

Summary Basis for Regulatory Action

Date: October 27, 2015

From: Ramjay S. Vatsan, Ph.D., Chair of the Review Committee

BLA/ STN#: 125518/0

Applicant Name: Amgen, Inc.

Date of Submission: July 28, 2014

PDUFA Goal Date: October 27, 2015

Proprietary Name: IMLYGIC[®]

Non-Proprietary Name: talimogene laherparepvec

Indication: IMLYGIC is a genetically modified oncolytic viral therapy indicated for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery.

Limitation of Use: IMLYGIC has not been shown to improve overall survival or have an effect on visceral metastases.

Recommended Action: Approval

Signatory Authorities Action:

Offices Signatory Authority:

Celia Witten, PhD, MD, Office Director, OCTGT

- I concur with the summary review.
- I concur with the summary review and include a separate review to add further analysis.
- I do not concur with the summary review and include a separate review.

Mary Malarkey, Director, Office of Compliance and Biologics Quality

- I concur with the summary review.
- I concur with the summary review and include a separate review to add further analysis.
- I do not concur with the summary review and include a separate review.

Material Reviewed/ Consulted, Specific Documentation Used in Developing the SBRA

Material Reviewed/ Consulted	Reviewer Name – Document(s) Date
CMC Review	Oct 15, 2015 Vatsan, Aksamit, Byrnes, Havert Jan 22, 2015 Wernly
CBER Lot Release	Oct 19, 2015 Campbell
Facilities Review	Aug 20, 2015 Ballica, Harman
Environmental Assessment FONSI	Oct, 6, 2015 Oct 27,2015
Establishment Inspection Report	Aug 7, 2015 Ballica, Waites, Vatsan, Aksamit
Nonclinical Pharmacology/Toxicology Review	July 30, 2015 Huang
Clinical Review	Oct 26, 2015 Bross, Le, O'Leary
Medical Officer Memo	Oct 8, 2015 O'Leary
Statistical Review	Aug 6, 2015 Luo
Pharmacovigilance Review	Aug 13, 2015 Alimchandani, Jankosky
Advertising and Promotional Labeling Review	Mar 6, 2014; Aug 20, 2015; Jun 25, 2015 Nguyen
Bioresearch Monitoring Review	May 12, 2015 Ortega, Holobaugh
Advisory Committee Transcript	Apr 29, 2015
DCEPT Division Director Memo	Oct 23, 2015 Bryan

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1. Introduction

Biologics License Application (BLA) 125518 is for talimogene laherparepvec, IMLYGIC, which is manufactured by BioVex Inc., a wholly owned subsidiary of Amgen. IMLYGIC is a genetically modified oncolytic viral therapy indicated for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery. The label includes the following limitation of use: IMLYGIC has not been shown to improve overall survival or have an effect on visceral metastases.

IMLYGIC is a replication-competent, attenuated derivative of herpes simplex virus type 1 (HSV-1) that can infect tumor cells and cause tumor lysis. IMLYGIC constitutively expresses a biologically active form of human granulocyte macrophage colony stimulating factor (GM-CSF).

The mechanism of action of IMLYGIC is thought to be by direct infection and lysis of tumor cells. GM-CSF expression by IMLYGIC is proposed to enhance the response to tumor antigens released during virus replication in tumor cells. However, the exact mechanisms of action of IMLYGIC are not fully understood.

This document summarizes the basis for approval for IMLYGIC, highlighting key review issues. The review team recommends approval of this BLA with a postmarketing observational study and a postmarketing clinical trial to assess potential IMLYGIC-associated herpetic infection of non-tumor tissue in patients, close contacts, and healthcare providers.

2. Background

The American Cancer Society (ACS) estimated that there were 76,100 new melanoma cases and 9,710 deaths from melanoma in the U.S. in 2014. (ACS, 2014) According to Surveillance, Epidemiology and End Results (SEER) data, between 2004 and 2010, approximately 84% of patients with melanoma were diagnosed with localized disease, 9% with regional disease, 4% with distant metastatic disease, and 3% unstaged. (Howlader N, 2014)

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

Until 2011, the treatment options for patients with unresectable stage III, stage IV, and recurrent melanoma were limited to high-dose interleukin-2 (IL-2) and dacarbazine (DTIC), neither of which has been demonstrated to prolong overall survival (OS) (Balch et al., 2009) (Howard et al., 2012) (Howlander N, 2014). Since 2011, however, therapeutic options for patients with unresectable or metastatic melanoma have expanded. The current standard care options for the initial treatment of these patients include not only IL-2, but also ipilimumab, an immune checkpoint inhibitor, and BRAF signal transduction inhibitors (for patients whose tumors express the BRAF V600E mutation), such as vemurafenib, dabrafenib and trametinib. Both ipilimumab and vemurafenib have been shown to prolong OS. In addition, dabrafenib and trametinib were approved in 2014, based on an effect on progression-free survival, for treatment of patients with unresectable or metastatic melanoma and BRAF V600E mutations. Programmed death 1 (PD-1) inhibitors pembrolizumab and nivolumab were granted Accelerated Approval in 2014. These therapies have demonstrated improvements in durable objective response rates, and ongoing clinical trials are being conducted to verify their clinical benefit. In 2015, nivolumab in combination with ipilimumab was granted accelerated approval for the treatment of patients with BRAF V600 wild-type, unresectable or metastatic melanoma. Thus, patients with unresectable or metastatic melanoma now have multiple systemic treatment options.

Regulatory History and Considerations

Key regulatory milestones in the development of IMLYGIC are summarized below.

April 2008	FDA Special Protocol Assessment granted for Phase 3 Study 005/05
April 2009	First subject enrolled in Study 005/05
January 2011	Fast Track designation granted
March 2011	Orphan drug designation granted
December 2012	Data cut-off for primary endpoint for Study 005/05
July 2014	Final BLA Module 5 (clinical) submitted
November 2014	BLA major CMC amendment submitted
April 29, 2015	FDA Advisory Committee meeting

3. Chemistry Manufacturing and Controls (CMC)

a) *Product Quality*

Product Description

IMLYGIC was derived from a novel primary HSV-1 isolate (JS1, ECACC Accession Number 01010209) that demonstrates enhanced oncolytic activity towards tumor cells, as compared to the commonly used laboratory strains (e.g., 17syn+). To produce IMLYGIC, the JS1 strain was genetically modified by deleting the virulence genes that code for ICP34.5 (also called the neurovirulence gene) and ICP47 (an immune escape gene). Wild type HSV-1 contains two copies of the gene for ICP34.5, and both copies were functionally deleted in IMLYGIC by inserting two copies of human GM-CSF gene sequences. Each copy of hGM-CSF is constitutively expressed under the control of a cytomegalovirus (CMV) immediate-early promoter. Deletion of the ICP47 gene also resulted in converting the HSV-1 late gene U_S11 into an immediate early gene, under the ICP47 promoter. The IMLYGIC virions are enveloped and have a diameter of about (b) (4). Each virion contains a capsid that encloses a double-stranded DNA genome of roughly (b) (4). IMLYGIC contains an intact thymidine kinase gene and the virus is sensitive to the antiviral drug acyclovir.

The IMLYGIC (b) (4) and drug product (DP) are manufactured at BioVex Inc., a wholly owned subsidiary of Amgen located in Woburn, Massachusetts, USA

Manufacturing Controls

IMLYGIC is grown in VERO cells (b) (4) purification (b) (4). The purified virus is filter sterilized (b) (4) sodium chloride, (b) (4) sorbitol, (b) (4) myo-inositol (b) (4) to obtain the DP with the required final (b) (4) (strength). IMLYGIC DP is filled into cyclic olefin polymer (COP) plastic resin vials, stoppered, capped, inspected, labeled, and frozen to -80°C ± 10°C, and is maintained in a frozen condition until thawed at the point of use. Each IMLYGIC vial (b) (4) 10 PFU/mL or 10 PFU/mL.

Manufacturing controls include controls on the quality of the manufacturing reagents, starting materials of biological origin; a series of risk assessment based evaluations of process parameters with in-process controls that have rejection limits, followed by lot release tests to ensure identity, purity, sterility, and potency of the final product (see table below).

Drug Product Specification and Tests for 10⁶ PFU/mL

Attribute	Parameter	Test Method	
		Description	Test Method Type
Identity	Identity	(b)	(4)
Appearance	Clarity		
	Color		
	Appearance		
Potency/ Strength	(b) (4)		
Potency			
Purity			

Attribute	Parameter	Test Method Description	Test Method Type	Acceptance Criteria
General Tests	pH	(b)	(4)	
	Osmolality			
	Volume			
	Subvisible Particles			
Safety-Adventitious agents	Sterility	(b)	(4)	
	Bacterial Endotoxin			
Safety-Toxicity	Abnormal Toxicity	(b)	(4)	

IMLYGIC is sensitive to light and the vials are individually packaged in paper cartons that are designed to protect the DP vial from light. The stability of the frozen IMLYGIC was evaluated based on identity (b) (4), safety (sterility, endotoxin), potency assays (b) (4) pH, appearance, and container closure integrity, and found to be stable for 48 months, when stored under recommended storage conditions (at -80 C ± 10 C), and protected from light.

Manufacturing Risks

The greatest risks associated with the manufacturing of this oncolytic viral product are (b) (4)

(b) (4)

Due to these risks there is a need to maintain control of the manufacturing process, maintain in-process controls through testing, and maintain control of source materials of biological origin used in the manufacturing process.

Potential genetic instability is minimized for every production run, by the use of well characterized (b) (4)

(b) (4)

(b) (4)

The risk of product contamination with a replicating AVA is minimized by the use of (b) (4)

b) CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. Samples were submitted to CBER in support of the BLA, tested by CBER and found to be acceptable. For routine lot release, the applicant will submit final container samples together with lot release protocols. A lot release testing plan was developed by CBER and will be used for routine lot release.

c) Facilities review/inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of IMLYGIC are listed in the table below. The activities performed and inspectional histories are noted in the table and are further described in the paragraphs that follow.

Manufacturing Facilities Table for IMLYGIC

Name/Address	FEI number	DUNS number	Inspection/waiver	Justification /Results
(b) (4) <i>Drug Product Manufacturer</i> BioVex Inc. , a wholly owned subsidiary of Amgen (Referred to as Amgen Woburn Massachusetts or AWM) <i>34 Commerce Way</i> <i>Woburn MA 01801 USA</i>	3006702185	796490766	Pre-License Inspection	CBER February 2015 VAI* (6/05/2015 endorsement)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

(b) (4)

*VAI: Voluntary action indicated

** Under FDASIA Section 712, Recognition of Foreign Government Inspections

The announced pre-license inspection (PLI) of BioVex Inc. was conducted by CBER February 10-13, 2015 for the (b) (4) drug product manufacturing. This inspection was the first CBER inspection conducted at the BioVex manufacturing site. There is no prior inspection history for this facility.

This inspection covered quality, facility and equipment, materials, production, and laboratory control systems. At the conclusion of the inspection, a Form FDA 483 containing three observations was issued. Observations were related to cleaning, review of documentation, and validation of aseptic processing. The firm responded to the 483 observations on February 27, 2015 and the corrective actions were reviewed. The corrective actions to the observations were found to be adequate.

d) *Container Closure System*

(b) (4) container closure system

(b) (4)

Drug Product container closure system

The primary container closure system for IMLYGIC drug product consists of a (b) (4) cyclic olefin polymer (COP) plastic resin vial, a (b) (4) elastomeric stopper with a (b) (4), and an aluminum seal with a flip-off dust cover. The ready-to-use vials (b) (4) are manufactured by (b) (4). The primary container closure system is labeled at BioVex, Inc.

The stopper is composed of a chlorobutyl elastomer (b) (4) with (b) (4) at BioVex, Inc.

Container closure system integrity for stability lots is evaluated by (b) (4) test method. This method is validated for its intended use.

e) *Environmental Assessment*

An environmental assessment (EA) was prepared pursuant to 21 CFR part 25. The EA provided a quantitative assessment of IMLYGIC environmental exposure and environmental stability. No significant environmental impacts on the quality of the human environment were identified. A Finding of No Significant Impact (FONSI) memorandum has been prepared.

4. Nonclinical Pharmacology/Toxicology

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

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

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

Systemic viral infection was observed following intratumoral injection of IMLYGIC in immunodeficient, tumor-bearing mice. Adverse findings in non-tumor tissues (e.g.,

gastrointestinal tract, brain) and body weight loss were also detected. These findings were consistent with the findings reported in immunocompetent or immunodeficient mice following wild-type HSV-1 infection.

No adverse effects on embryo-fetal development were observed following repeat intravenous administration of IMLYGIC during organogenesis in immunocompetent pregnant mice at dose levels up to 4×10^8 PFU/kg (approximately 60-fold higher than the maximum clinical dose level specified in the label). Levels of IMLYGIC DNA in pooled fetal blood were at or below the assay detection level. However, the relevancy of these data to humans is unclear due to study design limitations which included: 1) administration of IMLYGIC expressing huGM-CSF, which is not biologically active in mice; 2) the transplacental kinetics of IMLYGIC following intravenous administration in pregnant mice are not known; and 3) the significance of IMLYGIC dose extrapolation from animal to human, based on body weight, is not known.

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

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

5. Clinical Pharmacology

The biodistribution and shedding of intralesionally administered IMLYGIC are being investigated in an ongoing study measuring talimogene laherparepvec DNA and virus in blood, oral mucosa, urine, injection site, and occlusion dressings. The design of this study is described in Section 7.5, and this study is the subject of a postmarketing requirement (PMR) (Section 11d). Preliminary data suggest that IMLYGIC DNA and virus are present at the site of injection for the duration of treatment, and in bodily fluids immediately after injection.

6. Clinical / Statistical

a) *Clinical Program*

The safety and efficacy of intralesional injections of IMLYGIC compared with subcutaneously administered GM-CSF were evaluated in a multicenter, open-label, randomized clinical study of patients with stage IIIB, IIIC, and IV melanoma that was not surgically resectable. Patients with active cerebral metastases, bone metastases, extensive visceral disease, primary ocular or mucosal melanoma, evidence of immunosuppression, or receiving treatment with a systemic anti-herpetic agent were excluded from the study.

Patients were randomized in a 2:1 ratio to receive either IMLYGIC or GM-CSF (N= 436; 295 IMLYGIC, 141 GM-CSF). IMLYGIC was administered by intralesional injection at an

initial concentration of 10^6 (1 million) PFU per mL on Day 1, followed by a concentration of 10^8 (100 million) PFU per mL on Day 21 and every 2 weeks thereafter, at a dose of up to 4 mL.

The mean age of the study subjects was 63 (range: 22 to 94) years. The study included 250 (57%) men and 186 (43%) women. Most patients were white (98%). Seventy percent of subjects had baseline Eastern Cooperative Oncology Group (ECOG) performance status of zero. Seventy percent of subjects had stage IV disease (27% M1a; 21% M1b and 22% M1c). Fifty-three percent of subjects had received prior therapy for melanoma (other than or in addition to surgery, adjuvant therapy, or radiation), and 58% were seropositive for wild-type HSV-1 at baseline.

Clinical Efficacy Findings

The primary efficacy endpoint was durable response rate (DRR), defined as the percent of subjects with complete response (CR) or partial response (PR) maintained continuously for a minimum of 6 months. Tumor responses were determined according to World Health Organization (WHO) response criteria modified to allow patients who developed new lesions or disease progression of existing lesions to continue the treatment and be evaluated later for tumor response. The DRR was 16.3% in the talimogene laherparepvec arm and 2.1% in the GM-CSF arm. The unadjusted relative risk was 7.6 (95% CI: 2.4, 24.1), with a p-value < 0.0001.

Subgroups formed by age (< 65 vs. ≥ 65 years) or sex demonstrated treatment effects of similar magnitude for DRR. There were an insufficient number (n = 9) of non-White subjects for a meaningful subgroup analysis by race.

Median overall survival (OS) was 22.9 months (95% CI: 19.6 to 29.7) and 19.0 months (95% CI: 16.2 to 24.3) for the talimogene and GM-CSF arms, respectively. The difference in OS was not statistically significant (p=0.116).

Efficacy Review Issues

- 1) There was substantial discussion within the review team regarding the clinical meaningfulness of DRR and the regulatory pathway for approval. Some members of the review team did not accept DRR as clinically meaningful, but considered DRR as a surrogate endpoint reasonably likely to predict a clinical benefit such as prolongation of overall survival. Therefore, some members of the review team recommended Accelerated Approval for IMLYGIC with a requirement that Amgen conduct another Phase 3 trial to confirm the clinical benefit of IMLYGIC. However, other members of the review team accepted DRR as clinically meaningful, particularly in consideration of statements during the Advisory Committee meeting. At the Advisory Committee meeting, patients and their caregivers spoke of the value, both cosmetic and psychological, of watching their skin lesions disappear. The BLA includes data on a few subjects who had the benefit of having their unresectable lesions become resectable. In addition, the Advisory Committee voted strongly (22-1) in favor of regular approval. Based on this evidence,

FDA accepts DRR as clinically meaningful in Study 005. Therefore, FDA believes that the DRR endpoint is sufficient for regular approval, so that the Accelerated Approval pathway is not necessary for this BLA.

- 2) There was evidence that bias may have influenced the conduct of this open-label study. For example, almost two thirds of the control group subjects discontinued study agent administration by the third month, as compared with only one third of the subjects in the talimogene arm. However, the FDA reviewers conclude that the possible bias in the study conduct would not have substantially altered the study results and conclusions with regard to DRR.
- 3) Study 005 did not show a statistically significant effect on overall survival (OS). The pre-specified primary analysis of OS gave a p-value of 0.051, favoring the talimogene arm. However, FDA was concerned about informative censoring and asked the applicant to provide additional survival data. This additional data resulted in a revised p-value of 0.116, with median OS of 22.9 months in the talimogene arm and 19.0 months in the control arm. The review team believes this revised p-value is more accurate.
- 4) Subgroup analyses of the Study 005/05 data suggested that the benefit of talimogene laherparepvec might be greater in, or occur only in, patients with less advanced melanoma. Some members of the review team, along with some members of the Advisory Committee (see Section 8), proposed that the indicated population should be limited to patients with less advanced disease. However, other members advocated for a broader indicated population, and the Advisory Committee did not reach a consensus on this issue. Considering the deliberations of the Advisory Committee, and that subgroup analyses should be interpreted with caution, FDA does not believe that the indicated population should be limited to patients with less advanced disease.
- 5) One issue was whether Study 005 meets the regulatory standard for a single trial to provide the primary evidence of effectiveness to support a marketing approval. The FDA Guidance on *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (1998) states that "... reliance on a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible." Study 005 does not provide evidence of a clinically meaningful effect on such an outcome measure, and it is conceivable that a confirmatory trial could be conducted. However, the available treatments and clinical management for melanoma have changed substantially since Study 005 was conducted. As a result of these changes, it would not be feasible for a second trial to provide data that substantially refutes the Study 005 conclusion of an effect on DRR in patients with advanced melanoma. Thus, due to the relatively unique circumstances involving the changes in practice since Study 005 was conducted, FDA views the available evidence as sufficient to support marketing approval at this time.

Bioresearch Monitoring

CBER conducted Bioresearch Monitoring (BIMO) Inspections at four clinical study sites that enrolled subjects in support of this BLA. The inspected sites represented approximately 13% of the 437 total randomized subjects. BIMO inspections at the four clinical sites did not reveal substantive problems that impact the data submitted in the BLA.

In 2012, a BIMO inspection was conducted at another clinical study site, Site 066, in response to a complaint regarding the clinical investigator's alleged mismanagement of the study, failure to adhere to Good Clinical Practice, and the lack of data integrity in Study 005/05. The inspection identified significant problems at Site 066 that could potentially impact the data submitted to the BLA. These problems included, but were not limited to, failure to protect the rights of the subjects, failure to follow the study protocol, and failure to maintain adequate records. Excluding this site from the ITT analysis set does not lead to material change in the conclusions regarding the DRR and OS endpoints. For example, the OS primary analysis excluding this site has a p-value of 0.056, compared to 0.051 with the ITT set. Therefore, the review team decided to include the results from the 25 subjects at Site 066 in the ITT analysis.

Efficacy Conclusion

Based on the available data, the BLA provides substantial evidence of the effectiveness of IMLYGIC, with the primary evidence of effectiveness coming from Study 005.

b) *Pediatrics*

Orphan Drug designation for the indicated population of Stage IIIB, IIIC, and IV melanoma was granted on March 14, 2011. Therefore, the product is exempt from the Pediatric Research Equity Act (PREA) regulations. No pediatric data were presented in the BLA.

7. Safety

The primary safety analysis was based on Study 005, including 292 subjects who received at least one dose of IMYLGIC (talimogene laherparepvec). A total of 290 of 292 subjects (99.3%) exposed to IMYLGIC had at least one treatment-emergent adverse event (T-E AE) (grades 1-5). Of these, 93 subjects (31.9%) experienced Grade 3 and 13 subjects (4.5%) experienced Grade 4 AEs. The most frequent treatment-emergent adverse events were fatigue, chills, pyrexia, nausea, influenza-like illness, and injection-site pain.

In Study 005, T-E Serious AEs (T-E SAEs) occurred in 75/290 subjects (25.9%) who experienced an AE in the IMYLGIC arm and 17/126 subjects (13.4%) who experienced an AE in the control arm. The most common T-E SAEs were disease progression and cellulitis. In the IMLYGIC arm, a total of 17 subjects (5.8%) developed cellulitis; seven of these events (2.4%) were categorized as serious, requiring hospitalization.

Other adverse reactions associated with IMLYGIC in Study 005 include glomerulonephritis, vitiligo, cellulitis, and oral herpes.

IMLYGIC infections and shedding

IMLYGIC is a first-in-class oncolytic therapy with a genetically modified replication competent HSV-1. IMLYGIC retains the 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 an infected person (proxy for transmission), and transmission through unintended exposure.

In Study 005/05, 16 subjects (5.5%) in the IMLYGIC arm had AEs related to HSV infection, compared to 2 subjects (1.6%) in the control (GM-CSF) arm; none of the subjects were qPCR tested to further characterize the causative infectious agent (IMLYGIC v. wild type HSV-1). With IMLYGIC treatment, 15 subjects had lesions of oral herpes and one subject developed herpetic keratitis. Accidental exposure to IMLYGIC leading to IMLYGIC-associated infection was documented in one healthcare provider who sustained a needle-stick injury to the finger and developed a whitlow lesion at the site of injury (direct inoculation) that tested positive for IMLYGIC DNA by qPCR assay.

IMLYGIC viral shedding is under investigation in an ongoing single-arm clinical study (Amgen 20120324) to evaluate the biodistribution and shedding of IMLYGIC in treated patients. This study is the subject of a postmarketing requirement (PMR) (Section 11d). In the initial 20 (of the planned 60) melanoma subjects enrolled into Amgen Study #20120324 who received IMLYGIC intralesional injections at a dose and schedule similar to that of Study 005/05, IMLYGIC DNA was present in the blood in 17 (85%) of subjects and in the urine of four (20%) of the subjects. The exterior of the occlusive dressings was positive for IMLYGIC DNA in 14 subjects (70%). Based on these data, the IMLYGIC labeling reflects concern about the risk of infections to close contacts.

In addition, limited IMLYGIC viral shedding data make it difficult to adequately assess the risk of IMLYGIC transmission to healthcare providers and close patient contacts. However, potential IMLYGIC-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. Thus, IMLYGIC-associated herpetic infection of non-tumor tissue in patients (primary infection or reactivation/latency) and contacts (transmission/accidental exposure) is considered to meet criteria under 505(o) of the Federal Food, Drug, and Cosmetic Act for required post approval studies “to identify an unexpected serious risk when available data indicates the potential for a serious risk.” Therefore, IMLYGIC-associated herpetic infection in non-tumor tissue of treated patients (primary infection or reactivation/latency) and contacts (transmission/accidental exposure) will be further investigated in a PMR study, planned to be a prospective observational cohort study (Amgen 20130193) (Section 11d).

8. Advisory Committee Meeting

A joint meeting of CBER's Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) and CDER's Oncologic Drugs Advisory Committee (ODAC) was held on April 29, 2015 in order to provide advice to FDA regarding safety, dosing, and an overall benefit-risk assessment for IMLYGIC. There was extensive discussion, with no clear consensus, regarding whether the efficacy of IMLYGIC was limited to a definable subset of the Study 005 population (e.g., those subjects with less advanced disease). The committee voted 22 to 1 (Yes to No) to the question, "does talimogene laherparepvec have an overall favorable benefit-risk profile to support traditional approval for the treatment of injectable, regionally or distantly metastatic melanoma?"

9. Other Relevant Regulatory Issues

None

10. Labeling

The proposed proprietary name for the product, IMLYGIC, was reviewed by the Advertising and Promotional Labeling Branch (APLB) and recommended to be acceptable on March 6, 2014. The product labeling (i.e., prescribing information and medication guide) and the product package and container labels were reviewed by APLB from a promotional and comprehension perspective.

The review team had substantial concern regarding how IMLYGIC would be used in clinical practice. Study 005 provides evidence of a local effect of IMLYGIC on cutaneous, subcutaneous, and nodal lesions. The BLA provides insufficient evidence to conclude that IMLYGIC has an effect on overall survival or visceral metastases. There are FDA-approved medications that have a proven benefit on overall survival. Patients with Stage III or Stage IV melanoma should not use IMLYGIC in place of such medications with an expectation of an effect on survival or visceral lesions. Also, the BLA does not contain any data on whether IMLYGIC would be effective in combination with any of these other medications. To decrease the risk that healthcare providers will prescribe IMLYGIC with unreasonable expectations, or when another medication would be more appropriate, the indication statement should state that IMLYGIC is indicated for the treatment of lesions in patients with melanoma, as opposed to the treatment of melanoma in general. Furthermore, the indication statement should explicitly state that IMLYGIC has not been shown to have an effect on overall survival or on visceral lesions.

Multiple discussions about the labeling were held between review team members and Amgen, which resulted in multiple rounds of revisions until final agreement was reached. The most significant changes are summarized below:

- The proposed indication was revised to explicitly state that IMLYGIC treatment is for local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery.
- A “Limitation of use” statement indicates that IMLYGIC has not been shown to improve overall survival or have an effect on visceral metastases.
- Several sections were revised to add or clarify procedures and precautions regarding product dose, preparation, and administration.
- Several sections were revised to reflect concerns about the risk of infections to close contacts.
- The Contraindications section was revised to specify that talimogene laherparepvec is contraindicated in immunocompromised patients and pregnant patients.
- The Clinical Study Section was revised to reflect the major efficacy outcome data that support the indication, including the absence of a statistically significant effect on overall survival.
- Biohazard information was revised and grouped under Section 2.
- The label includes a dedicated phone number for reporting of adverse events to Amgen. The review team viewed the dedicated phone number as particularly important to gather data on the risk of shedding.
- A Medication Guide, in accordance with 21 CFR 208, will be included in labeling to optimize the awareness and education of patients about the potential risks of IMLYGIC to patients and contacts and associated safe use precautions, and risk to vulnerable populations (immunocompromised hosts and pregnant women).

11. Recommendations and Risk / Benefit Assessment

a) Recommended Regulatory Action

OCTGT recommends approval of IMLYGIC for local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery, with a limitation of use that IMLYGIC has not been shown to improve overall survival or have an effect on visceral metastases.

b) Risk / Benefit Assessment

The benefit of IMLYGIC is improvement in cutaneous, subcutaneous, and nodal lesions in patients with melanoma. This benefit is at least partially cosmetic. There may be associated psychological benefit, which may be substantial in patients who can see their visible lesions recede. For a few patients, IMLYGIC may have the benefit of changing their lesions from unresectable to resectable. One of the greatest concerns with approval of IMLYGIC is that patients will receive IMLYGIC instead of a product with a proven benefit on overall survival. This indirect risk has been mitigated by labeling that 1) states that IMLYGIC is for the treatment of lesions, not for the treatment of melanoma, and 2) includes a limitation of use that states that IMLYGIC has not been shown to improve overall survival or have an effect on visceral metastases. The direct risks of IMLYGIC administration, as described in the label, are mostly mild and moderate adverse events (fatigue, chills, pyrexia, nausea

influenza-like illness, and injection-site pain) that resolve within 72 hours. The most common serious adverse event is cellulitis, which is readily treatable. These risks of IMLYGIC are further mitigated by the Contraindications (pregnancy; immunocompromised patients) and the Warnings and Precautions in the labeling. The risk of shedding, including the risk of transmission of infection to close contacts and healthcare providers, will be assessed in two postmarketing studies. Thus, although patients with advanced melanoma may have a life-threatening disease, and IMLYGIC has not been shown to have an effect on survival, the benefits of IMLYGIC are clinically meaningful and may be important for many patients. These benefits are sufficient to justify the risks of IMLYGIC, which are generally mild or moderate, and can be mitigated as described above. Therefore, IMLYGIC has an overall favorable benefit-risk profile for some patients with melanoma.

The label states that IMLYGIC is indicated for treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery, reflecting the population that was studied in Study 005, and is not limited to patients with a particular stage of metastatic melanoma. Ultimately, the healthcare provider will decide which individual patients have a clinical situation for which IMLYGIC offers an overall favorable balance of benefits and risks. This assessment will be highly individualized, following consideration of the benefits and risks of other available treatments for melanoma.

c) Recommendation for Postmarketing Risk Management Activities

The available clinical trial safety data do not suggest a safety concern that would require a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of IMLYGIC outweigh its risks.

d) Recommendation for Postmarketing Activities

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

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

Post-marketing Requirement (PMR) studies for Safety under 505 (o):

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:” IMLYGIC-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, 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 PMR study and PMR trial. The PMR study and trial were concurred by CBER FDAAA SWG on June 25, 2015; Amgen was notified on July 20, 2015 and has agreed to the following milestone dates.

PMR #1:

Conduct a prospective observational cohort study of 920 IMLYGIC-treated patients to characterize the risk of herpetic infection among patients, close contacts, and healthcare providers; each subject will be followed for 5 years after initiating IMLYGIC (study Protocol #20130193).

Final Protocol Submission: April 30, 2016
Study Completion: August 31, 2024
Final Report Submission: February 28, 2025

PMR #2:

Complete the ongoing single-arm trial to evaluate the biodistribution and shedding of IMLYGIC in 60 IMLYGIC-treated subjects (study protocol #20120324).

Final Protocol Submission: November 30, 2015
Study Completion: September 30, 2016
Final Report Submission: May 31, 2017

12. References

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