old man (010005) developed squamous cell carcinoma of skin on day 319/443 days of Talimogene.
- 70 year old woman (010002) with tonsillar neoplasm (NOS) on day 148/205 of Talimogene.

2 subjects on the GM-CSF arm:

- 81 year old man (051003) developed meningioma
- 70 year old man (035006) developed adenoma of the prostate and squamous cell carcinoma of the left cheek.

**Deaths**

In Study 005/05:

- Talimogene arm: total 12 deaths occurred within 30 days of the last dose of study treatment
    - 10 in the Talimogene arm of Study 005/05, as well as an additional 2 deaths within 30 days of the last Talimogene dose in the 005/05 Extension Study
    - 9 subjects died due to progressive disease
    - 3 subjects died due to myocardial infarction, cardiac arrest, and sepsis; none were treatment related.
- Control GM-CSF arm: total 2 deaths, both due to progressive disease.

Reviewer comment: There were no treatment related deaths. Most frequent cause of death was due to progressive disease.

**Additional Safety Data**

Additional safety data was provided 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 AEs in this additional safety data were generally similar to the safety profile of Study 005/05. The exception is that these other studies had an increased incidence of certain treatment-emergent adverse events that were attributable

to, and particular to, the specific disease or its concomitant therapy (for example, increased incidence of ascites in Study 005/04, the pancreatic cancer study). There was one additional report of cellulitis at the injection site.

### 4.4 Safety Conclusions[16]

- 90% of subjects who received Talimogene experienced "flu-like symptoms"
- The most common Talimogene treatment-emergent AEs were fatigue, chills, pyrexia, nausea, influenza-like illness and injection site pain.
- Cellulitis at the injection site, impaired wound healing, HSV-1 infections, injection site reactions, and vitiligo were identified by Amgen as AEs of special interest for Talimogene.
- In one subject, following Talimogene treatment, a wound became resistant to medical therapy, and required below-the-knee amputation. Prior to the study, the patient had a history of melanoma lesions in the left foot, peripheral vascular disease, radiation, surgery.
- Disease progression was the most common Grade 3 or above AE, the most common reason for early discontinuation, the most common treatment emergent serious adverse event, and the most common preferred term for treatment-emergent fatal event.

## 5. PHARMACOVIGILANCE PLAN

### 5.1 Overview of the important risks and proposed actions

Amgen proposes routine pharmacovigilance, postmarketing studies and risk minimization activities. Passive surveillance includes routine spontaneous AE reports which will be captured in the Amgen Global Safety Database. Postmarketing studies to evaluate long-term safety include a postmarketing prospective cohort study (#20130193) and an observational clinical trial registry study (#20120139) as well as continuation and completion of the ongoing viral shedding study (#20120324). Amgen's proposed risk minimization activities include Risk Evaluation and Mitigation Strategy (REMS) and a Medication Guide. Amgen's PV Plan for important identified risks, potential risks and missing information, is summarized in the table below.



[16] Adapted from FDA Briefing Document for Cellular, Tissue, and Gene Therapies Advisory Committee and Oncologic Drugs Advisory Committee Meeting Advisory Committee, April 29, 2015.

| | |
|---|---|
| **Important Identified Risks** | |
| 1.) Disseminated herpetic infection in *severely** immunocompromised individuals<br>*congenital or acquired cellular/humoral immunodeficiencies | ▪ Routine PV and labeling<br>▪ Medication Guide<br>▪ Postmarketing Study 20130193<br>▪ REMS* |
| 2.) Accidental exposure of HCP (needle stick injury, spill, or splash back during administration) | ▪ Routine PV and labeling<br>▪ Postmarketing Study 20130193<br>▪ Ongoing shedding Study 20120324<br>▪ REMS* |
| 3.) Cellulitis at injection site | ▪ Routine PV and labeling<br>▪ Medication Guide |
| **Important Potential Risks** | |
| 1.) Disseminated herpetic infection in immunocompromised* individuals<br>*HIV/AIDs, immunosuppressive medications, chronic steroids | ▪ Routine PV and labeling<br>▪ Medication Guide<br>▪ Postmarketing Study 20130193<br>▪ REMS* |
| 2.) Symptomatic Talimogene-associated infection in non-tumor tissue in treated patients | ▪ Routine PV and labeling<br>▪ Postmarketing Study 20130193<br>▪ Ongoing shedding Study 20120324<br>▪ Medication Guide<br>▪ REMS* |
| 3.) Transmission of Talimogene from patient to CC or HCPs via direct contact with injected lesions or body fluids resulting in symptomatic infection | ▪ Routine PV and labeling<br>▪ Postmarketing Study 20130193<br>▪ Ongoing shedding Study 20120324<br>▪ Medication Guide<br>▪ REMS* |
| 4.) Symptomatic herpetic infection due to latency and reactivation of Talimogene or wild-type HSV-1 in patients | ▪ Routine PV and labeling<br>▪ Postmarketing Study 20130193<br>▪ Ongoing shedding Study 20120324<br>▪ Medication Guide<br>▪ REMS* |
| 5.) Immune-mediated AEs<br>6.) Plasmacytoma at the injection site<br>7.) Impaired wound healing at site of injection | ▪ Routine PV and labeling<br>▪ Medication Guide |
| 8.) Talimogene mediated anti-GM-CSF antibody response | ▪ Routine PV<br>▪ Amgen plans to develop anti-GM-CSF Ab assay |
| **Important Missing Information** | |
| 1.) Additional clinical biodistribution and shedding data | Ongoing shedding Study 20120324 |
| 2.) Recombination of Talimogene with wild-type HSV-1 | None |
| 3.) Pregnant and lactating women | ▪ Routine PV (Amgen surveillance programs) and labeling<br>▪ Medication Guide<br>▪ REMS* |
| 4.) Pediatric patients<br>5.) Patients with renal or hepatic impairment | Routine PV and labeling |
| 6.) Long-term safety data | Postmarketing Study 20130193 and Registry Study 20120139 |

*Proposed REMS further discussed in section 5.5. At this time, data do not suggest a safety concern to necessitate REMS.

## 5.2 Safety Concerns

Safety concerns and proposed PV actions are reviewed below.

**Cellulitis at injection site:** important identified risk
Data**:** In study 005/05, there was a higher incidence of bacterial cellulitis with Talimogene treatment compared to GM-CSF, though overall incidence of serious AE of cellulitis was low (2.4% with Talimogene).

| | **Talimogene treatment arm** | **GM-CSF control arm** |
|---|---|---|
| **AEs related to bacterial cellulitis** (includes non-serious AEs) | 18 subjects (6.2%) | 2 subjects (1.6%) |
| **Serious AEs of cellulitis** | 7 subjects (2.4%) | 1 subject (0.8%) |

PV actions: Routine PV and labeled in the Package Insert (PI) [sections Warnings and Precautions; Adverse Reactions]; Medication Guide.
Reviewer comment**:**
Cellulitis at the injection site is an important TEAE due to the intralesional route of administration of Talimogene and its mechanism of action causing tumor lysis and necrosis. Additionally, the indicated population of patients with metastatic melanoma may well be post-surgery and/or radiation prior to recurrence of their melanoma, with an increased risk for poor wound healing, damaged tissues, and local increased infection risk. However, it is reassuring to note that in clinical trial data, the incidence of *serious* AE of cellulitis was low. At this time, the proposed PVP is acceptable.

**Immune-mediated AEs:** important potential risk
Data: Immune-mediated AEs considered *possibly* related to Talimogene were reported in 6 subjects in the phase 3 study 005/05 (2%) and 1 subject in the phase 3 extension study, and included vasculitis, glomerulonephritis, acute renal failure, pneumonitis, and worsening psoriasis. "Causality was not clearly established as other contributory factors were identified in several of these cases, including pre-existing immune-mediated conditions, other concurrent medications, and intercurrent medical events." [See section 4.3 for description of individual cases.]
PV actions: Routine PV and labeled in the PI [section Warnings and Precautions]; Medication Guide.
Reviewer comment: At this time, the proposed PVP is acceptable.

**Plasmacytoma at the injection site**: important potential risk
Data: In study 005/05, 1 subject developed a plasmacytoma near the injection site of a scalp tumor, after 9 cycles of Talimogene treatment. Talimogene was subsequently discontinued. This patient had a prior history of pre-existing (smoldering) multiple myeloma, and the plasmacytoma was thought to be a secondary plasmacytoma which developed at the injection site due to recruitment of plasma cells in response to Talimogene. Amgen considered this plasmacytoma case as possibly related to Talimogene treatment.
No other cases of plasmacytoma have been reported to date.

PV actions: Routine PV and labeled in the PI [section Warnings and Precautions]; Medication Guide.
Reviewer comment: At this time, the proposed PVP is acceptable.

**Impaired wound healing at site of injection:** important potential risk
Data: In study 005/05, 1 subject experienced poor wound healing in a recurrent lower extremity melanoma lesion treated with Talimogene, and subsequently required a below-the-knee amputation ( *7 months* status post last Talimogene injection). Confounding factors were prior history of peripheral vascular disease, and prior radiation and recurrent cellulitis in the area. Amgen states "Despite these confounding factors, it was not possible to rule out a potential contributory role of treatment with Imlygic in this case."

Additionally, 16 subjects (5.5%) experienced AEs in impaired wound healing category in Talimogene treatment arm V. 3 subjects (2.4%) in control GM-CSF arm. Wound complication and wound secretion were reported in > 1% of subjects treated with Talimogene. However, Amgen states that "the cases reported did not meet the case definition of impaired healing, but were thought to represent injection site reactions or complications of local infection."

PV actions: Routine PV and labeled in the PI [section Warnings and Precautions]; Medication Guide.
Reviewer comment: As previously mentioned, it is important to note that the indicated population of patients with metastatic melanoma may well be post-surgery and/or radiation prior to recurrence of their melanoma, with an increased risk for poor wound healing, damaged tissues, and local increased infection risk. At this time, the proposed PVP is acceptable.

**Talimogene mediated anti-GM-CSF antibody response**: important potential risk
There is a theoretical concern that patients treated with GM-CSF producing Talimogene may develop anti-GM-CSF antibodies that may also react with endogenous GM-CSF. Clinical manifestations associated with auto-antibodies to GM-CSF include case reports of cryptococcal meningitis and pulmonary alveolar proteinosis[17]. Additionally autoantibodies to GM-CSF have been detected sporadically in the general population (up to 9.6%)[18].
Data: In study 005/05, anti-GM-CSF antibody response was NOT measured in Talimogene treated patients.
PV actions: Routine PV (spontaneous AE reporting).

Reviewer comments: Talimogene (b) (4) is NOT labeled in the currently proposed PI and its inclusion in the label was proposed to the clinical review team. However, upon further discussion, it was felt that this is mostly a theoretical risk with no available clinical trial data, and would not be included in the label at this time. Amgen states that they will "facilitate testing of (b) (4) for patients with reported AEs suggestive of Talimogene-(b) (4) response" and an (b) (4) will be available prior to product launch." In response to FDA information

[17] Rosen LB, Freeman AF, Yang LM, et al. Anti-GM-CSF autoantibodies in patients with cryptococcal meningitis. J Immunol. 2013;190:3959-3966.
[18] Meager A, Wadhwa M, Bird C, et al. Spontaneously occurring neutralizing antibodies against granulocyte-macrophage colony-stimulating factor in patients with autoimmune disease. Immunology. 1999;97:526-532.

request regarding (b) (4) , Amgen responded that (b) (4) These will be provided to the agency when available." FDA will review Amgen's proposed (b) (4) when it is submitted to the BLA.

**Talimogene associated disseminated herpetic infection in immunocompromised individuals**
Data: Talimogene was not studied in immunocompromised patients.

- "Severely immunocompromised" – Amgen refers to those with congenital or acquired cellular/humoral immunodeficiencies as *severely* immunocompromised, and considers this an important identified risk and contraindication to Talimogene use. Preclinical animal data using intratumoral injection of Talimogene in mouse xenograft models, showed lethal systemic viral infection in 100% of severe combined immunodeficiency (SCID) mice and up to 20% of (b) (4) nude mice (deficient in T lymphocyte and partially deficient in B lymphocyte function).
- "Immunocompromised" – Amgen refers to those with HIV/AIDS, leukemia, lymphoma, common variable immunodeficiency, or those requiring high-dose steroids or other immunosuppressive agents as immunocompromised individuals, and considers this an important potential risk.

PV actions:

- Routine PV and labeled in PI
  - Severely immunocompromised: labeled under sections Warnings and Precautions; Contraindications; Nonclinical Toxicology.
  - Immunocompromised: labeled under section Warnings and Precautions.
- Additional PV activity: Medication guide
- Postmarketing Study 20130193: secondary objective to estimate the incidence rate of herpetic manifestations (eg, keratitis, encephalitis, disseminated infection) among immunocompromised patients treated with Talimogene.

Reviewer comment: At this time, the proposed PVP is acceptable inclusive of the Medication Guide, and the sponsor's proposed postmarketing study (#20130193) that the FDA will require as a PMR. Additionally, under expanded adverse experience reporting, FDA will require that all reports of herpetic infection in patients and contacts, with Talimogene qPCR results when available, be submitted as 30-day (monthly) reports if not previously filed as 15-day reports.

**Talimogene exposure to patient contacts and associated herpetic infection in contacts**

**a.) Accidental exposure of HCP** (needle stick injury, spill, or splash back during administration): important identified risk
Data:

In study 005/05, there were a total of 5 reports of accidental exposure to HCPs; 4 cases had no associated AEs; 1 case of HCP who experienced a herpetic whitlow at the site of an accidental needle-stick to the finger (direct inoculation). The lesion was qPCR positive for Talimogene. It resolved with acyclovir.

PV Actions:

- Routine PV and labeled in PI [sections Dosage and Administration; Warnings and Precautions; How Supplied/Storage and Handling]
- Additional PV activities
    - Medication guide
    - Targeted questionnaire and Talimogene qPCR assay planned to be made available in postmarketing setting for follow-up testing of herpetic infection in patient contacts (close contacts and HCPs).
- Postmarketing studies
    - Postmarketing study 20130193 (secondary objective): case counts of the number of HCPs having a herpetic infection positive for Talimogene DNA by qPCR and further characterization of herpetic manifestations (eg, keratitis, encephalitis, disseminated infection) among HCPs. Targeted questionnaire and Talimogene qPCR assay for follow-up testing of herpetic infection in HCPs.
    - The ongoing viral shedding study (#20120324) includes a periodic survey to gather data on exposure of HCPs and includes Talimogene qPCR assay for follow-up testing of herpetic infection in HCPs.

**b.) Transmission of Talimogene from patient to close contact (CC) or HCPs via direct contact with injected lesions or body fluids resulting in symptomatic infection (primary or reactivation):** important potential risk

Data on transmission to close contacts**:** To date, there are no cases of confirmed - Talimogene transmission to close contacts. In study 005/05, there was approximately 50% compliance with questionnaires for household contacts; 14% for medical personnel.

Data on Talimogene viral shedding and risk for transmission**:** The potential for Talimogene viral transmission from patient to contacts has not yet been fully characterized. Additional clinical biodistribution and shedding data is considered important missing information. Viral shedding data serves as a proxy for the risk of transmission through unintended exposure. Preliminary studies (protocol #20120324) in Talimogene treated subjects have documented the presence of Talimogene DNA in the blood, urine, body fluids (oral swab), site of injection, and exterior of occlusive dressing.

PV actions:

- Routine PV and labeled in PI [sections Warnings and Precautions, How Supplied/Storage and Handling, and Patient Counseling Information].
- Additional PV activities

- Medication guide
- Targeted questionnaire and Talimogene qPCR assay planned to be made available in postmarketing setting for follow-up testing of herpetic infection in patient contacts (close contacts and HCPs).

- Postmarketing studies
  - Postmarketing study 20130193 (secondary objectives): Targeted questionnaire and Talimogene qPCR assay for follow-up testing of herpetic infection in close contacts and HCPs. Case counts of the number of HCPs having a herpetic infection positive for Talimogene DNA by qPCR and further characterization of herpetic manifestations (eg, keratitis, encephalitis, disseminated infection) among HCPs.
  - The ongoing viral shedding study (#20120324) includes a periodic survey to gather data on exposure of patient contacts, and includes Talimogene qPCR assay for follow-up testing of herpetic infection in contacts.

Reviewer comments: The preliminary Talimogene shedding data suggests that Talimogene may potentially be transmitted to patient contacts. Presence of viral DNA should be taken as an indication of potentially infectious virus. A preliminary trend of low risk of Talimogene shedding beyond the local injection site is suggested. At this time, the medication guide and proposed PVP, including the postmarketing study (#20130193) and viral shedding study (#20120324) are acceptable; both studies will be PMRs. Additionally, under expanded adverse experience reporting, FDA will require that all reports of herpetic infection in patients and contacts, with Talimogene qPCR results when available, be submitted as 30-day (monthly) reports if not previously filed as 15-day reports.

**Symptomatic Talimogene-associated herpetic infection in treated patients in non-tumor tissue (primary infection or reactivation/latency of Talimogene or wild-type HSV-1):** Important Potential Risk Data:

- In Phase 3 Study 005/05, 16 subjects (5.5%) in Talimogene arm had AEs related to HSV infection, compared to 2 subjects (1.6%) in control (GM-CSF) arm; but none were qPCR tested for Talimogene. Fifteen subjects had lesions of oral herpes and 1 subject developed herpetic keratitis (this subject had a past history of herpetic keratitis due to wild-type HSV-1; however additional testing to confirm wild type HSV-1 V. Talimogene was not done).
- Though latency and reactivation of Talimogene has not been confirmed to date in patients, preclinical data from mouse models support this potential risk: “In a mouse model, Imlygic was detected in the spinal dorsal root ganglia following injection into the foot. This suggests that the virus had established latency in the nerve root innervating the site of injection. The virus was reactivated in ex vivo cell culture.”

PV actions:

- Routine PV and labeled in PI [Label: Symptomatic Talimogene infection in non-tumor tissue in treated patients is labeled in Package Insert under Warnings and Precautions; Patient Counseling Information. Symptomatic herpetic infection due to latency and reactivation of

Talimogene or wild-type HSV-1 in patients is labeled in PI under section Warnings and Precautions.]

- Additional PV activities
  - Medication guide
  - Targeted questionnaire and Talimogene qPCR assay planned to be made available in postmarketing setting for follow-up testing of herpetic infection in patients.
- Postmarketing studies
  - Postmarketing study 20130193.
    Primary objectives: (i) to estimate the incidence rate of herpetic infections containing Talimogene DNA among patients for 5 years after initiating Talimogene treatment and (ii) to estimate the incidence proportion of patients having a herpetic infection containing Talimogene DNA within 6 months of initiating Talimogene treatment.
    Secondary objective: to estimate the incidence rate of herpetic lesions positive for Talimogene DNA among patients after ending treatment with Talimogene (ie, symptomatic reactivation).
  - Viral shedding study (#20120324)
    Herpetic infections in non-injected lesions will be qPCR tested for Talimogene. After the end of treatment, the incidence of Talimogene shedding will be assessed to evaluate asymptomatic reactivation.

Reviewer comment**:** At this time, the proposed medication guide and PVP, which includes the postmarketing study (#20130193) and viral shedding study (#20120324) are acceptable; both studies will be PMRs. Additionally, under expanded adverse experience reporting, FDA will require that all reports of herpetic infection in patients and contacts, with Talimogene qPCR results when available, be submitted as 30-day (monthly) reports if not previously filed as 15-day reports.

**Recombination of Talimogene with wild-type HSV-1:** important missing information
The theoretical risk of potential recombination of Talimogene with wild-type HSV-1 creating a chimeric stable recombinant virus is very low. Additionally, due to the nature of the genetic modifications in Talimogene, "even a potential recombination event between Talimogene laherparepvec and wild type virus could only results in a reversion to wild type like interactions[19]."

Data: In study 005/05, Amgen did NOT develop a PCR assay to evaluate the potential recombination of Talimogene with wild-type HSV-1.

PV actions: This missing information is NOT labeled in the package insert. No PV actions have been proposed.

Reviewer comment**:** We note that i) risk for potential recombination of Talimogene with wild-type HSV-1 is low; ii) stable propagation of a chimeric virus would be low; iii) the chimeric virus would behave like wild-type HSV-1, and iv) there is no assay to detect a chimeric viral product from recombination of wild-

[19] Environmental Assessment; BLA 125518, module 1.12.14, p.9.

type HSV-1 and Talimogene, were this to occur. FDA CMC and clinical reviewers agree that risk of recombinant Talimogene and wild type HSV-1 is theoretical at this time, with no data from clinical trials.

**Pregnant and lactating women:** important missing information
Since Talimogene shares similar biologic properties to wild-type HSV-1; there could be similar serious risks to the fetus/neonate of patients or patient contacts. There is potential for Talimogene to cross the placental barrier and also a risk of transmission during birth due to blood exposure and potential viremia. Additionally, transplacental metastases of malignant melanoma can occur, and there could be a risk of fetal exposure to Talimogene from transplacental metastasis of Talimogene containing tumor tissue. Talimogene associated herpetic infections in the fetus/neonate may lead to serious clinical sequelae, including multi-organ failure and death.

Data: Pregnant women were excluded from study 005/05, and there have been no reports, to date, of accidental exposure of a pregnant woman to Talimogene. Pre-clinical animal studies did not show effects on embryo-fetal development.

PV actions:

- Routine PV and labeled in PI under sections Use in Specific Populations (contraindicated in pregnant and lactating women); Patient Counseling Information. Amgen Global Pregnancy Surveillance Programs will collect data (spontaneous reports, medical literature reports, clinical trials) on pregnancies for which the mother or father was exposed to an Amgen product prior to conception or during pregnancy, and Amgen will conduct clinical follow-up after authorization for participation, through 12 months post-delivery. Pregnancies associated with AEs will be reported to FDA. There is also a similar global lactation surveillance program for women exposed to an Amgen product during lactation.
- Additional PV activity: Medication Guide

Reviewer comment**:** At this time, the proposed PVP is acceptable.

**Pediatric patients:** important missing information
Data: Children were excluded from study 005/05.
PV actions: Routine PV and labeled in PI [Use in Specific Populations].
Reviewer comment**:** At this time, the proposed PVP is acceptable.

**Patients with renal or hepatic impairment:** important missing information
Data: Patients with renal or hepatic impairment were excluded from study 005/05.
PV actions: Routine PV and labeled in PI [Use in Specific Populations].
Reviewer comment**:** At this time, the proposed PVP is acceptable.

**Long-term safety data:** important missing information
Safety data is from clinical studies only; there is no postmarketing safety data since Talimogene is not currently licensed in any country.
Data: The safety analysis set for Talimogene (study 005/05 and other clinical studies in subjects with

melanoma) include a total of 342 subjects treated with Talimogene. 206 subjects received Imlygic for < 6 months, 94 subjects for 6 to < 12 months, 22 subjects for 12 to < 18 months, and 20 subjects for ≥ 18 months (maximum exposure of 30 months). Amgen states that "available data have not identified any new safety concerns of longer treatment with Imlygic."

PV actions: The sponsor has proposed two postmarketing studies to collect long-term safety data on Talimogene treated patients: a multicenter observational registry study (# 20120139) is currently ongoing to evaluate subjects treated with Talimogene in clinical trials; and the postmarketing study (#20130193) will collect data on Talimogene treated patients post-licensure, for 5 years after initiation of Talimogene treatment. Information from these studies will be labeled in the PI under section Clinical Studies.

Reviewer comment**:** At this time, the proposed PVP is acceptable. FDA will request that the post-marketing observational study (#20130193) is a PMR; the Registry study (# 20120139) will be a voluntary postmarketing study.

### 5.3 Postmarketing study Protocol 20130193[20]

| |
|---|
| **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 melanoma patients treated with Talimogene in real world clinical practice |
| **Study duration:** 5 years |
| **Inclusion criteria:** enroll patients after initiation (or within 1 month ) of first Talimogene treatment. |
| **Exclusion criteria:** Patients participating in ongoing or previous clinical trials of Talimogene |
| **Primary Objectives/ Endpoints**<br>- Incidence rate of herpetic lesions containing Talimogene DNA in subjects, for 5 years*<br>- Proportion of subjects with a herpetic lesion containing Talimogene DNA within 6 months*<br><br>*time from initiating Talimogene treatment |
| **Secondary Objectives/ Endpoints**<br>- Incidence rate of herpetic manifestations, specifically in immunocompromised patients<br>- Incidence rate of a herpetic lesion, positive for Talimogene DNA by qPCR, occurring more than 30 days after ending use of Talimogene i.e. symptomatic reactivation<br>- Case counts of close contacts and HCPs with product-positive herpetic lesion "occurring during treatment period of subject."<br>- Characterization of herpetic manifestations in close contacts and HCPs<br>- Adverse Drug Reactions, Serious Adverse Drug Reactions (Adverse Drug Reactions (ADRS) listed in section 7 of Appendix 3).<br>- Data on demographics, disease characteristics, and treatment use |

[20] Amgen BLA 125518, Imlygic (Talimogene laherparepvec), module 1.16, United States Risk Management Plan dated 25 June 2014, Appendix 3.

- Overall survival will be estimated with Kaplan-Meier method with the time to death being calculated from the date of study enrollment. 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 (clinical follow-up regarding nature of lesion, exposure, underlying risk factors) to HCP and provides a list of "acceptable swabs" for sample collection. . HCP determines if qPCR testing is required for the suspected herpetic lesion. Individual returns to HCP for swabbing of lesion. Amgen also sends a kit for "qPCR sample retrieval" to HCP office, to aid HCP in shipping swab sample to central laboratory for qPCR test to detect Talimogene laherparepvec DNA.

**Statistical plan**

Estimate two measures of product-positive herpetic lesions:

- incidence rate of herpetic lesions: number of events/ subject-years
- 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 Timeline**

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".

Reviewer comments: FDA will require study 20130193 to be a PMR (concurred by CBER FDAAA SWG on June 25, 2015; Amgen notified on July 20, 2015) and milestone study dates proposed by Amgen (see Amgen response to IR dated July 31, 2015) are as follows:

> Final Protocol Submission: April 2016
> Study Completion: August 2024
> Final Report Submission: February 2025

**Definitions of herpetic "manifestations" v. "lesions":** In the protocol, herpetic lesions (mucocutaneous) were defined separately from other clinical manifestations (keratitis, encephalitis, disseminated infection). In response to FDA query to clarify if both herpetic lesions and manifestations would be qPCR tested for Talimogene, Amgen replied:

> "In our overall clinical program and in the proposed protocol for the observational study 20130193, we propose qPCR testing for product DNA in both herpetic lesions and herpetic manifestations (eg, keratitis, encephalitis, disseminated infection) among patients, close contacts, and health care providers. The final protocol will specify that both herpetic lesions and herpetic manifestations will be qPCR-tested for product DNA."

**Sample collection from close contacts/HCPs**: Postmarketing assessment of the risk of Talimogene transmission to patient contacts (close contacts and HCPs through occupational exposure) will be via spontaneous reporting of herpetic lesions suspected to be associated with Talimogene. Passive surveillance is known for underreporting AEs. Amgen has proposed a targeted questionnaire and qPCR assay to detect Talimogene DNA in suspected herpetic infections in patient contacts. This process is described in postmarketing study#20130193 and will also be offered outside of the postmarketing study.

Amgen modified their original protocol to "exclude the option of self-collection" of samples, and their currently proposed postmarketing process of sample collection from patient contacts is complicated and poses logistical challenges (see Appendix A). It involves reporting through primary care providers, who may not be familiar with Talimogene, the availability of qPCR testing for Talimogene DNA, adequate sample collection and shipment of the sample to Amgen's central laboratory. Sample collection itself may require multiple visits to the primary care site, and the burden is on the primary care physician and the individual reporting a suspected herpetic lesion, to coordinate this process with Amgen. Additionally, as stated by Amgen and supported by published literature[21], sample collection needs to occur within approximately 3 days of the occurrence of a suspected herpetic lesion to yield qPCR assay results; thus this entire process, involving possibly two visits to the HCP office, may not be feasible in achieving results in the real world clinical setting. Of note, clinical trial 005/05 lacks data on the causative agent of herpetic infection in non-tumor tissue of treated subjects due to crusting over/resolution of lesions before sample collection could take place.

[21] Boivin et al. Longitudinal evaluation of herpes simplex virus DNA load during episodes of herpes labialis. J Clin Virol. 2006 Dec;37(4):248-51.

BLA 125518 was the subject of a joint Cellular, Tissue, and Gene Therapies Advisory Committee and Oncologic Drugs Advisory Committee Meeting on April 29, 2015, and discussed the following question: "Please discuss proposed postmarketing study (protocol 20130193) and make suggestions for improvement in the process for sample collection to monitor for transmission of Talimogene laherparepvec to contacts (with qPCR confirmation). The AC recommended that "each health-care provider have kit(s) already on store, and instructions, ready for one-stop shop. If there is a report of a contact in the family or someone else or a health-care provider, they can come in, get everything swabbed and sent, and not have to wait around and get a kit sent. Then Amgen would replace the kits as they are sent in."[22]

At this time, Amgen has not agreed to FDA request to develop a more logistically feasible method to collect samples from patient contacts. At this time, we accept Amgen's proposed method and will reassess at a future date if the interim data from this study demonstrates that Amgen is unable to adequately obtain qPCR follow-up for spontaneously reported herpetic infections in patient contacts. Additionally, the availability of Amgen qPCR assay for Talimogene DNA will be included in label, urging individuals with herpetic infection to contact Amgen for testing and further characterization of suspected Talimogene associated herpetic infection.

**Follow-up of patients and sample collection**: At the end of Talimogene treatment, solicited follow-up will be at quarterly intervals by phone or clinic visit. As per the sponsor's response to an IR[23], a kit for self-collection of samples will *not* be provided to patients. Sample collection will be done by an HCP during a clinic visit. We note that the time elapsed in quarterly solicited follow-up may be too long for sample collection in a timely manner from herpetic lesions that resolve quickly. As regards under-reporting of herpetic lesions, Amgen states, "*To measure the degree of incomplete data from under-reporting of suspected herpetic lesions by study subjects, the difference will be reported between incidence proportion of subjects with suspected herpetic lesion and incidence proportion (3% to 5%) of the general population with frequent recurrences of oro-labial lesions*.(Page 23 of Appendix 3.)"

**Wild type HSV-1 and potential recombinant Talimogene:** The current protocol does not include testing for wild type HSV-1 by qPCR assay or recombinant Talimogene. Amgen has agreed to revise protocol to include qPCR testing for both Talimogene and wild type HSV-1 DNA.

> Please see following recommendation by Dr. Mark Pallansch (CDC, Director of Viral Diseases), member of AC committee (received post-AC discussion, via e-mail on May 13, 2015):
>
> "The (current) assays are designed to identify (only T-VEC) and would not detect natural HSV-1 infection/reactivation. This is a missed opportunity to characterize clinical episodes to help with both determinations of adverse events and determine the background rate of infection/reactivation in this population. Secondly, one of the safety concerns relates to stability of T-VEC and recombination with latent HSV-1 (or less likely concurrent acute infection). The second suggested characterization would be to explicitly test for the three major introduced genetic modifications."

[22] BLA 125518 at joint Cellular, Tissue, and Gene Therapies Advisory Committee and Oncologic Drugs Advisory Committee Meeting on April 29, 2015: AC transcript.
[23] Amgen BLA 125518, Imlygic (Talimogene laherparepvec), module 1.11.3, Response to Questions

**Study population**: The study is designed for a sample size of 920 patients who are *not* participating in ongoing clinical trials. We note that enrollment of 920 patients will be difficult from a practical standpoint, since the population of patients with advanced melanoma who opt for Talimogene over other therapies, may be limited. As Amgen states, "*The number of patients in this source population is limited to the small number of unresected melanoma cases that are regionally or distantly metastatic and the expanding use of other melanoma therapies approved since 2011 (ipilimumab, vemurafenib, dabrafenib, trametinib) or considered in the near future (lambrolizumab, nivolumab). The pool of study sites is limited by the small number of academic centers and specialty clinics treating cases of advanced melanoma, unique characteristics of Talimogene laherparepvec that inherently limit the number of sites (eg., -70°C storage requirements), and yet unknown regulatory approval and reimbursement decisions."*

FDA Statistics reviewer [Dr. Yuqun (Abigail) Luo] comment:

The precision or CI for the incidence rate when 0 out of 1600 subject-years show herpetic lesion, or when 0 out of 920 subjects show herpetic lesion was verified.
FDA verified that with a median duration of survival of 2 years, enrolling 800 subjects in 3 years with duration of entire study being 5 years, would result in 1600 subject-years. Of note, the number of subject-years would change if the actual enrollment rate or survival time differs from these assumptions. It will be important to ensure that there will be 1600 evaluable subject-years, and at least 920 evaluable subjects, in order to detect with 80% power an event rate for herpetic infection of 1/1000 subject-years.

## 5.4 Clinical trial Registry Study 20120139 (Study 009/07)

In the registry study, subjects previously treated with Talimogene on a clinical trial, will be evaluated with quarterly solicited follow-up for Talimogene laherparepvec-related adverse events and survival status. The protocol is summarized in the table below.

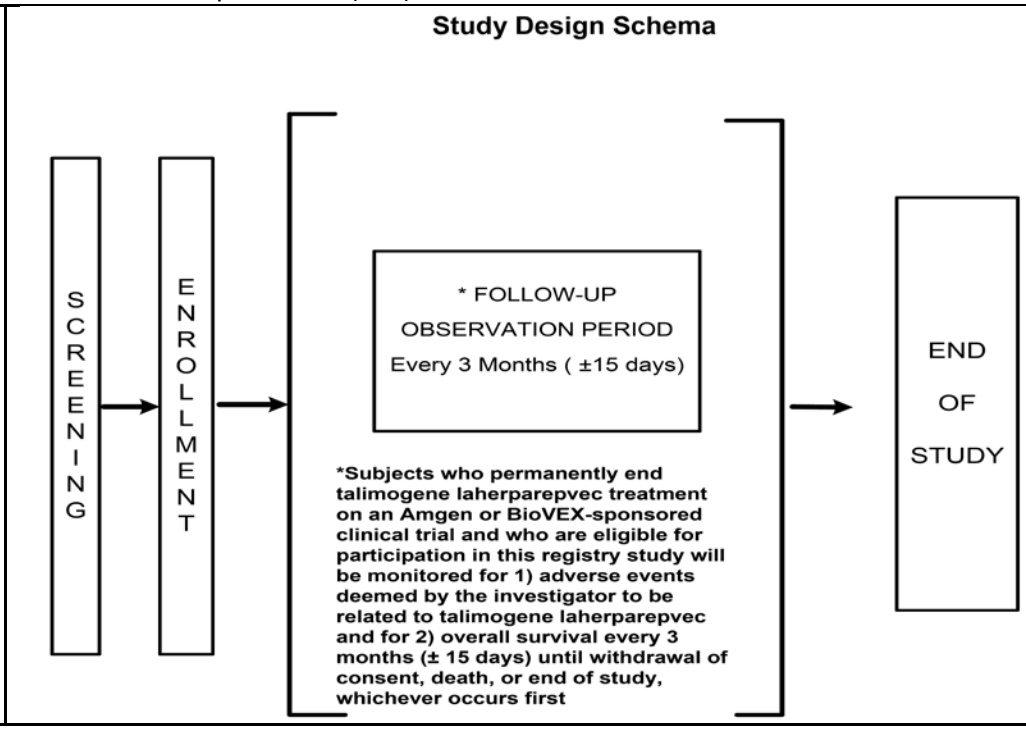
| |
|---|
| **Study title: A Registry Study to Evaluate the Survival and Long-Term Safety of Subjects With Melanoma who Previously Received Talimogene** Laherparepvec (previously called Study 009/07 OncoVEX GM-CSF Registry) |
| **Study design**: international, multicenter, non-interventional observational, registry study |
| **Study population:** Subjects who received at least one dose of Talimogene on an Amgen or BioVEX-sponsored clinical trial, and ended treatment and reporting period on that trial.<br>Key exclusion criteria: Subject must not currently receive or plan to receive Talimogene 30 days following registry enrollment. Subject may receive standard of care treatment, with the exclusion of Talimogene and any experimental treatment. |
| **Study size:** Total number of subjects determined by the number of subjects who remain alive at the end of the previous Amgen or BioVEX-sponsored Talimogene clinical trial in which they participated. |
| Primary Objectives: Long-term safety and Overall survival (OS) |
| Primary Endpoints<br>1.) Subject incidence of all treatment-related AEs – this includes any grade, grade ≥ 3 AEs, serious AEs, fatal |

AEs, and AEs of interest
2.) OS

Statistical plan
No formal hypothesis and no formal statistical analysis. Descriptive statistical reporting of the safety endpoints and OS.

**Data collection:**
Solicited follow-up, via phone or clinic visit, every 3 months (± 15 days) to collect the following info: (i) Talimogene-related AEs (determined by investigator) and (ii) survival status. Additional information collected on subsequent anticancer melanoma therapy.
Data entry into electronic case report forms (CRF).

Study Schema




**Study Timeline**
Study status: ONGOING; no interim analysis is planned; primary analysis will be performed at end of study.
End of study: "The registry study will end when the sponsor (in consultation with the regulatory authorities) has determined that the collection of long-term safety and survival data are no longer necessary."

**Results**
Synopsis of Study 009/07 (BLA module 5.3.5.4 Study 009/07 OncoVEX GM-CSF Registry)[24]:
"There have been no Talimogene laherparepvec-related adverse events reported in subjects included in the registry and of the 7 deaths, 6 were due to disease progression, the cause of death was not known for 1 case. To date, there have been no long-term safety concerns of Talimogene laherparepvec identified during the course of this registry."

(b) (4)

Reviewer comments:

- Difficulties in evaluation of primary endpoint: Patients may develop progressive disease and undergo subsequent treatments (confounders), thus assessment of the relatedness of TEAE to prior Talimogene therapy will be difficult. There is also no follow-up testing for herpetic infection in this study.
- The original protocol does not describe the study timeline and there are no planned interim analyses. Amgen was contacted for further details on study timeline and interim analyses, and responded as follows:

| | |
|---|---|
| Study status | ongoing |
| Study initiated | December 3, 2007 |
| Number of enrolled subjects | 21 subjects; as of March 30, 2015 |
| Completion of enrollment | March 30, 2020 (anticipated) |
| End of study | March 2023 |
| Submission of final analysis | July 2023 |
| Interim analysis | None. "…analyses will be conducted at regular, periodic intervals before the planned primary analysis." |

- Small numbers of enrolled subjects to date (21 subjects as of March 30, 2015) and limited data.
- The protocol excludes subjects receiving Talimogene re-treatment outside of a clinical trial, even though standard-of-care treatment in the post-licensure period is accepted. We are concerned that exclusion of subjects who experience disease progression and re-initiate Talimogene treatment would eliminate subjects with poorer overall survival. Amgen was asked to provide rationale for exclusion criteria that excludes subjects receiving Talimogene re-treatment. It was suggested to Amgen to include these subjects, with option of a secondary descriptive analysis of subjects receiving Talimogene retreatment.
    - Amgen responded that: "For patients participating in ongoing clinical trials, exclusion from the registry will be maintained since patients will be followed in the parent clinical trial. Patients receiving Talimogene laherparepvec retreatment outside of a clinical trial will not be excluded from the registry. Protocol 20120139 will be amended by October 2015 to clarify this concept as well as to include enrollment of subjects with tumor types other than melanoma who have participated in an Amgen-sponsored clinical trial of Talimogene laherparepvec."

## 5.5 Medication Guide

Amgen has proposed a Medication Guide (MG) as an additional risk communication activity (please note that this was not proposed as a component of the proposed REMS). The proposed MG provides information on the product and patient education on the risk of life-threatening herpetic infection in immunocompromised individuals; the risk to pregnant/lactating women; cold sores or serious herpetic infection in patients during or after treatment; the risk of transmission to close contacts and safe use instructions and precautions for patients and contacts to reduce accidental exposure to Talimogene; additional information on serious treatment related AEs (such as poor wound healing) and common AEs

(such as flu-like symptoms). Based on OBE/DE review of the clinical trial safety data for Talimogene, our recommendations are:

- Include information in labeling (under section 17: Patient Counseling Information) that optimizes the awareness and education of patients about the potential risks of Talimogene to patients and contacts (transmission) and associated safe use precautions, risk to vulnerable populations (immunocompromised hosts and pregnant women). The MG as proposed by Amgen, may be chosen as a mechanism for providing patients and contacts with appropriate information on these risks and precautions. Of note, though the MG emphasizes risk of Talimogene associated herpetic infection in patients and contacts, it does not provide information on Amgen's proposed follow-up with targeted questionnaire and qPCR testing for Talimogene DNA. Availability of Amgen's Talimogene qPCR assay for further characterization of herpetic infection should be included in the patient counseling materials.
- FDA has the option to require MG as labeling under 21 CFR 208 since it meets the criteria that MG is "safety-related, addressing serious risk(s) (relative to benefits) of which patients should be made aware." Under these regulations, the MG would be required to be distributed to patients in outpatient settings, at the time of treatment by administering physicians[25], which is a likely scenario for Talimogene, should it be approved. Additionally, patients could be advised of where to access the MG. On June 25, 2015, Talimogene was discussed by the CBER FDAAA SWG, and MG as labeling was presented to the SWG, who concurred.
- However, we realize that other mechanisms that will similarly educate and caution patients on these risks may also be an option. The content and format of patient counseling materials will be reviewed by Advertising and Promotional Labeling Branch (APLB).

## 5.6 Risk Evaluation and Mitigation Strategy (REMS)

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require a Risk Evaluation and Mitigation Strategy (REMS) if it is determined that such a strategy is necessary to ensure that the benefits of the biological product outweigh the risks (section 505-1(a)(1)). Amgen has voluntarily submitted REMS in the original BLA 125518, as part of their proposed Risk Management Plan for pharmacovigilance of Talimogene.

Proposed goals: The goals of the REMS are to "inform healthcare providers (HCPs) and patients about the risks of herpetic infection and accidental exposure associated with Imlygic."

Proposed content of REMS: Communication Plan in accordance with FDCA, Section 505-1(e)(3):

Amgen proposes to provide a Dear Healthcare Provider (DHCP) letter and a Patient brochure to HCPs, within 60 days of approval and annually thereafter for 3 years. These materials will be sent via mail or electronically to HCPs. Hard copies of these materials will be distributed by sales representatives to HCPs at the time of initial contact; in answer to questions related to risks; and upon request.

[25] FDA Guidance Medication Guides — Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS). November 2011. http://www.fda.gov/downloads/Drugs/.../Guidances/UCM244570.pdf

Additionally, Amgen will distribute these materials annually (continuing for 3 years) at the American Society of Clinical Oncology and Society of Surgical Oncology meetings. DHCP letter and Patient brochure will also be available on a REMS website in electronic and print format.

**Dear Healthcare Provider (DHCP) letter** provides information on risks of

i. Talimogene associated disseminated herpetic infection in severely immunocompromised patients:

a. Contraindication to use in patients who are severely immunocompromised such as severe congenital or acquired cellular and/or humoral immune deficiency.

b. Consideration of risk benefit profile in immunocompromised patients such as HIV/AIDS, leukemia, lymphoma, common variable immunodeficiency, or those who require chronic high dose steroids or other immunosuppressive agents

ii. Accidental exposure of HCPs and close contacts may lead to transmission of Talimogene

iii. Potential harm to the fetus or neonate in pregnancy
HCPs are instructed to advise patients of the potential hazards to the fetus and/or neonate if Talimogene is used during pregnancy or if the patient becomes pregnant while taking Talimogene.

HCP is also instructed to review information in, and provide copies of the Medication Guide and patient brochure. Instructions on reporting Adverse Events (AEs) to Amgen and FDA (MedWatch) are provided.

**Patient brochure** provides information on the risks listed in the DHCP letter, describes signs and symptoms of herpetic infection that may occur in the patient (due to infection of non-tumor tissue or symptomatic reactivation), and provides information to patients and their contacts on precautions to prevent accidental exposure to Talimogene (information from Amgen's draft patient brochure is summarized in tabular form below).

Proposed Timetable of Assessment (pursuant to Section 505-1(d)): Assessments will be submitted at 18 months, 3 years, and 7 years. The reporting interval of each assessment may conclude 60days before the submission due date.

Assessment will include an assessment of the Communication Plan and safety surveillance.

Assessment of Communication Plan will include:

- launch date of the communication plan
- number of HCPs targeted by the REMS
- REMS communications materials (DHCP Letter and Patient Safety Brochure): number of communications sent to HCPs via email and US mail and the dates sent; number successfully delivered by e-mail; number undeliverable by US mail.
- REMS website: date that the website went live and number of unique site visits during the assessment period and cumulatively
- scientific meetings: list of scientific meetings where REMS information was distributed

Assessment of safety surveillance:

- summary and analysis of all postmarketing case reports of herpetic infection in immunocompromised or pregnant patients and signs or symptoms of herpetic infection in HCPs and close contacts that are accidentally exposed to Talimogene

Reviewer comment: At this time, the available clinical trial safety data do not suggest a safety concern that would require a REMS to ensure that benefits of Talimogene outweigh its risks. This BLA was the subject of discussion at the June 25, 2015 CBER FDAAA Safety Working Group (SWG), and the SWG concurred with OBE/DE, that REMS was not required for Talimogene. As per FDA Guidance[26], FDA will notify applicants who voluntarily submit proposed REMS whether the REMS will be required. The sponsor was notified (teleconference on July 20, 2015) that FDA will not require a REMS.

The proposed REMS does not include Elements to Assure Safe Use (ETASU) or an implementation system. While the Communication Plan highlights serious risks, this information is already included in the Package Insert and Medication Guide. Although the sponsor mentions an "assessment of safety surveillance," this is a part of the required routine pharmacovigilance. Assessment of REMS will thus be limited to providing the FDA a list of materials distributed, and the number of visits to the REMS website. This assessment will not provide sufficient metrics to make a determination of mitigation of risks. There does not appear to be a measurable means in the proposed assessment to determine if the elements of the REMS have had any impact on altering the benefit risk balance, and it is of note that a REMS will be implemented per regulations only if the implementation is necessary to ensure that the benefits of the biological product outweigh the risks.

After review of the material submitted in the BLA, we have determined that the sponsor proposed REMS is not necessary to ensure that the benefits of Talimogene to treat melanoma patients outweigh the risks of Talimogene to patients as well as potential risk groups (immunocompromised individuals, pregnant women, close contacts and HCPs). To date, there are no reported cases of Talimogene transmission to patient contacts; there is 1 case of an accidental needle-stick injury (direct inoculation) in an HCP with subsequent Talimogene positive whitlow lesion at the site of injury. FDA will require that Amgen's proposed postmarketing study (#20130193) will be a postmarketing requirement (PMR) in order to monitor potential Talimogene associated herpetic infection in treated patients (primary infection/reactivation-latency) and their contacts (transmission).

FDA will monitor the safety profile of Talimogene in the post-licensure period through safety data from required postmarketing studies (PMRs), registry studies, and the spontaneous reporting of adverse events. FDA may reassess the need for a REMS in the future.

[26] FDA Guidance: Format and Content of Proposed REMS, REMS Assessments, and Proposed REMS Modifications, September 2009
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf

# 6. OBE/DE ASSESSMENT AND RECOMMENDATIONS

## 6.1 Postmarketing Requirements (PMRs)

Talimogene is a first-in-class oncolytic therapy with genetically modified replication competent HSV-1. Talimogene retains biological properties of wild type HSV-1, and is capable of in vivo amplification, spread to uninjected tissue, recombination with wild-type HSV-1, life-long latency and symptomatic reactivation, viral shedding from infected person (proxy for transmission), transmission through unintended exposure.

Although the Phase 3 study (Study 005/05) showed a 5.5% incidence of herpetic infection in the Talimogene arm, qPCR testing to confirm the causative agent (Talimogene v. wild type HSV-1) was not done. Data from preclinical studies in the murine model suggested that Talimogene could establish latency. Preliminary shedding studies have documented the presence of Talimogene virus in the blood and body fluids, injection site and exterior of occlusive dressing in treated patients.

The potential incidence of serious Talimogene associated herpetic infection in treated patients and contacts cannot be assessed by a single clinical trial because of the rarity of serious (wild-type HSV-1) herpetic infection. The existing safety database is not large enough to exclude a possible association with rare serious and life-threatening events such as herpetic encephalitis, keratitis, and disseminated infection.

**Postmarketing Requirements under 505(o)**

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)).

OBE/DE has concluded that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess signals of the serious risks as defined under FDAAA.

1. There is currently insufficient clinical biodistribution and Talimogene viral shedding data in treated patients to predict the risk for potential transmission and subsequent potential Talimogene associated herpetic infection in patient contacts
2. There is currently insufficient data on the risk of Talimogene associated herpetic infection in treated patients
    a. Talimogene infection of non-tumor tissue
    b. symptomatic herpetic infection due to latency and reactivation of Talimogene
3. There is currently insufficient data on herpetic manifestations in immunocompromised hosts
    a. immunocompromised status of patient at time of initiating Talimogene or subsequent immunocompromised condition following treatment and reactivation from latency

b. immunocompromised patient contacts who are infected with Talimogene due to transmission

Furthermore, the new pharmacovigilance system (Sentinel) under section 505(k)(3) of the FDCA is not sufficient at this time, to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that Amgen is required, if Talimogene is approved, pursuant to Section 505(o) of the FDCA (amended by FDAAA, Title IX, Section 901), to conduct two postmarketing studies, "**to identify unexpected serious risk(s) when available data indicate the potential for serious risk(s)**" of potential Talimogene associated herpetic infection of non-tumor tissue in patients (primary infection/latency and reactivation) and contacts (transmission/ accidental exposure). The proposed PMR studies were concurred by CBER FDAAA SWG on June 25, 2015; Amgen was notified on July 20, 2015.

**PMR #1**: A single-arm trial to evaluate the biodistribution and shedding of Talimogene in treated subjects.
The ongoing viral shedding study protocol #20120324 evaluates the biodistribution and shedding of Talimogene in treated subjects; sample size of 60 subjects.
Amgen has agreed to revise final protocol to include updated sample size rationale for N = 60 subjects.
Milestone study dates proposed by Amgen (see Amgen response to IR dated July 31, 2015):

Final Protocol Submission: November 2015
Study Completion: September 2016
Final Report Submission: May 2017

**PMR #2**: A prospective observational cohort study of Talimogene treated patients to characterize the risk of herpetic infection among patients, close contacts, and healthcare providers; sample size of 920 subjects, study duration 5 years.
Amgen has agreed to revise final protocol to specify that both herpetic lesions and herpetic manifestations will be tested. Amgen has agreed to include qPCR assay for testing of wild-type HSV-1 in addition to Talimogene. Amgen has not agreed to FDA suggestions for a more logistically feasible method for sample collection from patient contacts. At this time, we accept Amgen's proposed method and will reassess at a future date if the interim data from this PMR demonstrates that Amgen is unable to obtain qPCR follow-up for spontaneously reported herpetic infections in patients, contacts, or health care providers. Availability of Amgen qPCR assay for Talimogene DNA will be included in the medication guide or label.
Milestone study dates proposed by Amgen (see Amgen response to IR dated July 31, 2015):

Final Protocol Submission: April 2016
Study Completion: August 2024
Final Report Submission: February 2025

## 6.2 Voluntary postmarketing study: Registry study protocol #20120139

The ongoing registry study protocol #20120139 will continue post-licensure as a voluntary postmarketing study to collect additional long term safety data.

The current protocol excludes subjects receiving Talimogene re-treatment outside of a clinical trial. This is of concern since exclusion of subjects who experience disease progression and re-initiate Talimogene treatment would eliminate subjects with poorer overall survival. Amgen has agreed that the protocol will be amended as follows: "For patients participating in ongoing clinical trials, exclusion from the registry will be maintained since patients will be followed in the parent clinical trial. Patients receiving Talimogene laherparepvec retreatment outside of a clinical trial will not be excluded from the registry. Protocol 20120139 will be amended by October 2015 to clarify this concept as well as to include enrollment of subjects with tumor types other than melanoma who have participated in an Amgen-sponsored clinical trial of Talimogene laherparepvec."

## 6.3 Conclusion

Final determination of the benefit/risk profile of Talimogene is pending the final clinical, statistical and product reviews. At the joint Cellular, Tissue, and Gene Therapies Advisory Committee and Oncologic Drugs Advisory Committee (AC) Meeting discussion of this BLA on April 29, 2015 the AC decided by a vote of 22 to 1, that Talimogene had an overall favorable benefit-risk profile to support approval. The single pivotal phase 3 clinical trial 005/05 met its primary efficacy endpoint demonstrating higher durable response rate (DRR) Odds Ratio = 12.8 ($P < 0.0001$), with Talimogene (N = 46; 15.6%) compared to GM-CSF control (N = 2, 1.4%). The most common AEs with Talimogene were flu-like symptoms (N = 264 subjects; 90%). The most common serious AEs were disease progression or events related to disease progression. The most commonly reported treatment-related serious AE was cellulitis (incidence of 2.4% (N=7) in Talimogene arm). There were no treatment related deaths. There was limited clinical trial safety data on Talimogene-associated herpetic infection of non-tumor tissue in patients (primary infection/latency and reactivation) or contacts (transmission, accidental exposure).

OBE/DE has completed a review of the Amgen proposed PVP dated June 25, 2014 submitted in BLA 125518. OBE/DE agrees with the planned activities listed in the PVP and adds the recommendations for two PMR studies and expanded AE reporting of herpetic infections in patients/contacts, should the product be licensed. OBE/DE has reviewed the proposed REMS voluntarily submitted by Amgen. At this time a REMS is not necessary to ensure that the benefits of Talimogene to treat melanoma patients outweigh the risks of Talimogene to patients as well as potential risk groups (immunocompromised individuals, pregnant women, close contacts and HCPs).

Of note, this BLA was discussed by the CBER FDAAA Safety Working Group (SWG) on June 25, 2015, and the SWG "concurred with the recommendation of issuing the two Title IX PMRs and the medication guide, which will be required as part of labeling. SWG also agreed that the safety data at this time do not suggest a safety concern that would require a REMS to ensure that the benefits of Talimogene outweigh its risks" (quoted from SWG meeting minutes).

## 6.4 OBE/DE Recommendations

Based on the review of the pre-licensure safety data, and the sponsor's proposed PVP, OBE/DE recommends the following actions:

1. Routine pharmacovigilance: Adverse event reporting in accordance with 21 CFR 600.80 and quarterly periodic safety reports for 3 years (annual PSURs thereafter).

2. Expanded adverse experience reporting (in addition to complying with the requirements under 21 CFR 600.80) to FAERS for 3 years following product licensure as follows:

Due to the concern for potential Talimogene associated herpetic infection of non-tumor tissue in patients (primary infection/latency and reactivation) and contacts (transmission/accidental exposure), we recommend that all reports of herpetic infection in patients and contacts, with Talimogene qPCR results when available, be submitted as 30-day (monthly) reports if not previously filed as 15-day reports.

3. Labeling: OBE/DE recommendations as follows:

i.) Include information in labeling (under section 17: Patient Counseling Information) that optimizes the awareness and education of patients about the potential risks of Talimogene to patients and contacts (transmission) and associated safe use precautions, risk to vulnerable populations (immunocompromised hosts and pregnant women), and the availability of Amgen's Talimogene qPCR assay for further characterization of herpetic infection.

The Medication Guide (MG), as proposed by Amgen, may be chosen as a mechanism for providing patients and contacts with appropriate information on these risks and precautions. FDA has the option to require MG as labeling under 21 CFR 208 and require MG to be distributed to patients in outpatient settings, at the time of treatment by administering physicians, which is a likely scenario for Talimogene, should it be approved. MG as labeling was presented to the CBER FDAAA SWG, who concurred. However, we realize that other mechanisms that will similarly educate and caution patients on these risks may also be an option. The content and format of patient counseling materials will be reviewed by Advertising and Promotional Labeling Branch (APLB).

ii.) Currently, risk of herpetic infection associated with Talimogene is included in Package Insert (PI) and MG, but there is no information regarding availability of Talimogene qPCR assay for follow-up testing. Availability of Amgen's Talimogene qPCR assay for further characterization of herpetic infection should be included in both PI and MG.

iii.) Instructions to prevent possible contamination of the exterior of occlusive dressings should be included in both PI and MG.

4. Active surveillance: postmarketing studies

A.) <u>Post-marketing Requirement (PMR) studies for Safety under 505 (o)</u>:

FDA has determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify the following "unexpected serious risk when available data indicates the potential for a serious risk:" Talimogene 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 will not be sufficient to identify this serious risk.

Therefore, based on appropriate scientific data, if Talimogene is approved, FDA has determined that Amgen is required, under Section 505(o) of the FDCA (amended by FDAAA, Title IX, Section 901), to conduct the following two PMR studies. The PMR studies were concurred by CBER FDAAA SWG on June 25, 2015; Amgen was notified on July 20, 2015 and has provided the following milestone dates.

**PMR #1**: Complete the ongoing single-arm trial to evaluate the biodistribution and shedding of Talimogene in 60 talimogene-treated subjects (study protocol #20120324).
Amgen has agreed to revise final protocol to include updated sample size rationale for N = 60 subjects.

Final Protocol Submission: November 2015
Study Completion: September 2016
Final Report Submission: May 2017

**PMR #2:** Conduct a prospective observational cohort study of 920 Talimogene-treated patients to characterize the risk of herpetic infection among patients, close contacts, and healthcare providers; study duration 5 years (study protocol 20130193).

Amgen has agreed to revise final protocol to specify that both herpetic lesions and herpetic manifestations will be tested. Amgen has agreed to include qPCR assay for testing of wild-type HSV-1 in addition to Talimogene. Amgen has not agreed to FDA suggestions for a more logistically feasible method for sample collection from patient contacts. At this time, we accept Amgen's proposed method and will reassess at a future date if the interim data from this PMR demonstrates that Amgen is unable to obtain qPCR follow-up for spontaneously reported herpetic infections in patient contacts. Availability of Amgen qPCR assay for Talimogene DNA should be included in both PI and MG.

Final Protocol Submission: April 2016
Study Completion: August 2024
Final Report Submission: February 2025

B. **Voluntary postmarketing study:** Ongoing registry study protocol #20120139 will continue as a voluntary postmarketing study. Amgen has agreed to amend the final protocol to revise the exclusionary criteria for this study to include subjects who receive retreatment with Talimogene outside of a clinical trial in the post-licensure period; as per Amgen the final protocol will be submitted October 31, 2015.

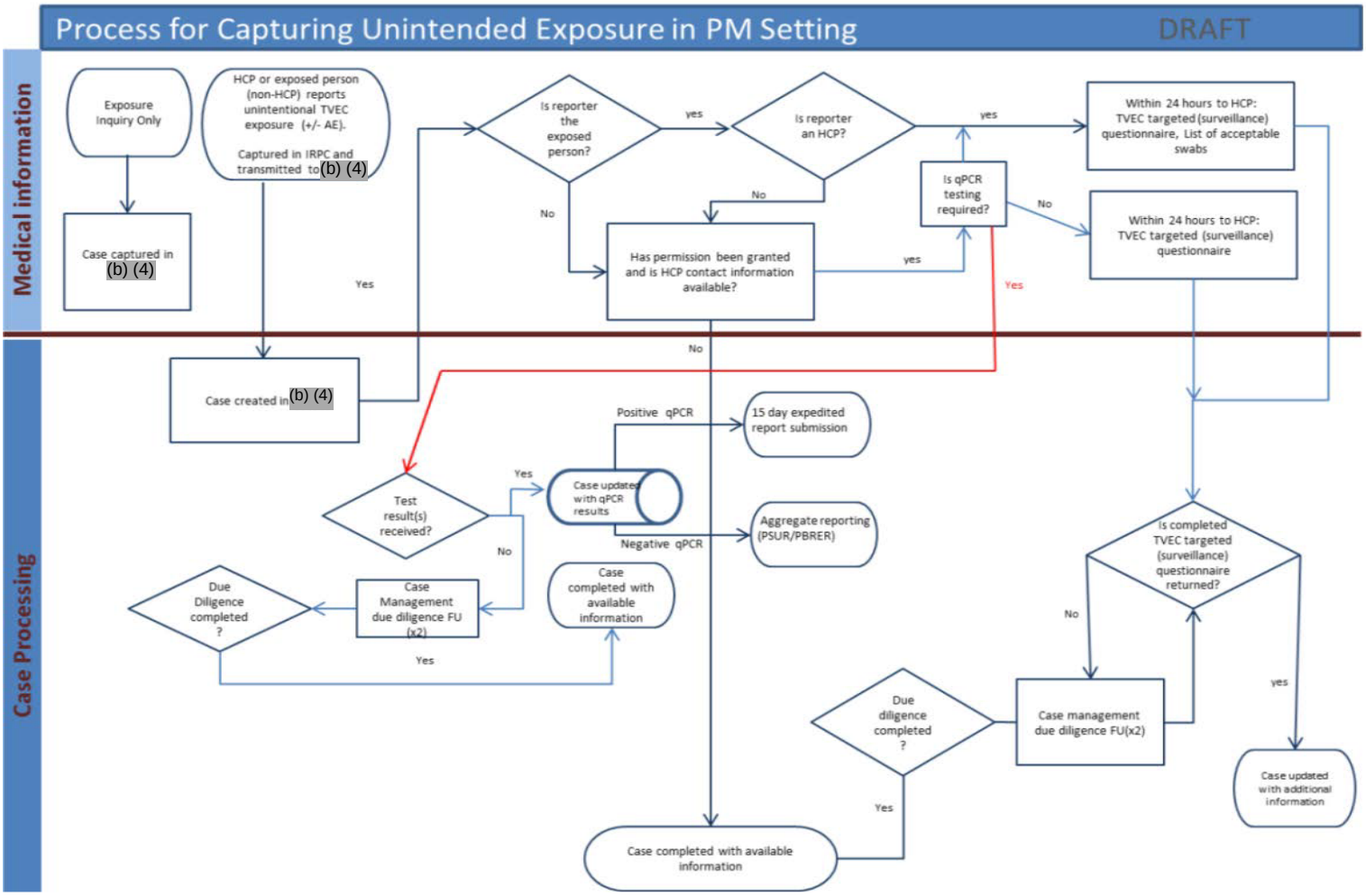
5. Additional PV activities: In the postmarketing setting (outside of a clinical study), Amgen will provide a questionnaire and the option of qPCR testing for Talimogene DNA in spontaneously reported suspected herpetic infection in patients/contacts. Availability of Amgen qPCR assay for Talimogene DNA should be included in both PI and MG.

6. At this time, the available clinical trial safety data do not suggest a safety concern that would require a 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.

## Appendix A

Source: Amgen response to FDA IR regarding process for sample collection and testing to detect potential Talimogene transmission to patient contacts.

**Figure 1. Process for Capturing Unintended Exposure in PM Setting (Revised)**



## Appendix B

**Table 1. Number of Subjects Receiving Talimogene Laherparepvec by Duration of Cumulative Exposure**

| | ≥ 1 dose | 0 to <6 months | 6 to <12 months | 12 to <18 months | 18 months and longer |
|---|---|---|---|---|---|
| Overall total exposure (Program-Wide Analysis Set) | 408 | 269 | 96 | 23 | 20 |
| Melanoma studies (Supportive Melanoma Analysis Set)[a] | 342 | 206 | 94 | 22 | 20 |
| Non-melanoma studies[b] | 66 | 63 | 2 | 1 | 0 |

[a] Includes exposure data from subjects in Studies 002/03, 002/03-E, 005/05, and 005/05-E.
[b] Includes exposure data from subjects in Studies 001/01, 004/04, 005/04, and 006/09.
The Program-Wide Analysis Set includes all subjects who were enrolled in Studies 001/01, 002/03, 002/03-E, 004/04, 005/04, 005/05, 005/05-E, and 006/09 and received ≥ 1 dose of study treatment. Data from subjects in the extensions of Studies 005/05 and 002/03 were combined with data from the parent study on the subject level prior to being summarized.
Source: Table IAS-5.1

**Table 3-4. Number of Subjects Exposed to Imlygic in Amgen-sponsored Clinical Trials (Safety Analysis Set)**

| Treatment | Number of Subjects |
|---|---|
| All Completed and Ongoing Studies | |
| Talimogene Laherparepvec | 416 |
| Comparator/Placebo | 130 |
| Completed Studies | |
| Melanoma Studies[a] | |
| Talimogene Laherparepvec | 342 |
| Comparator/Placebo | 127 |
| Head & Neck Studies[b] | |
| Talimogene Laherparepvec | 19 |
| Comparator/Placebo | 3 |
| Pancreatic Studies[c] | |
| Talimogene Laherparepvec | 17 |
| Other Solid Tumor Studies[d] | |
| Talimogene Laherparepvec | 30 |
| Ongoing Studies | |
| Melanoma Studies[e] | |
| Talimogene Laherparepvec | 8 |

Safety Analysis Set includes all subjects who received at least one dose of a protocol-specified treatment and is based on the actual treatment received.
Data as of 6/6/2013 (snap shot date of study 00505) is used.
[a]Studies 002-03, 002-03E, 005-05, and 005-05E.
[b]Studies: 004-04, and 006-09
[c]Study: 005-04
[d]Study: 001-01
[e]Study 20110264.